**Endocrinology (Hormones: Diabetes, Thyroid)**

What is Endocrinology? Endocrinology is the branch of medicine that focuses on the study and treatment of the endocrine system, a collection of glands that are responsible for producing and releasing hormones. Hormones are chemical messengers that regulate important body functions like metabolism, growth, mood, and reproduction.

Hormones are essential for regulating key bodily functions, including metabolism, growth, mood, energy levels, and reproduction.

The endocrine system includes glands such as the thyroid, pancreas, adrenal glands, and ovaries. The endocrine glands—including the thyroid gland, adrenal glands, pituitary gland, and pancreas—release hormones that travel through the bloodstream to target organs. These hormones help maintain balance in the body, affecting things like blood pressure, heart rate, and blood sugar levels. If any of these glands or hormones go out of balance, or when these glands don’t function properly, it can lead to a variety of health problems, including diabetes, hormonal imbalances. thyroid disorders, or adrenal disorders.

**Endocrinology services** offer specialized care to diagnose, treat, and manage these conditions. ensuring patients’ hormones are functioning properly. Whether you’re struggling with weight management, infertility, or chronic fatigue, an endocrinologist can help bring your hormones back into balance and improve your overall health.

## **The Role of the Endocrine System in Your Body**

The **endocrine system** is like the body’s internal communication network, sending chemical messages through hormones to different organs. These hormones help control functions that are critical to your well-being. For example, the pituitary gland, often called the “master gland,” controls other glands and regulates growth hormone production, which affects growth and development.

The thyroid gland, shaped like a butterfly and located in the neck, controls metabolism through the hormone thyroxine, affecting energy levels, weight, and heart rate. The adrenal glands, located on top of the kidneys, release hormones that help manage stress, blood pressure, and the body’s reaction to emergency situations.

A problem with any of these glands or the hormones they produce can disrupt the entire system, leading to hormonal imbalances that require professional care.

## **Common Endocrine Conditions and How They Affect You**

Hormonal imbalances can lead to a variety of endocrine conditions that affect overall health and daily life. Thyroid disorders, for instance, can result in symptoms such as unexplained weight gain or loss, fatigue, and depression.

Overactive thyroid (hyperthyroidism) or underactive thyroid (hypothyroidism) can cause significant disruptions in metabolism and energy. Similarly, adrenal disorders like Addison’s disease or Cushing’s syndrome, which affect the adrenal glands, can lead to symptoms such as high blood pressure, extreme fatigue, and weight gain.

Another common issue is diabetes, which involves problems with the blood sugar regulation system, often caused by insufficient insulin production or the body’s inability to use insulin properly. Hormonal imbalances can also affect reproductive health, resulting in issues like infertility or irregular menstrual cycles. Endocrinology services specialize in diagnosing and treating these conditions, restoring balance and helping patients manage symptoms.

## **How Endocrinologists Diagnose and Treat Hormonal Imbalances**

**Endocrinologists** are specialists trained to diagnose and treat conditions related to the endocrine system. They often start by conducting a thorough medical history and performing physical exams. Blood tests are crucial to check hormone levels and determine whether the endocrine glands are functioning correctly.

These tests may include measuring thyroid hormone levels to diagnose thyroid disorders, checking cortisol levels for adrenal disorders, or assessing blood sugar levels for diabetes. Based on the results, an endocrinologist can create a treatment plan tailored to each patient’s specific condition. This might include hormone replacement therapy, medications to regulate hormone production, or lifestyle changes such as diet and exercise adjustments. For patients in Houston, visiting a local endocrinologist for professional care is essential to effectively manage hormone-related health problems.

Below is a list of diseases that can be found under endocrinology:

1. **Diabetes (Diabetes and Glucose Regulation Disorders)**

* Type 1
* Type 2
* Type 3c
* Gestational diabetes
* Maturity Onset Diabetes of the Young (MODY)
* Diabetic myopathy
* Hypoglycemia (including insulinoma)
* Insulinoma
* Neonatal diabetes
* Wolfram syndrome
* Alstrom syndrome
* Latent autoimmune diabetes in adults (lada)
* Glucagonoma
* Monogenic diabetes
* Diabetic complications (neuropathy, nephropathy, retinopathy, peripheral vascular disease)

1. **thyroid disorder**

* Goiter
* Hyperthyroidism (including Graves’ disease, toxic multinodular goitre)
* Toxic multinodular goiter
* Hypothyroidism
* Hypothyroidism myopathy
* Hashimoto hypothyroidism / disease
* Thyroiditis
* Thyroid cancer
* Thyroid nodules
* Menstrual irregularities
* Menstrual disorder

1. **PITUITARY GLAND DISORDERS**

* Acromegaly
* Gigantism
* Pituitary adenomas (tumors)
* Prolactinoma (hyperprolactinemia)
* Hypopituitarism (panhypopituitarism)
* Cushing’s disease (pituitary origin)
* Diabetes insipidus
* Syndrome of inappropriate antidiuretic hormone secretion (SIADH)

1. **ADRENAL GLANDS DISORDERS**

* Addison’s disease (adrenal insufficiency)
* Congenital adrenal hyperplasia
* Adrenal tumors (benign and malignant)
* Adrenal crisis
* Hyperaldosteronism (Conn’s syndrome)
* Hypoaldosteronism
* Pheochromocytoma
* Adrenoleukodystrophy

1. **PARATHYROID AND CALCIUM DISORDERS**

* Hyperparathyroidism (primary, secondary, tertiary)
* Hypoparathyroidism
* Pseudohypoparathyroidism
* Osteoporosis
* Osteomalacia
* Rickets
* Paget’s disease of bone

1. **GONADAL AND REPRODUCTIVE ENDOCRINE DISORDERS**

* Polycystic Ovary Syndrome (PCOS)
* Hypogonadism (male and female)
* Klinefelter syndrome
* Turner syndrome
* Delayed puberty
* Precocious puberty
* Menopause-related hormonal disorders
* Infertility (hormonal causes)
* Disorders of sex development (intersex conditions, androgen insensitivity)

1. **MULTIPLE GLAND AND GENETIC DISORDERS**

* Multiple Endocrine Neoplasia (MEN) types 1 and 2
* Carcinoid syndrome
* Autoimmune polyendocrine syndromes

1. **OTHER NOTABLE ENDOCRINE DISORDERS**

* Metabolic syndrome
* Obesity (endocrine causes)
* Hirsutism
* Galactorrhea
* High/low cholesterol (endocrine causes)
* Endocrine tumors (neuroendocrine tumors, carcinoid tumors)

**ENDOCRINOLOGY**

Endocrinology is the branch of medicine that looks at the endocrine system, which controls hormones. Often, problems stem from when your body secretes too much or too little of a hormone. These conditions include diabetes, thyroid disorders, and problems with sex hormones such as fertility issues.

**THE ENDOCRINE SYSTEM**

The endocrine system is a network of tissues (mainly glands) that produce and release hormones which help to maintain countless bodily functions. Hormones are chemicals that coordinate different important functions in your body, including the body’s ability to change calories into energy that powers; it helps carry messages through your blood to your organs, skin, muscles and other tissues. These signals tell your body what to do and when to do it. Hormones are essential for life and your health.

The endocrine system affects how your heart beats, how your bones and tissues grow, and even your ability to make a baby.

Disorders of the endocrine system happen if your hormone levels are too high or too low, or if your body doesn't respond to hormones in the expected way. You may develop diabetes, thyroid disease, growth disorders, and a host of other hormone-related disorders.

**Glands of the Endocrine System**

Endocrine tissues include your pituitary gland, thyroid, pancreas and others. There are several conditions related to endocrine system issues-usually due to a hormone imbalance or problems directly affecting the tissue.

Each gland of the endocrine system releases specific hormones into your bloodstream. These hormones travel through your blood to other cells and help control or coordinate many body processes.

Endocrine glands include:

* **Adrenal glands:** Two glands that sit on top of the kidneys that release the hormone cortisol.
* **Hypothalamus:** A part of the lower middle brain that tells the pituitary gland when to release hormones.
* **Islet cells in the pancreas:** Cells in the pancreas that control the release of the hormone’s insulin and glucagon.
* **Ovaries:**The female reproductive organs that release eggs and produce sex hormones.
* **Parathyroid:** Four tiny glands in the neck that play a role in bone development.
* **Pineal gland**: A gland located near the center of the brain that may be linked to sleep patterns.
* **Pituitary gland:** It's present at the base of the brain behind the sinuses. It is often called the "master gland" because it influences many other glands, especially the thyroid. Problems with the pituitary gland can affect bone growth, a woman's menstrual cycles, and the release of breast milk.
* **Testes:**The male reproductive glands that produce sperm and sex hormones.
* **Thymus:** A gland in the upper chest that helps develop the body's immune system early in life.
* **Thyroid:** A butterfly-shaped gland in the front of the neck that controls metabolism.

Even the slightest hiccup with the function of one or more of these glands can throw off the delicate balance of hormones in your body and lead to an endocrine disorder, or endocrine disease.

*REFERENCE:*

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**ENDOCRINOLOGY DISEASES (HORMONES: DIABETES, THYROID)**

Endocrinology diseases involve disorders of the endocrine system, which is a network of glands and organs that produce hormones. These diseases can result from the body making too many or too few hormones, or from the body not responding properly to hormones. Common endocrine diseases include **diabetes, thyroid disorders, and adrenal gland disorders**.

**DIABETES**

This is the most common endocrine disorder. It occurs when the body has trouble regulating blood sugar levels, often due to issues with insulin production or use. Diabetes can be managed through diet, exercise, medication, and sometimes insulin therapy.

**Types of Diabetes**

You may be aware of the most common types of diabetes, those being Type 1, Type 2 and gestational diabetes but did you know that there are also at least 6 other types?!

Below are some of the known types of diabetes, they include:

**TYPE 1 DIABETES**

*ALTERNATIVE NAMES:*Type 1 diabetes was once also known as Juvenile diabetes or Insulin-dependent diabetes.

**DEFINITION / DESCRIPTION**

Type 1 diabetes, once known as juvenile diabetes or insulin dependent diabetes, is a chronic condition. In this condition, the pancreas cannot produce enough of a hormone called insulin which helps to regulate blood glucose. Insulin is a hormone the body uses to allow sugar (glucose) to enter cells to produce energy. This type of diabetes causes the level of glucose, known as sugar, in your blood to become too high. Type 1 diabetes is not influenced by your diet or your lifestyle and can affect people of any age

**CAUSES**

The exact cause of type 1 diabetes is unknown. Usually, the body's own immune system, which normally fights harmful bacteria and viruses, destroys the insulin-producing (islet) cells in the pancreas. Other possible causes of Type 1 diabetes may include:

* Genetics
* Exposure to viruses and other environmental factors

**THE ROLE OF INSULIN**

Once a large number of islet cells are destroyed, the body will produce little or no insulin. Insulin is a hormone that comes from a gland behind and below the stomach (pancreas).

* The pancreas puts insulin into the bloodstream.
* Insulin travels through the body, allowing sugar to enter the cells.
* Insulin lowers the amount of sugar in the bloodstream.
* As the blood sugar level drops, the pancreas puts less insulin into the bloodstream.

**THE ROLE OF GLUCOSE**

Glucose (a sugar) is a main source of energy for the cells that make up muscles and other tissues.

Glucose comes from two major sources: food and the liver.

Sugar is absorbed into the bloodstream, where it enters cells with the help of insulin.

The liver stores glucose in the form of glycogen.

When glucose levels are low, such as when you haven't eaten in a while, the liver breaks down the stored glycogen into glucose. This keeps glucose levels within a typical range.

In type 1 diabetes, there's no insulin to let glucose into the cells. Because of this, sugar builds up in the bloodstream. This can cause life-threatening complications.

**RISK FACTORS**

Some factors that can raise your risk for type 1 diabetes include:

* Family history: Anyone with a parent or sibling with type 1 diabetes has a slightly higher risk of developing the condition.
* Genetics: Having certain genes increases the risk of developing type 1 diabetes.
* Geography: The number of people who have type 1 diabetes tends to be higher as you travel away from the equator.
* Age: Type 1 diabetes can appear at any age, but it appears at two noticeable peaks. The first peak occurs in children between 4 and 7 years old. The second is in children between 10 and 14 years old.

**SIGNS / SYMPTOMS**

The symptoms of type 1 diabetes often show quickly, sometimes in just a matter of days. These are the some of the main symptoms of Type 1 diabetes:

* Increased thirst
* Urinating more than usual
* Bedwetting in children who have never wet the bed during the night
* Feeling fatigued, tired and weak
* Feeling very hungry
* Feeling irritable or having other mood changes
* Unexplained weight-loss
* Having blurry vision
* Nausea, and vomiting
* Fat
* Flu-like symptoms.
* Slow healing cuts, sores
* Vaginal yeast infections

**DIAGNOSIS METHODS**

Diagnosis tests for Type 1 diabetes can include:

* **Glycated hemoglobin (A1C) test.** This blood test shows your average blood sugar level for the past 2 to 3 months. It measures the amount of blood sugar attached to the oxygen-carrying protein in red blood cells (hemoglobin). The higher the blood sugar levels, the more hemoglobin you'll have with sugar attached. An A1C level of 6.5% or higher on two separate tests means you have diabetes.

If the A1C test isn't available, or if you have certain conditions that can make the A1C test inaccurate, such as pregnancy or an uncommon form of hemoglobin (hemoglobin variant), your provider may use these tests:

* **Random blood sugar test.** A blood sample will be taken at a random time and may be confirmed by additional tests. Blood sugar values are expressed in milligrams per deciliter (mg/dL) or millimoles per liter (mmol/L). No matter when you last ate, a random blood sugar level of 200 mg/dL (11.1 mmol/L) or higher suggests diabetes.
* **Fasting blood sugar test.** A blood sample will be taken after you don't eat (fast) overnight. A fasting blood sugar level less than 100 mg/dL (5.6 mmol/L) is healthy. A fasting blood sugar level from 100 to 125 mg/dL (5.6 to 6.9 mmol/L) is considered prediabetes. If it's 126 mg/dL (7 mmol/L) or higher on two separate tests, you have diabetes.

If you're diagnosed with diabetes, your provider may also run blood tests. These will check for autoantibodies that are common in type 1 diabetes. The tests help your provider decide between type 1 and type 2 diabetes when the diagnosis isn't certain. The presence of ketones, byproducts from the breakdown of fat, in your urine also suggests type 1 diabetes, rather than type 2.

**After the diagnosis**

You'll regularly visit your provider to talk about managing your diabetes. During these visits, the provider will check your A1C levels. Your target A1C goal may vary depending on your age and various other factors. The American Diabetes Association generally recommends that A1C levels be below 7%, or an average glucose level of about 154 mg/dL (8.5 mmol/L).

A1C testing shows how well the diabetes treatment plan is working better than daily blood sugar tests. A high A1C level may mean you need to change the insulin amount, meal plan or both.

GP's will complete a urine test and will also check your blood sugar levels. They will use these samples to check cholesterol levels, as well as thyroid, liver and kidney function. Your provider will also take your blood pressure and check the sites where you test your blood sugar and deliver insulin.

If they are under the belief that you do have diabetes, you will be advised to go to the hospital immediately where an assessment will be carried out. You will be required to stay in the hospital until your blood test results are ready, usually the same day.

Should the assessment determine that you do have type 1 diabetes, a specialist diabetes nurse will talk you through everything you need to know and what you will need to do to manage it.

**TREATMENT OPTIONS**  
Type 1 diabetes can be managed by daily injections of insulin, or an insulin pump which helps to keep your blood sugar levels under control.

Treatment for type 1 diabetes includes:

* Taking insulin
* Counting carbohydrates, fats and protein
* Monitoring blood sugar often
* Eating healthy foods
* Exercising regularly and keeping a healthy weight

The goal is to keep the blood sugar level as close to normal as possible to delay or prevent complications. Generally, the goal is to keep the daytime blood sugar levels before meals between 80 and 130 mg/dL (4.44 to 7.2 mmol/L). After-meal numbers should be no higher than 180 mg/dL (10 mmol/L) two hours after eating.

**Insulin and other medications**

Anyone who has type 1 diabetes needs insulin therapy throughout their life.

**There are many types of insulin,** including:

* **Short-acting insulin.** Sometimes called regular insulin, this type starts working around 30 minutes after injection. It reaches peak effect at 90 to 120 minutes and lasts about 4 to 6 hours. Examples are Humulin R, Novolin R and Afrezza.
* **Rapid-acting insulin.** This type of insulin starts working within 15 minutes. It reaches peak effect at 60 minutes and lasts about 4 hours. This type is often used 15 to 20 minutes before meals. Examples are glulisine (Apidra), lispro (Humalog, Admelog and Lyumjev) and aspart (Novolog and FiAsp).
* **Intermediate-acting insulin.** Also called NPH insulin, this type of insulin starts working in about 1 to 3 hours. It reaches peak effect at 6 to 8 hours and lasts 12 to 24 hours. Examples are insulin NPH (Novolin N, Humulin N).
* **Long- and ultra-long-acting insulin.** This type of insulin may provide coverage for as long as 14 to 40 hours. Examples are glargine (Lantus, Toujeo Solostar, Basaglar), detemir (Levemir) and degludec (Tresiba).

You'll probably need several daily injections that include a combination of a long-acting insulin and a rapid-acting insulin. These injections act more like the body's normal use of insulin than do older insulin regimens that only required one or two shots a day. A combination of three or more insulin injections a day has been shown to improve blood sugar levels.

**Insulin delivery options**

Insulin can't be taken by mouth to lower blood sugar because stomach enzymes will break down the insulin, preventing it from working. You'll need to either get shots (injections) or use an insulin pump.

**Injections.** You can use a fine needle and syringe or an insulin pen to inject insulin under the skin. Insulin pens look like ink pens and are available in disposable or refillable varieties.

If you choose shots (injections), you'll probably need a mixture of insulin types to use during the day and night.

**An insulin pump.** This is a small device worn on the outside of your body that you program to deliver specific amounts of insulin throughout the day and when you eat. A tube connects a reservoir of insulin to a catheter that's inserted under the skin of your abdomen.

There's also a tubeless pump option that involves wearing a pod containing the insulin on your body combined with a tiny catheter that's inserted under your skin.

**Blood sugar monitoring**

Depending on the type of insulin therapy you select or need, you may have to check and record your blood sugar level at least four times a day.

The American Diabetes Association recommends testing blood sugar levels before meals and snacks, before bed, before exercising or driving, and whenever you think you have low blood sugar. Careful monitoring is the only way to make sure that your blood sugar level remains within your target range. More frequent monitoring can lower A1C levels.

Even if you take insulin and eat on a strict schedule, blood sugar levels can change. You'll learn how your blood sugar level changes in response to food, activity, illness, medications, stress, hormonal changes and alcohol.

**Continuous glucose monitoring**

Continuous glucose monitoring (CGM) monitors blood sugar levels. It may be especially helpful for preventing low blood sugar. These devices have been shown to lower A1C.

Continuous glucose monitors attach to the body using a fine needle just under the skin. They check blood glucose levels every few minutes.

**Closed loop system**

A closed loop system is a device implanted in the body that links a continuous glucose monitor to an insulin pump. The monitor checks blood sugar levels regularly. The device automatically delivers the right amount of insulin when the monitor shows that it's needed.

The Food and Drug Administration has approved several hybridized closed loop systems for type 1 diabetes. They are called "hybrid" because these systems require some input from the user. For example, you may have to tell the device how many carbohydrates are eaten, or confirm blood sugar levels from time to time.

A closed loop system that doesn't need any user input isn't available yet. But more of these systems currently are in clinical trials.

**Other medications**

Other medications could also be prescribed for people with type 1 diabetes, such as:

* **High blood pressure medications.** Your provider may prescribe angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) to help keep your kidneys healthy. These medications are recommended for people with diabetes who have blood pressures above 140/90 millimeters of mercury (mm Hg).
* **Aspirin.** Your provider may recommend you take baby or regular aspirin daily to protect your heart. Your provider may feel that you have an increased risk of a cardiovascular event. Your provider will discuss the risk of bleeding if you take aspirin.
* **Cholesterol-lowering drugs.** Cholesterol guidelines are stricter for people with diabetes because of their higher risk of heart disease.

The American Diabetes Association recommends that low-density lipoprotein (LDL, or "bad") cholesterol be below 100 mg/dL (2.6 mmol/L). High-density lipoprotein (HDL, or "good") cholesterol is recommended to be over 50 mg/dL (1.3 mmol/L) in women and over 40 mg/dL (1 mmol/L) in men. Triglycerides, another type of blood fat, should be less than 150 mg/dL (1.7 mmol/L).

**Healthy eating and monitoring carbohydrates**

There's no such thing as a diabetes diet. However, it's important to center your diet on nutritious, low-fat, high-fiber foods such as:

* Fruits
* Vegetables
* Whole grains

Your registered dietitian will recommend that you eat fewer animal products and refined carbohydrates, such as white bread and sweets. This healthy-eating plan is recommended even for people without diabetes.

You'll need to learn how to count the amount of carbohydrates in the foods you eat. By doing so, you can give yourself enough insulin. This will allow your body to properly use those carbohydrates. A registered dietitian can help you create a meal plan that fits your needs.

**Physical activity**

Everyone needs regular aerobic exercise, including people who have type 1 diabetes. First, get your provider's OK to exercise. Then choose activities you enjoy, such as walking or swimming, and do them every day when you can. Try for at least 150 minutes of moderate aerobic exercise a week, with no more than two days without any exercise.

Remember that physical activity lowers blood sugar. If you begin a new activity, check your blood sugar level more often than usual until you know how that activity affects your blood sugar levels. You might need to adjust your meal plan or insulin doses because of the increased activity.

**Activities of concern**

Certain life activities may be of concern for people who have type 1 diabetes; these may include:

* **Driving.** Low blood sugar can occur at any time. It's a good idea to check your blood sugar anytime you're getting behind the wheel. If it's below 70 mg/dL (3.9 mmol/L), have a snack with 15 grams of carbohydrates. Retest again in 15 minutes to make sure it has risen to a safe level before you start driving.
* **Working.** Type 1 diabetes can pose some challenges in the workplace. For example, if you work in a job that involves driving or operating heavy machinery, low blood sugar could pose a serious risk to you and those around you. You may need to work with your provider and your employer to ensure that certain adjustments are made. You may need additional breaks for blood sugar testing and fast access to food and drink. There are federal and state laws that require employers to provide these adjustments for people with diabetes.
* **Being pregnant.** The risk of complications during pregnancy is higher for people with type 1 diabetes. Experts recommend that you see your provider before you get pregnant. A1C readings should be less than 6.5% before you try to get pregnant.

The risk of diseases present at birth (congenital diseases) is higher for people with type 1 diabetes. The risk is higher when diabetes is poorly controlled during the first 6 to 8 weeks of pregnancy. Careful management of your diabetes during pregnancy can lower your risk of complications.

* **Being older or having other conditions.** For those who are weak or sick or have difficulty thinking clearly, tight control of blood sugar may not be practical. It could also increase the risk of low blood sugar. For many people with type 1 diabetes, a less strict A1C goal of less than 8% may be appropriate.

**Potential future treatments**

**Pancreas transplant.** With a successful pancreas transplant, you would no longer need insulin. But pancreas transplants aren't always successful — and the procedure poses serious risks. Because these risks can be more dangerous than the diabetes itself, pancreas transplants are generally used for those with very difficult-to-manage diabetes. They can also be used for people who also need a kidney transplant.

**Islet cell transplantation.** Researchers are experimenting with islet cell transplantation. This provides new insulin-producing cells from a donor pancreas. This experimental procedure had some problems in the past. But new techniques and better drugs to prevent islet cell rejection may improve its chances of becoming a successful treatment.

**PREVENTION TIPS**

There's no known way to prevent type 1 diabetes. But researchers are working on preventing the disease or further damage of the islet cells in people who are newly diagnosed.

Ask your provider if you might be eligible for one of these clinical trials. It is important to carefully weigh the risks and benefits of any treatment available in a trial.

**OUTLOOK / PROGNOSIS**

Having type 1 diabetes shortens life expectancy by about 12 years on average.

Insulin therapy has improved life expectancy but diabetes can still put you at risk for complications that impact long-term health.

Further, proper treatment, care, and lifestyle choices can help extend life expectancy and contribute to a good quality of life.

**How Type 1 Diabetes Affects Lifespan**

Even though medical advancements have improved outcomes for people with type 1 diabetes, the disease still shortens life expectancy by about 12 years.

People with type 1 diabetes can increase their chances of living longer by managing their condition and preventing other complications related to this condition, like:

Kidney disease: Any injury to the kidneys or the blood vessels that supply it results in the inability to filter blood properly. The main culprits of kidney damage related to diabetes are high blood pressure (hypertension) and uncontrolled blood sugar levels.

Heart disease and stroke: People with type 1 diabetes have nearly double the risk for heart disease or stroke as someone without diabetes, and these conditions tend to develop at a younger age.

Mental health issues: Emotional health impacts physical health. Managing diabetes can cause stress, anxiety, and depression. If left untreated, mental health issues can worsen diabetes.

Nerve damage (neuropathy): Diabetic neuropathy affects sensory and motor nerves, causing pain, loss of sensation, and muscle weakness.

Neoplasms: A neoplasm is an abnormal growth of cells in the body. It can be a small, benign (non-cancerous) growth like a mole, or a malignant (cancerous) or precancerous tumor.

Working closely with your healthcare provider to monitor your health helps to uncover the early warning signs of complications.

**Unique Factors in Men and Women**

Women with type 1 diabetes live three or four years longer than men with diabetes, whereas those without type 1 diabetes live five to seven years longer. When comparing people with type 1 diabetes, women are more likely than men to have fatal complications such as cardiovascular events.

**Trends in Life Expectancy When Dealing with Type 1 Diabetes**

While the generally accepted lifespan is about 12 years shorter for those with type 1 diabetes, newer research is showing better outcomes.

Life expectancy for people with type 1 diabetes has vastly improved over time due to major advances in treatment. Before the medical advancement of insulin therapy, type 1 diabetes was fatal, with 50% of people dying within two years and 90% within five years of diagnosis.

**How Does Age of Diagnosis Affect Lifespan?**

Earlier ages at diagnosis correlate with lower life expectancies for those with type 1 diabetes. Men diagnosed before age 10 lived about 14 years less than men without diabetes (life expectancy 81 years). Women diagnosed before 10 lived about 18 years less than women without diabetes (life expectancy 84 years). Men and women diagnosed after age 20 each live about 10 years less, on average.

**How to Live Longer When Dealing with Type 1 Diabetes**

Living a longer, healthier life with type 1 diabetes involves making healthy lifestyle decisions related to managing your condition. By doing this, you can improve your long-term prognosis.

* Control Blood Sugar

For diabetes treatment, it is important to learn how to balance blood sugar levels with medications taken by mouth and insulin.Additionally, preventing complications of diabetes can significantly impact increasing life expectancy.

You can increase life expectancy by closely monitoring blood glucose levels and maintaining levels between 70 and 130 milligrams per deciliter (mg/dL) before meals and below 180 mg/dL after meals.

Managing blood sugar levels over time and maintaining an A1C level below 7% is incredibly beneficial for your health and longevity. For people with diabetes, having an A1C of 9% or higher significantly increases the risk of diabetic complications.

Diabetic Coma

Severe low blood sugar (hypoglycemic or insulin shock) is a medical emergency that can lead to diabetic coma or death. According to one study, 21% of deaths among those with type 1 diabetes under 50 years of age resulted from diabetic coma and related causes.

**PREVENTING COMPLICATIONS**

This can help improve your life expectancy and overall health.

Lifestyle behaviors that can help boost longevity and health for those dealing with type 1 diabetes, include:

* Eating healthy, well-balanced meals
* Being physically active
* Receiving regular care from health professionals
* Not smoking
* Managing stress levels
* Caring for mental and emotional health
* Controlling blood pressure, ideally keeping it below 140/90
* Balance cholesterol levels by keeping low-density lipoprotein (LDL) cholesterol below 130 mg/dL and high-density lipoprotein (HDL) levels above 40 mg/dL for men and above 50 mg/dL for women

**POSSIBLE COMPLICATIONS**

Over time, type 1 diabetes complications can affect major organs in the body. These organs include the heart, blood vessels, nerves, eyes and kidneys. Having a normal blood sugar level can lower the risk of many complications.

Diabetes complications can lead to disabilities or even threaten your life. Some of the possible complications that may come with Type 1 diabetes include:

Heart and blood vessel disease: Diabetes increases the risk of some problems with the heart and blood vessels. These include coronary artery disease with chest pain (angina), heart attack, stroke, narrowing of the arteries (atherosclerosis) and high blood pressure.

Nerve damage (neuropathy): Too much sugar in the blood can injure the walls of the tiny blood vessels (capillaries) that feed the nerves. This is especially true in the legs. This can cause tingling, numbness, burning or pain. This usually begins at the tips of the toes or fingers and spreads upward. Poorly controlled blood sugar could cause you to lose all sense of feeling in the affected limbs over time.

Damage to the nerves that affect the digestive system can cause problems with nausea, vomiting, diarrhea or constipation. For men, erectile dysfunction may be an issue.

Kidney damage (nephropathy): The kidneys have millions of tiny blood vessels that keep waste from entering the blood. Diabetes can damage this system. Severe damage can lead to kidney failure or end-stage kidney disease that can't be reversed. End-stage kidney disease needs to be treated with mechanical filtering of the kidneys (dialysis) or a kidney transplant.

Eye damage: Diabetes can damage the blood vessels in the retina (part of the eye that senses light) (diabetic retinopathy). This could cause blindness. Diabetes also increases the risk of other serious vision conditions, such as cataracts and glaucoma.

Foot damage: Nerve damage in the feet or poor blood flow to the feet increases the risk of some foot complications. Left untreated, cuts and blisters can become serious infections. These infections may need to be treated with toe, foot or leg removal (amputation).

Skin and mouth conditions: Diabetes may leave you more prone to infections of the skin and mouth. These include bacterial and fungal infections. Gum disease and dry mouth also are more likely.

Pregnancy complications: High blood sugar levels can be dangerous for both the parent and the baby. The risk of miscarriage, stillbirth and birth defects increases when diabetes isn't well-controlled. For the parent, diabetes increases the risk of diabetic ketoacidosis, diabetic eye problems (retinopathy), pregnancy-induced high blood pressure and preeclampsia.

**WHEN TO SEE A DOCTOR / RED FLAG**

Talk to your health care provider if you notice any of the aforementioned symptoms in you or your child.

**Signs of trouble**

Despite your best efforts, sometimes problems will happen. Certain short-term complications of type 1 diabetes, such as low blood sugar, require care immediately.

**Low blood sugar (hypoglycemia)**

Diabetic hypoglycemia occurs when someone with diabetes doesn't have enough sugar (glucose) in the blood. Ask your provider what's considered a low blood sugar level for you. Blood sugar levels can drop for many reasons, such as skipping a meal, eating fewer carbohydrates than called for in your meal plan, getting more physical activity than normal or injecting too much insulin.

Learn the symptoms of hypoglycemia. Test your blood sugar if you think your levels are low. When in doubt, always test your blood sugar. Early symptoms of low blood sugar include:

* Looking pale (pallor)
* Shakiness
* Dizziness or lightheadedness
* Sweating
* Hunger or nausea
* An irregular or fast heartbeat
* Difficulty concentrating
* Feeling weak and having no energy (fatigue)
* Irritability or anxiety
* Headache
* Tingling or numbness of the lips, tongue or cheek

Nighttime hypoglycemia may cause you to wake with sweat-soaked pajamas or a headache. Nighttime hypoglycemia sometimes might cause an unusually high blood sugar reading first thing in the morning.

If diabetic hypoglycemia isn't treated, symptoms of hypoglycemia worsen and can include:

* Confusion, unusual behavior or both, such as the inability to complete routine tasks
* Loss of coordination
* Difficulty speaking or slurred speech
* Blurry or tunnel vision
* Inability to eat or drink
* Muscle weakness
* Drowsiness

Severe hypoglycemia may cause:

* Convulsions or seizures
* Unconsciousness
* Death, rarely

You can raise your blood sugar quickly by eating or drinking a simple sugar source, such as glucose tablets, hard candy or fruit juice. Tell family and friends what symptoms to look for and what to do if you're not able to treat the condition yourself.

If a blood glucose meter isn't readily available, treat for low blood sugar anyway if you have symptoms of hypoglycemia, and then test as soon as possible.

Inform people you trust about hypoglycemia. If others know what symptoms to look for, they might be able to alert you to early symptoms. It's important that family members and close friends know where you keep glucagon and how to give it so that a potentially serious situation can be easier to safely manage. Glucagon is a hormone that stimulates the release of sugar into the blood.

Here's some emergency information to give to others. If you're with someone who is not responding (loses consciousness) or can't swallow due to low blood sugar:

* Don't inject insulin, as this will cause blood sugar levels to drop even further
* Don't give fluids or food, because these could cause choking
* Give glucagon by injection or a nasal spray
* Call 911 or emergency services in your area for immediate treatment if glucagon isn't on hand, you don't know how to use it or the person isn't responding

**Hypoglycemia unawareness**

Some people may lose the ability to sense that their blood sugar levels are getting low. This is called hypoglycemia unawareness. The body no longer reacts to a low blood sugar level with symptoms such as lightheadedness or headaches. The more you experience low blood sugar, the more likely you are to develop hypoglycemia unawareness.

If you can avoid having a hypoglycemic episode for several weeks, you may start to become more aware of coming lows. Sometimes increasing the blood sugar target (for example, from 80 to 120 mg/DL to 100 to 140 mg/DL) at least for a short time can also help improve low blood sugar awareness.

**High blood sugar (hyperglycemia)**

Blood sugar can rise for many reasons. For example, it can rise due to eating too much, eating the wrong types of foods, not taking enough insulin or fighting an illness.

Watch for:

* Frequent urination
* Increased thirst
* Blurred vision
* Fatigue
* Headache
* Irritability

If you think you have hyperglycemia, check your blood sugar. If it is higher than your target range, you'll likely need to administer a "correction." A correction is an additional dose of insulin given to bring your blood sugar back to normal. High blood sugar levels don't come down as quickly as they go up. Ask your provider how long to wait until you recheck. If you use an insulin pump, random high blood sugar readings may mean you need to change the place where you put the pump on your body.

If you have a blood sugar reading above 240 mg/dL (13.3 mmol/L), test for ketones using a urine test stick. Don't exercise if your blood sugar level is above 240 mg/dL or if ketones are present. If only a trace or small amounts of ketones are present, drink extra noncaloric fluids to flush out the ketones.

If your blood sugar is persistently above 300 mg/dL (16.7 mmol/L), or if your urine ketones stay high in spite of taking correction doses of insulin, call your provider or seek emergency care.

**Increased ketones in your urine (diabetic ketoacidosis)**

If your cells are starved for energy, the body may begin to break down fat. This produces toxic acids known as ketones. Diabetic ketoacidosis is a life-threatening emergency.

Symptoms of this serious condition include:

* Nausea
* Vomiting
* Abdominal pain
* A sweet, fruity smell on your breath
* Shortness of breath
* Dry mouth
* Weakness
* Confusion
* Coma

If you suspect ketoacidosis, check the urine for excess ketones with an over-the-counter ketones test kit. If you have large amounts of ketones in the urine, call your provider right away or seek emergency care. Also, call your provider if you have vomited more than once and you have ketones in the urine.

**DIFFERENTIAL DIAGNOSIS FOR TYPE 1 DIABETES**

**Genetic syndromes that need consideration**

Recently it has become apparent that not all diabetes that is present in childhood is type 1. Increasingly type 2 diabetes, secondary diabetes, maturity onset diabetes of the young, and rare syndromic forms of diabetes such as Wolfram syndrome and Alstrom syndrome have been identified in children. Although individually rare, collectively they make up about 5% of children seen in diabetes clinics. The importance of these syndromes for children lies in the recognition of treatable complications, and for their parents, the possibility of genetic counselling. The scientific importance is enormous as they are experiments of nature that reveal basic mechanisms of insulin and glucose metabolism. Science is currently researching how to offer mutation analysis to correlate the clinical pattern to the genotype, and advice to seek novel therapeutic approaches based on the developing knowledge of gene and protein functions. This review focuses on monogenic syndromes of diabetes, particularly where significant advances have been made in our understanding recently. Neonatal diabetes is a specialist field in its own right and is not included, except to discuss Kir6.2 diabetes which may develop in infancy.

**RECENT GUIDELINES OR UPDATES**

## **INTRODUCTION**

Type 1 diabetes mellitus (T1DM) is a chronic autoimmune condition resulting in absolute shortage of pancreatic insulin production. Regular and life-long insulin administration is therefore necessary to prevent hyperglycemia, metabolic decompensation and life-threatening diabetic ketoacidosis (DKA). According to the International Diabetes Federation (IDF), there were approximately 425 million people living with diabetes worldwide in 2017, out of which 5% to 10% are estimated to have T1DM (42.5 to 95 million) . Management of T1DM requires good understanding of this condition by patients and their physicians. At the same time, it imposes significant financial costs on health systems worldwide. Optimal management of T1DM leading to good metabolic control with prevention of micro- and macrovascular complications with concomitant avoidance of hypoglycemia is therefore of significant social and economic importance.

intensive therapy consisting of insulin administration by three or more daily injections or by a pump with self-monitoring of blood glucose (SMBG) 4 times/day or more and frequent insulin dose adjustments reduced risk of microvascular complications in comparison to conventional therapy of that time (one to two insulin injections/day, daily self-monitoring of urine or blood glucose [BG] and education about diet and exercise). The incidence of severe hypoglycemia (SH) was approximately three times higher in the intensive group; however, intensive therapy with frequent SMBG, patient education and avoidance or minimizing occurrence of hypoglycemia have since then become the pillars of modern T1DM management.

novel insulin preparations, ways of insulin administration and glucose monitoring and the role of metformin or sodium-glucose co-transporter 2 (SGLT2) inhibitors in T1DM management.

**INSULIN PREPARATIONS AND ADMINISTRATION** Insulin administration represents the mainstay of T1DM treatment. The purpose of insulin administration is to prevent the development of DKA due to the absolute shortage of intrinsic insulin production and to maintain BG levels within the physiologic range. Insulin administration should thus ideally prevent, or at least delay development of micro- and macrovascular complications of hyperglycemia and, at the same time, should cause as little hypoglycemia as possible. To achieve this, pharmacokinetic and pharmacodynamic properties of administered insulin should ideally, mimic those of physiologic insulin release from pancreatic β-cells in healthy individuals in whom basal continuous insulin secretion into the portal vein together with super-added peak insulin secretions closely following the rise in plasma glucose concentration 30 to 60 minutes after eating can be observed. This has proven to be a challenging task as the physiological mechanisms controlling glucose metabolism are extremely complex. Thus, current insulin formulations and modes of delivery are unable to fully reproduce the physiology of the β-cell. Since the discovery of insulin in the 1920s remarkable steps towards achieving this goal have been made, but there is still a long way to go.The production of porcine insulin is being continued, however. The amino acid sequence of insulin was reported in 1955 and insulin was the first therapeutic protein to be produced by recombinant DNA technology in late 1970s. Commercial production of human insulin in the early 1980s enabled production of synthetic human insulin in virtually unlimited quantities and in a cost-effective way. The tendency of human soluble insulin to aggregate into dimers and hexamers in higher concentrations with resulting delay in release of insulin monomers into the bloodstream from the subcutaneous depot has important consequences for its pharmacokinetic and pharmacodynamic properties and has prompted the development of rapid-acting insulin analogues. Their pharmacokinetic and pharmacodynamic profiles show more rapid rise after injection to higher plasma insulin levels together with more rapid fall of their concentration in comparison to regular insulin resulting in improved postprandial plasma glucose (PPG) profiles. Initial trials comparing the use of rapid-acting analogues versus regular insulin (combined with intermediate insulins isophane or ultralente since long-acting insulin analogues were introduced some years later) showed a significant reduction of overall rates of hypoglycaemia and SH, with the most prominent reduction observed in episodes at night in those with tight metabolic control (glycosylated hemoglobin [HbA1c] <7.5%). The latest step towards the goal of replicating endogenous prandial insulin secretion profiles is the introduction of faster insulin aspart (Fiasp®; Novo Nordisk Ltd.), a formulation of insulin aspart with additional L-arginine and niacinamide (vitamin B3) that promote stability and faster formation of insulin aspart monomers after subcutaneous injection. In a 26-week, double-blinded, treat-to-target trial (ONSET 1), mealtime Fiasp® significantly reduced HbA1c versus insulin aspart with estimated treatment difference (ETD) −0.15% (95% confidence interval [CI], −0.23 to −0.07; *P*=0.0003) and also significantly reduced post-PPG increments at 1 hour (ETD, −1.18 mmol/L; 95% CI, −1.65 to −0.71; *P*<0.0001) and at 2 hours (ETD, −0.67 mmol/L; 95% CI, −1.29 to −0.04; *P*=0.0375) without increasing risk of overall hypoglycaemia . BioChaparone insulin lispro (Adocia, Lyon, France) uses polysaccharides that can be modified with amino acids to facilitate its absorption into blood circulation and clinical trials of this formulation are currently in progress.

Symptoms of T1DM may include the following:

* Increased thirst
* Increased urination
* Extreme hunger, nausea, and vomiting
* Unintentional/unexplained weight loss
* Blurred vision
* Fatigue, mood changes and irritability
* Flu-like symptoms.
* Bedwetting in children who are already successfully potty-trained, frequent full diapers in infants.
* Slow healing cuts, sores
* Vaginal yeast infections

**EPIDEMIOLOGY**

Type 1 diabetes (T1D) is a condition characterized by the destruction of pancreatic beta cells, leading to absolute insulin deficiency. Its epidemiology varies by demographic, geographic, and other factors.

Worldwide, the incidence of T1D has been increasing by 2-5% annually, and the prevalence of T1D is approximately 1 in 300 in the US by 18 years of age.

In the United States, about 304,000 children and adolescents have type 1 diabetes.

The epidemiology of T1D differs between children and young adults. Incidence and prevalence rates vary among racial and ethnic groups. For example, the incidence and prevalence of T1D among African Americans (AA) are lower compared to non-Hispanic Whites (NHW).

Similarly, Hispanic and Asian populations also show varying rates of incidence and prevalence.

Research on risk factors for T1D is an active area of study to identify genetic and environmental triggers that could be targeted for intervention.

Epidemiological studies continue to play a crucial role in understanding the complex causes, clinical care, prevention, and potential cure of T1D.

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## [American **Diabetes** Association Releases 2023 Standards of Care i…](https://www.bing.com/ck/a?!&&p=2d064920479901f5239e856105a90f2b660b11e760d9ae5c132732d72d25f1d1JmltdHM9MTc0NzM1MzYwMA&ptn=3&ver=2&hsh=4&fclid=15dee221-f5f9-676d-2b22-f73bf439668e&psq=recent+guidelines+or+updates+for+type+1+diabetes&u=a1aHR0cHM6Ly9kaWFiZXRlcy5vcmcvbmV3c3Jvb20vYW1lcmljYW4tZGlhYmV0ZXMtYXNzb2NpYXRpb24tMjAyMy1zdGFuZGFyZHMtY2FyZS1kaWFiZXRlcy1ndWlkZS1mb3ItcHJldmVudGlvbi1kaWFnbm9zaXMtdHJlYXRtZW50LXBlb3BsZS1saXZpbmctd2l0aC1kaWFiZXRlcyM6fjp0ZXh0PUJhc2VkJTIwb24lMjB0aGUlMjBsYXRlc3QlMjBzY2llbnRpZmljJTIwcmVzZWFyY2glMjBhbmQlMjBjbGluaWNhbCxjYXJkaW92YXNjdWxhciUyMGFuZCUyMHJlbmFsJTIwcmlzayUyQyUyMGFuZCUyMGltcHJvdmUlMjBoZWFsdGglMjBvdXRjb21lcy4&ntb=1)

[**Recent Updates on Type 1 Diabetes Mellitus Management for Clinicians - PMC**](https://pmc.ncbi.nlm.nih.gov/articles/PMC5842299/)

**TYPE 2 DIABETES**

*ALTERNATIVE NAMES:* Type 2 diabetes is also known as “diabetes mellitus type 2”, “adult-onset diabetes”, or “non-insulin-dependent diabetes mellitus (NIDDM)”, “Diabetes - type II”, “Diabetic - type 2 diabetes”, “Oral hypoglycemic - type 2 diabetes”, “High blood sugar - type 2 diabetes”

**DEFINITION / DESCRIPTION**

Type 2 diabetes happens when the body cannot use insulin correctly and sugar builds up in the blood. It was once called adult-onset diabetes.

This type of diabetes is a condition which causes the level of glucose in your blood to become too high. It is caused by your body having problems with producing insulin, the hormone that controls your blood sugar levels. Type 2 diabetes can increase your risk of acquiring problems with your eyes, heart and nerves. There are links to type 2 diabetes with being overweight, inactive, and also, your genetics.

**CAUSES**

Type 2 diabetes is mainly as a result of two issues:

* Cells in muscle, fat and the liver don't respond to insulin as they should. As a result, the cells don't take in enough sugar.
* The gland that makes insulin, called the pancreas, can't make enough to keep blood sugar levels within a healthy range.
* Being overweight and not moving enough are key factors.

**How insulin works**

Insulin is a hormone that comes from a gland that sits behind and below the stomach. The gland is called the pancreas. Insulin manages how the body uses sugar in the following ways:

* Sugar in the bloodstream causes the pancreas to release insulin.
* Insulin in the bloodstream gets sugar into the cells.
* The amount of sugar in the bloodstream drops.
* Then the pancreas releases less insulin.

**The role of glucose**

A sugar called glucose is a main source of energy for the cells that make up muscles and other tissues. Glucose comes from two major sources. They are food and the liver.

Glucose goes into the bloodstream. There it enters cells with the help of insulin.

The liver stores glucose in the form of glycogen and also makes glucose.

When glucose levels are low, the liver breaks down stored glycogen into glucose. This keeps the body's glucose level within a healthy range.

In type 2 diabetes, this process doesn't work well. Instead of moving into the cells, sugar builds up in the blood. As blood sugar levels rise, the pancreas releases more insulin. Over time, the cells in the pancreas that make insulin are damaged. Then the cells can't make enough insulin to meet the body's needs.

**RISK FACTORS**

Factors that may increase the risk of having type 2 diabetes include:

* Excess weight: Being overweight or obese is a main risk.
* Waist size: Storing fat mainly in the belly rather than in the hips and thighs raises the risk. The risk of type 2 diabetes is higher in people assigned male at birth whose waists measure more than 40 inches (101.6 centimeters). For people assigned female at birth, a waist measure of more than 35 inches (88.9 centimeters) raises the risk.
* Sitting: The less active a person is, the higher the risk. Physical activity helps manage weight, uses up glucose as energy and helps cells take in insulin.
* Family history: Having a parent or sibling who has type 2 diabetes raises the risk.
* Blood lipid levels: A higher risk is linked with low levels of high-density lipoprotein. Also called HDL cholesterol, this is the "good" cholesterol. Higher risk also is linked with high levels of a certain type of fat in the blood, called triglycerides.
* Age: The risk of type 2 diabetes goes up with age, mainly after age 35.
* Prediabetes: Prediabetes is a condition in which blood sugar is higher than the standard range, but not high enough to be called type 2 diabetes. If not treated, prediabetes often moves on to become type 2 diabetes.
* Pregnancy-related risks: The risk of getting type 2 diabetes is higher in people who had gestational diabetes when they were pregnant. And it's higher in those who gave birth to a baby weighing more than 9 pounds (4 kilograms).
* Polycystic ovary syndrome: This condition results in irregular menstrual periods, excess hair growth and obesity. It raises the risk of diabetes.

**SIGNS / SYMPTOMS**

Symptoms of type 2 diabetes often come on slowly. In fact, people can live with type 2 diabetes for years and not know it. When there are symptoms, they may include:

* Needing to urinate more often, especially at night time
* A constant thirst that cannot be quenched
* Fatigue and tiredness
* Unexplained loss of weight
* More urination.
* More hunger.
* Blurred vision.
* Slow-healing sores.
* Frequent infections.
* Numbness or tingling in the hands or feet.
* Areas of darkened skin, most often in the armpits and neck.

**DIAGNOSIS METHODS**

It is not uncommon for type 2 diabetes to be uncovered via blood or urine tests taken by your GP for something else. If the tests come back that you do have diabetes, your GP will discuss with you what the condition is and the next steps you need to take.

The glycated hemoglobin test most often diagnosed type 2 diabetes. Also called the A1C test, it reflects the average blood sugar level for the past two to three months. Results mean the following:

* Below 5.7% is healthy.
* 5.7% to 6.4% is prediabetes.
* 6.5% or higher on two separate tests means diabetes.

If there are no A1C tests or if you have certain conditions that get in the way of A1C test results, your healthcare professional may use the following tests to diagnose diabetes:

**Random blood sugar test.** Blood sugar values show in milligrams of sugar per deciliter (mg/dL) or millimoles of sugar per liter (mmol/L) of blood. It doesn't matter when you last ate. A level of 200 mg/dL (11.1 mmol/L) or higher suggests diabetes. This is most likely if you also have symptoms of diabetes, such as urinating often and being very thirsty.

**Fasting blood sugar test.** You give a blood sample for testing after not eating overnight. Results are as follows:

* Less than 100 mg/dL (5.6 mmol/L) is healthy.
* 100 to 125 mg/dL (5.6 to 6.9 mmol/L) is prediabetes.
* 126 mg/dL (7 mmol/L) or higher on two tests is diabetes.

**Oral glucose tolerance test.** This mainly tests the blood sugar of people who are pregnant and those who have cystic fibrosis. You don't eat for a certain amount of time. Then you drink a sugary liquid at your healthcare team's office. You give blood samples over two hours to test blood sugar levels. Results are as follows:

* Less than 140 mg/dL (7.8 mmol/L) after two hours is healthy.
* 140 to 199 mg/dL (7.8 mmol/L and 11.0 mmol/L) is prediabetes.
* 200 mg/dL (11.1 mmol/L) or higher after two hours suggests diabetes.

**Screening.** The American Diabetes Association suggests that all adults age 35 or older have routine tests for type 2 diabetes. Others to be tested include:

* People younger than 35 who are overweight or obese and have one or more risk factors linked to diabetes.
* Women who had diabetes while pregnant, called gestational diabetes.
* People who have been diagnosed with prediabetes.
* Children who are overweight or obese and who have a family history of type 2 diabetes or other risk factors.

### **After a diagnosis**

If you're diagnosed with diabetes, your healthcare professional may do other tests to see whether you have type 1 or type 2 diabetes. Treatment depends on which condition you have.

Your healthcare team tests A1C levels at least two times a year and when your treatment changes. Target A1C goals depend on age and other factors. For most people, the American Diabetes Association suggests an A1C level below 7%.

You also have other tests to screen for complications of diabetes and other medical conditions.

**TREATMENT METHODS**

Living with type 2 diabetes involves learning about the condition and lifestyle changes. Diabetes education is an important part of managing the condition. Management includes:

* Healthy eating.
* Regular exercise.
* Weight loss if needed.
* Diabetes medicine or insulin therapy if needed.
* Keeping track of blood sugar.

These steps make it more likely that blood sugar will stay in a healthy range. And they may help delay or prevent complications.

### **Healthy eating**

There's no diabetes diet. But it's good to focus your eating on:

* A regular schedule for meals and healthy snacks.
* Smaller amounts of food.
* More high-fiber foods, such as fruits, non starchy vegetables and whole grains.
* Fewer refined grains, starchy vegetables and sweets.
* Modest servings of low-fat dairy, low-fat meats and fish.
* Healthy cooking oils, such as olive oil or canola oil.
* Fewer calories.

You may see a registered dietitian, who can help you:

* Make healthy food choices.
* Plan healthy meals.
* Make new habits and learn what stops you from changing habits.
* Watch carbohydrate intake to keep your blood sugar levels more stable.

### **Physical activity**

Exercise is important to lose weight or stay at a healthy weight. It also helps manage blood sugar. Talk with your healthcare team before starting or changing your exercise program to make sure the activities are safe for you.

* **Aerobic activity.** Choose activities that you enjoy. Try walking, swimming, biking or running. Aim to get about 30 minutes or more of moderate aerobic exercise on most days of the week, or at least 150 minutes a week.
* **Strength training.** Strength training increases your strength, balance and ability to do activities of daily living. Strength training can be done using free weights, resistance tubes, weight machines or your body weight for resistance. Aim to do strength training exercises for all major muscle groups at least two times a week.
* **Move more.** Breaking up long periods of inactivity, such as sitting at the computer, can help control blood sugar levels. Take a few minutes to stand, walk around or do some light activity every 30 minutes.

### **Weight loss**

Losing weight can help you manage blood sugar levels, cholesterol, triglycerides and blood pressure. If you're overweight, you may see these factors improve after you lose as little as 5% of your body weight. The more weight you lose, the better it is for your health.

Your healthcare professional or dietitian can help you set good weight-loss goals and make lifestyle changes to help you reach them.

### **Tracking your blood sugar**

Your healthcare team will tell you how often to check your blood sugar level. This is to make sure that your blood sugar stays in the target range. You may, for instance, need to check it once a day and before or after exercise. If you take insulin, you may need to check your blood sugar several times a day.

You can use a small, at-home device called a blood glucose meter. This measures the amount of sugar in a drop of blood. Keep a record to share with your healthcare team.

Continuous glucose monitoring is an electronic system that records blood sugar levels every few minutes from a sensor put under the skin. The sensor most often is in the arm. The system can send results to a mobile device such as a phone. And the system can alert you when levels are too high or too low.

### **Diabetes medicines**

If you can't stay at your target blood sugar level with diet and exercise, your healthcare team may prescribe diabetes medicines that help lower glucose levels. Or you may start insulin therapy. Medicines for type 2 diabetes include the following.

**Metformin (Fortamet, Glumetza, others)** is most often the first medicine prescribed for type 2 diabetes. It works mainly in two ways. It lowers the amount of glucose the liver makes. And it helps the body use insulin better.

Some people who take metformin, may get B-12 deficiency and may need to take supplements. There are other side effects that may get better over time. Side effects might include:

* Nausea.
* Belly pain.
* Bloating.
* Diarrhea.

**Sulfonylureas** help the body make more insulin. These include glipizide (Glucotrol XL) and glimepiride (Amaryl). Side effects might include:

* Low blood sugar.
* Weight gain.

Another sulfonylurea is glyburide (DiaBeta, Glynase). It has a higher risk of low blood sugar.

**Glinides** help the pancreas to make more insulin. They work faster than sulfonylureas. But their effect doesn't last as long. They include repaglinide and nateglinide. Side effects might include:

* Low blood sugar.
* Weight gain.

**Thiazolidinediones** help the body's tissues take in more insulin. These include pioglitazone (Actos) and rosiglitazone. Side effects might include:

* Weight gain.
* Broken bones.
* Fluid retention.
* Heart failure.

**DPP-4 inhibitors** help lower blood sugar levels. But they tend to have only a small effect. Medicines include alogliptin (Nesina), sitagliptin (Januvia), saxagliptin and linagliptin (Tradjenta). Side effects might include:

* Pancreatitis.
* Joint pain.

**GLP-1 receptor agonists** are medicines taken by shot, called injection. They slow digestion and help lower blood sugar levels. Their use is often linked with weight loss. Some lower the risk of heart attack and stroke.

These medicines include dulaglutide (Trulicity) exenatide (Byetta, Bydureon Bcise), liraglutide (Saxenda, Victoza) and semaglutide (Rybelsus, Ozempic, Wegovy). Side effects might include:

* Nausea.
* Vomiting.
* Diarrhea.

**SGLT2 inhibitors** affect how the kidneys filter blood. They block the return of glucose to the bloodstream. Excess glucose then leaves the body in the urine. These medicines may lower the risk of heart attack and stroke in people with a high risk of those conditions.

These medicines include canagliflozin (Invokana), dapagliflozin (Farxiga) and empagliflozin (Jardiance). Side effects might include:

* Vaginal yeast infections.
* Urinary tract infections.
* Low blood pressure.
* High cholesterol.
* Gangrene.
* Broken bones.
* Risk of amputation.

**Other medicines** your healthcare professional might prescribe are medicines to lower blood pressure and cholesterol. Low-dose aspirin may help prevent heart and blood vessel conditions.

### **Insulin therapy**

Some people who have type 2 diabetes need insulin therapy. In the past, people tried insulin therapy only after other treatments had failed. But today, it may be prescribed sooner if lifestyle changes and other medicines don't manage blood sugar levels.

Insulin types vary by how quickly they work and how long they last. Long-acting insulin, for instance, works overnight or throughout the day to keep blood sugar levels even. People most often take short-acting insulin at mealtimes.

Your healthcare professional prescribes the type of insulin that's right for you and advises you when to take it. Your insulin type, dosage and schedule may change. That depends on how stable your blood sugar levels are. People take most types of insulin as an injection.

A side effect of insulin is low blood sugar, called hypoglycemia.

### **Weight-loss surgery**

Weight-loss surgery changes the shape of the digestive system and how it works. This surgery may help you lose weight and manage type 2 diabetes and other conditions linked to obesity.

There are a few surgical procedures. All of them help people lose weight by limiting how much food they can eat. Some procedures also limit the amount of nutrients the body can absorb.

Weight-loss surgery is only one part of an overall treatment plan. Treatment also includes diet and nutritional supplements, exercise and mental health care.

Weight-loss surgery may be a choice for adults living with type 2 diabetes who have a body mass index (BMI) of 35 or higher. BMI is a formula that uses weight and height to estimate body fat. Surgery also may be a choice for someone with a BMI lower than 35. This depends on how bad the diabetes is or whether there are other medical conditions.

If you have weight-loss surgery, you need to make lifestyle changes for life. Long-term side effects may include not taking in enough nutrients and the bone-loss condition, osteoporosis.

### **Pregnancy**

People who have type 2 diabetes often need to change their treatment plan during pregnancy and follow a diet that controls carbohydrates. Many people need insulin therapy during pregnancy. They also may need to stop other treatments, such as certain blood pressure medicines.

You have a higher risk during pregnancy of getting a condition that affects the eyes, called diabetic retinopathy. This condition may get worse during pregnancy.

If you're pregnant, visit a specialist in eye care, called an ophthalmologist. Go each trimester of your pregnancy and one year after you give birth. Or go as often as your healthcare team advises.

### **Signs of trouble**

You need to track your blood sugar levels to keep from getting serious complications. Also, know of symptoms that may mean that blood sugar levels need care right away. They include:

**High blood sugar.** This condition also is called hyperglycemia. Eating certain foods or too much food, being sick, or not taking diabetes medicines at the right time can cause high blood sugar. Symptoms include:

* Urinating often.
* Extreme thirst.
* Dry mouth.
* Blurred vision.
* Tiredness.
* Headache.

**Hyperglycemic hyperosmolar nonketotic syndrome.** Also called HHNS, this life-threatening condition includes a blood sugar reading higher than 600 mg/dL (33.3 mmol/L). HHNS may be more likely if you have an infection, don't take medicines as prescribed, or take certain steroids or other medicines that cause you to urinate often. Symptoms include:

* Dry mouth.
* Extreme thirst.
* Drowsiness.
* Confusion.
* Dark urine.
* Seizures.

**Diabetic ketoacidosis.** Diabetic ketoacidosis happens when a lack of insulin results in the body breaking down fat for fuel rather than sugar. This causes a buildup of acids called ketones in the bloodstream.

Triggers of diabetic ketoacidosis include certain illnesses, pregnancy and medicines. The diabetes medicines called SGLT2 inhibitors can increase the risk of diabetic ketoacidosis, especially when used in people living with type 1 diabetes.

Diabetic ketoacidosis makes acids that are toxic. So, the condition can be life-threatening. Besides the symptoms of hyperglycemia, such as urinating often and more thirst, ketoacidosis may cause:

* Nausea.
* Vomiting.
* Belly pain.
* Shortness of breath.
* Fruity-smelling breath.

**Low blood sugar.** Low blood sugar is when blood sugar levels drop below the target range. This condition also is called hypoglycemia. Your blood sugar level can drop for many reasons. These include missing a meal, taking more medicine than usual or being more physically active than usual. Symptoms include:

* Sweating.
* Shakiness.
* Weakness.
* Hunger.
* Irritability.
* Dizziness.
* Headache.
* Blurred vision.
* Heart palpitations.
* Slurred speech.
* Drowsiness.
* Confusion.

If you have symptoms of low blood sugar, drink or eat something that raises your blood sugar level quickly. Try fruit juice, sugared soda, glucose tablets, hard candy or another source of sugar. Retest your blood in 15 minutes.

If levels are not at your target, eat or drink another source of sugar. Eat a meal after your blood sugar level returns to normal.

If you pass out, someone needs to give you a shot of glucagon. This hormone causes the release of sugar into the blood.

**OUTLOOK / PROGNOSIS**

Diabetes is a lifelong disease and there is no cure.

Some people with type 2 diabetes no longer need medicine for blood sugar control if they lose weight and become more active. When they reach their ideal weight, their body's own insulin and a healthy diet can control their blood sugar level.

**POSSIBLE COMPLICATIONS**

Type 2 diabetes affects many major organs. These include the heart, blood vessels, nerves, eyes and kidneys. Also, factors that raise the risk of diabetes are risk factors for other serious diseases. Managing diabetes and blood sugar can lower the risk for these complications and other medical conditions, including:

Heart and blood vessel disease. Diabetes is linked with a higher risk of heart disease, stroke, high blood pressure and narrowed blood vessels, called atherosclerosis.

Nerve damage in arms and legs. This condition is called neuropathy. High blood sugar over time can damage or destroy nerves. Neuropathy may cause tingling, numbness, burning, pain or loss of feeling. It most often begins at the tips of the toes or fingers and slowly spreads upward.

Other nerve damage. Damage to nerves of the heart can cause irregular heart rhythms. Nerve damage in the digestive system can cause problems with nausea, vomiting, diarrhea or constipation. Nerve damage also may cause erectile dysfunction.

Kidney disease. Diabetes may lead to long-term kidney disease or end-stage kidney disease that can't be reversed. End-stage kidney disease may need to be treated with mechanical filtering of the kidneys, called dialysis, or a kidney transplant.

Eye damage. Diabetes increases the risk of serious eye conditions. Conditions include cataracts and glaucoma. Diabetes also may damage the blood vessels of the retina, which is the part of the eye that senses light. This is called diabetic retinopathy. This damage can lead to blindness.

Skin conditions. Diabetes may raise the risk of some skin problems. Skin problems may include bacterial and fungal infections.

* Slow healing. Cuts and blisters that aren't treated can become serious infections. The infections may heal poorly. Bad damage can result in the need to use surgery to remove a toe, foot or leg. This surgery is called amputation.
* Hearing impairment. Hearing problems are more common in people with diabetes.
* Sleep apnea. Obstructive sleep apnea is common in people who have type 2 diabetes. Obesity may be the main cause of both conditions.
* Dementia. Type 2 diabetes seems to raise the risk of Alzheimer's disease and other conditions that cause dementia. Poorly managed blood sugar is linked to a faster loss of memory and other thinking skills.

**PREVENTION TIPS**

**First Line of Defense: Weight, Diet, and Exercise**

Losing extra pounds, eating better, and becoming more active are some of the most important steps you can take.

There are people who aren't overweight who have type 2 diabetes. But added pounds do put you at risk.

In one study, being overweight or obese was the single most important thing that predicted who would get diabetes. The study results showed that over 16 years, regular exercise -- at least 30 minutes a day, 5 days a week -- and a low-fat, high-fiber diet helped prevent it.

Some other ways of preventing type 2 diabetes include:

* Healthy lifestyle choices can help prevent type 2 diabetes. If you have prediabetes, lifestyle changes may slow the condition or keep it from becoming diabetes.
* A healthy lifestyle includes the following:
* Eat healthy foods. Choose foods lower in fat and calories and higher in fiber. Focus on fruits, vegetables and whole grains.
* Be active. Aim for 150 or more minutes a week of moderate to vigorous aerobic activity, such as brisk walking, bicycling, running or swimming.
* Lose weight. If you are overweight, losing some weight and keeping it off may slow prediabetes from becoming type 2 diabetes. If you have prediabetes, losing 7% to 10% of your body weight may lower the risk of diabetes.
* Don't sit for long. Sitting for long periods can raise the risk of type 2 diabetes. Get up every 30 minutes and move around for at least a few minutes.
* People with prediabetes may take metformin (Fortamet, Glumetza, others), a diabetes medicine, to lower the risk of type 2 diabetes. This is most often prescribed for older adults who are obese and who can't lower blood sugar levels with lifestyle changes.

**WHEN TO SEE A DOCTOR / RED FLAG**

See your healthcare professional if you have any symptoms of type 2 diabetes.

* Chest pain or pressure
* Fainting, confusion or unconsciousness
* Seizure
* Shortness of breath
* Red, painful skin that is spreading quickly

These symptoms can quickly get worse and become emergency conditions (such as seizures, hypoglycemic coma or hyperglycemic coma).

Also contact your provider if you have:

* Blood sugar levels that are higher than the goals you and your provider have set
* Numbness, tingling, or pain in your feet or legs
* Problems with your eyesight
* Sores or infections on your feet
* Frequent feelings of depression or anxiety
* Symptoms that your blood sugar is getting too low (weakness or fatigue, trembling, sweating, irritability, trouble thinking clearly, fast heartbeat, double or blurry vision, uneasy feeling)
* Symptoms that your blood sugar is too high (thirst, blurry vision, dry skin, weakness or fatigue, need to urinate a lot)
* Blood sugar readings that are below 70 mg/dL (3.9 mmol/L)

You can treat early signs of hypoglycemia at home by drinking orange juice, eating sugar or candy, or by taking glucose tablets. If signs of hypoglycemia continue or your blood glucose level stays below 60 mg/dL (3.3 mmol/L), go to the emergency room.

**DIFFERENTIAL DIAGNOSIS**

The list of differential diagnosis of diabetes mellitus consists of various conditions that would exhibit similar signs and symptoms:

* Drug-induced signs and symptoms due to corticosteroids, neuroleptics, pentamidine, etc.
* Genetic aberrations in beta-cell function and insulin action
* Metabolic syndrome (syndrome X)
* Infection
* Endocrinopathies such as acromegaly, Cushing disease, pheochromocytoma, hypothyroidism, etc.
* Complications of iron overload (hemochromatosis)
* Conditions affecting the exocrine part of the pancreas such as pancreatitis, cystic fibrosis, etc.

**RECENT GUIDELINES OR UPDATES**

*LIFESTYLE BEHAVIOR CHANGE FOR DIABETES PREVENTION*

Refer adults with overweight or obesity at high risk of type 2 diabetes, as seen in the Diabetes Prevention Program (DPP), to an intensive lifestyle behavior change program to achieve and maintain a weight reduction of at least 7% of initial body weight through healthy reduced-calorie diet and $150 min/week of moderate intensity physical activity.

A variety of eating patterns can be considered to prevent type 2 diabetes in individuals with prediabetes. Given the cost-effectiveness of lifestyle behavior modification programs for diabetes prevention, such diabetes prevention programs should be offered to adults at high risk of type 2 diabetes.

Diabetes prevention programs should be covered by third-party payers, and inconsistencies in access should be addressed. Based on individual preference, certified technology-assisted diabetes prevention programs may be effective in preventing type 2 diabetes and should be considered. The Diabetes Prevention Program Several major randomized controlled trials, including the Diabetes Prevention Program demonstrate that lifestyle/behavioral intervention with an individualized reduced-calorie meal plan is highly effective in preventing or delaying type 2 diabetes and improving other cardiometabolic risk factors (such as blood pressure, lipids, and inflammation). The DPP demonstrated that intensive lifestyle intervention could reduce the risk of incident type 2 diabetes by 58% over 3 years. Follow-up of three large trials of lifestyle intervention for diabetes prevention showed sustained reduction in the risk of progression to type 2 diabetes: The 7% weight loss goal was selected because it was feasible to achieve and maintain and likely to lessen the risk of developing diabetes (as well as improve other cardiometabolic risk factors). Participants were encouraged to achieve the $7% weight loss during the first 6 months of the intervention.

Further analysis suggests higher benefit for prevention of diabetes with at least 7–10% weight loss with lifestyle interventions. The recommended pace of weight loss was 1–2 lb/week. Calorie goals were calculated by estimating the daily calories needed to maintain the participant’s initial weight and subtracting 500–1,000 calories/day (depending on initial body weight). The initial focus of the dietary intervention was on reducing total fat rather than calories. After several weeks, the concept of calorie balance and the need to restrict calories and fat was introduced.

The goal for physical activity was selected to approximate at least 700 kcal/ week expenditure from physical activity. For ease of translation, this goal was described as at least 150 min of moderate intensity physical activity per week, similar in intensity to brisk walking. Participants were encouraged to distribute their activity throughout the week with a minimum frequency of three times per week and at least 10 min per session. A maximum of 75 min of strength training could be applied toward the total 150 min/week physical activity goal.

Increasing physical activity, self-monitoring, maintaining healthy lifestyle behaviors (such as how to choose healthy food options when eating out), and guidance on managing psychological, social, and motivational challenges.

However, evidence suggests that there is not an ideal percentage of calories from carbohydrate, protein, and fat for all people to prevent diabetes; therefore, macronutrient distribution should be based on an individualized assessment of current eating patterns, preferences, and metabolic goals. Based on other trials, a variety of eating patterns may also be appropriate for individuals with prediabetes, including Mediterranean-style and low-carbohydrate eating plans

Observational studies have also shown that vegetarian, plant-based (may include some animal products), and Dietary Approaches to Stop Hypertension (DASH) eating patterns are associated with a lower risk of developing type 2 diabetes. Evidence suggests that the overall quality of food consumed (as measured by the Healthy Eating Index, Alternative Healthy Eating Index, and DASH score), with an emphasis on whole grains, legumes, nuts, fruits, and vegetables and minimal refined and processed foods, is also associated with a lower risk of type 2 diabetes

As is the case for those with diabetes, individualized medical nutrition therapy is effective in lowering A1C in individuals diagnosed with prediabetes.

Physical Activity Moderate-intensity physical activity, such as brisk walking for 150 min/week, has shown beneficial effects in those with prediabetes. Similarly, moderate intensity physical activity has been shown to improve insulin sensitivity and reduce abdominal fat in children and young adults.

Health care professionals are encouraged to promote a DPP-style program to all individuals who have been identified to be at an increased risk of type 2 diabetes. In addition to aerobic activity, a physical activity plan designed to prevent diabetes may include resistance training. Breaking up prolonged sedentary time may also be encouraged, as it is associated with moderately lower postprandial glucose levels. The effects of physical activity appear to extend to the prevention of gestational diabetes mellitus (GDM).

Delivery and Dissemination of Lifestyle Behavior Change for Diabetes Prevention Because the intensive lifestyle intervention in the DPP was effective in preventing type 2 diabetes among those at high risk for the disease and lifestyle behavior change programs for diabetes prevention were shown to be cost-effective, broader efforts to disseminate scalable lifestyle behavior change programs for diabetes prevention with coverage by third-party payers ensued. Group delivery of DPP content in community or primary care settings has demonstrated the potential to reduce overall program costs while still producing weight loss and diabetes risk reduction.

The Centers for Disease Control and Prevention (CDC) developed the National Diabetes Prevention Program (National DPP), a resource designed to bring such evidence-based lifestyle change programs for preventing type 2 diabetes to communities. To be eligible for this program, individuals must have a BMI in the overweight range and be at risk for diabetes based on laboratory testing, a previous diagnosis of GDM, or a positive risk test.

During the first 4 years of implementation of the CDC’s National DPP, 36% achieved the 5% weight loss Such technology-assisted programs may deliver content through smartphones, web-based applications, and telehealth and may be an acceptable and efficacious option to bridge barriers, particularly for individuals with low income and people in rural locationsrecognition.htm) certifies technology assisted modalities as effective vehicles for DPP-based interventions; such programs must use an approved curriculum, include interaction with a coach, and attain the DPP outcomes of participation, physical activity reporting, and weight loss. Health care professionals should consider referring adults with prediabetes to certified technology-assisted programs.

**EPIDEMIOLOGY**

Diabetes is a worldwide epidemic. With changing lifestyles and increasing obesity, the prevalence of DM has increased worldwide. The global prevalence of DM was 425 million in 2017. According to the International Diabetes Federation (IDF), in 2015, about 10% of the American population had diabetes. Of these, 7 million were undiagnosed. With an increase in age, the prevalence of DM also increases. About 25% of the population above 65 years of age has diabetes.

Sixty studies from different Nigerian geopolitical zones met eligibility criteria, with a total sample size of 124,876 participants and a mean age of 48 ± 9.8 years. The pooled prevalence of T2DM in Nigeria was 7.0% (95% CI: 5.0-9.0%). Moderate publication bias was observed. The South-south zone had the highest prevalence at 11.35% (95% CI: 4.52-20.72%), while the North-central zone had the lowest at 2.03% (95% CI: 1.09-3.40%). Significant risk factors included family history (9.73), high socioeconomic status (6.72), physical inactivity (5.92), urban living (4.79), BMI > 25/m2 (3.07), infrequent vegetable consumption (2.68), and abdominal obesity (1.81).

The prevalence of T2DM in Nigeria (7.0%) nearly doubled the 2019 International Diabetes Federation estimate (3.7%) and shows a 21.3% increase from the 2019 review. Efforts should focus on modifying identified risk factors to reduce prevalence and prevent complications.

Over time, high blood sugar levels in type 2 diabetes can damage the eyes, kidneys, nerves and heart. This can happen because the pancreas doesn't make enough of a hormone called insulin that helps sugar enter the cells. It happens also because the cells respond poorly to insulin by taking in less sugar.

Both type 1 and type 2 diabetes can begin during childhood and adulthood. Type 2 is more common in older adults. But the increase in the number of children with obesity has led to more young people with type 2 diabetes.

There's no cure for type 2 diabetes. Losing weight, eating well and exercising can help manage the condition. If diet and exercise aren't enough to manage blood sugar, diabetes medicines or insulin therapy may help.

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**TYPE 3 DIABETES**

**ALTERNATIVE NAMES:** Type 3c diabetes is the alternative name for the type of diabetes that develops when another disease causes damage to the pancreas. Conditions related to type 3c diabetes include pancreatic cancer, pancreatitis, cystic fibrosis, or hemochromatosis.

Additionally, in April 2025, type 5 diabetes was officially recognized by the International Diabetes Federation (IDF) as a distinct type of diabetes related to malnutrition. It is primarily caused by chronic undernutrition, especially during childhood or adolescence.

No other alternative names specifically for "type 3 diabetes" were mentioned in the provided context. Type 3c diabetes is the term used for diabetes resulting from pancreatic damage.

Type 3 diabetes is also known as a pancreatogenic diabetes.

**DEFINITION / DESCRIPTION**

Type 3c diabetes occurs when there has been damage to someone's pancreas due to an illness or condition. Common conditions/illnesses that affect the pancreas are pancreatic cancer, cystic fibrosis and pancreatitis. It is also possible for someone to get type 3c diabetes if their pancreas has been removed for whatever reason. Type 3c diabetes happens when the pancreas isn't able to produce an adequate amount of insulin for the body. Further to this, it causes the pancreas to discontinue producing the enzyme required to digest food.

**You may have heard of the more common types of diabetes like type 1, type 2 and gestational. But there are actually many other types of diabetes that aren't as well known.**

Type 3c diabetes develops because of the damage to the pancreas, which can happen for a few different reasons. And although it's different to other types, you can get a wrong diagnosis of **type 2**because type 3c isn't as well known and the term 3c isn't always used. Type 3c can also be called diabetes related to disorders of the pancreas or a pancreatogenic diabetes mellitus.

Not getting the right diagnosis can be really difficult to deal with emotionally. You might feel angry at not getting the right treatment

or you could just get worn out by the whole process. So, make sure you find someone to talk to.

**CAUSES**

**What causes Type 3c diabetes?**

Type 3c diabetes develops when your pancreas experiences enough damage to affect its ability to make insulin. The damage is closely linked and can also result from the following underlying conditions or situations which affect the pancreas:

* Chronic pancreatitis.
* Acute pancreatitis.
* Pancreatic cancer.
* Hemochromatosis.
* Cystic fibrosis.
* Pancreatectomy.

**Chronic pancreatitis**

Chronic pancreatitis is long-term inflammation in your pancreas. Constant inflammation causes scarring of your pancreas tissues (fibrosis), which eventually stops it from making enzymes and hormones. About 25% to 80% of people with chronic pancreatitis develop Type 3c diabetes.

There are two main forms of chronic pancreatitis:

* **Acquired**: “Acquired” means “developed after birth.” Acquired chronic pancreatitis has several possible causes. The two most common causes are gallstones and excessive alcohol use.
* **Hereditary**: This form is due to genetic mutations you inherit from a biological parent. People with hereditary pancreatitis are born with genetic mutations, but they typically don’t experience the first episode of pancreatitis until late childhood.

Chronic pancreatitis is the most common cause of Type 3c diabetes — it represents about 79% of cases.

**Pancreatic cancer**

There’s a strong link between diabetes and pancreatic cancer, especially pancreatic ductal adenocarcinoma (the most common kind). About 50% of people diagnosed with pancreatic cancer also have diabetes.

Tumors from pancreatic cancer could potentially damage your pancreas and cause Type 3c diabetes. Researchers estimate that pancreatic cancer is the cause of about 8% of Type 3c diabetes cases.

**Hemochromatosis**

Hemochromatosis, also called iron overload, is a condition in which your body stores too much iron.

Normally, your intestines absorb just the right amount of iron from the food you eat. But with hemochromatosis, your body absorbs extra iron and stores it in your organs, especially your heart, liver and pancreas.

Iron stores in your pancreas can cause damage, leading to Type 3c diabetes.

Hemochromatosis causes about 7% of all Type 3c diabetes cases.

**Cystic fibrosis**

Cystic fibrosis (CF) is a genetic (inherited) condition that causes sticky, thick mucus to build up in organs, including your lungs and pancreas.

This mucus can scar and damage your pancreas, which can prevent it from producing enough insulin, resulting in Type 3c diabetes.

Sometimes, a person with cystic fibrosis experiences insulin resistance (like in Type 2 diabetes) due to the condition. This is more likely to happen when the person is sick, on steroid medications or is pregnant.

More than 35% of adults living with CF have Type 3c diabetes. This form of diabetes is also called CF-related diabetes (CFRD).

Cystic fibrosis causes about 4% of all Type 3c diabetes cases.

**Pancreatectomy**

A pancreatectomy is a surgery that removes part or all of your pancreas. You may need a pancreatectomy for many reasons, such as for pancreatic cancer, pancreatic cysts or severe chronic pancreatitis.

A pancreatectomy may or may not result in Type 3c diabetes. A partial pancreatectomy will leave some insulin-secreting cells behind. Sometimes they’re enough to keep your blood sugar in a healthy range.

If you’re having a total pancreatectomy, you’ll have diabetes afterward unless your surgeon can preserve some of your insulin-producing cells. Sometimes, your surgeon can transplant some of these cells into your liver.

Pancreatectomies cause about 2% of all Type 3c diabetes cases.

You can also develop type 3c if you have your pancreas removed because of any other damage.

Your doctor should be aware of your pancreatic issues if they're testing you for diabetes. But make sure you mention it to them so that they know that you're at risk for type 3c.

**RISK FACTORS**

Type 3 diabetes is not officially recognized as a distinct type of diabetes by national health organizations or the American Diabetes Association. Instead, it is a term used by some researchers to describe the hypothesis that insulin resistance and insulin-like growth factor dysfunction in the brain may cause Alzheimer's disease. This term is often used to highlight the potential link between type 2 diabetes and Alzheimer's disease, suggesting that poorly controlled blood sugar may increase the risk of developing Alzheimer's.

However, the risk factors for type 3 diabetes, as understood in this context, are primarily associated with the risk factors for type 2 diabetes and Alzheimer's disease. The main risk factors for type 2 diabetes include:

* Being overweight or obese.
* Having a large waist circumference, which is a risk factor for diabetes and heart disease, even if you have a normal BMI.
* Lack of physical activity.
* Age, as the risk increases with age.
* Family history of diabetes.
* **Race and ethnicity**, with certain groups being at higher risk.

**Regarding Alzheimer's disease, risk factors include:**

* Age, as the risk increases with age.
* Genetic factors, such as carrying the APOE-ε4 gene variant.
* **Poorly controlled blood sugar levels**, which may increase the risk of developing Alzheimer's.

Therefore, the risk factors for type 3 diabetes, as a concept linking type 2 diabetes and Alzheimer's disease, would encompass those for both conditions.

***Shared risk factors***

Because canonical risk factors for type 2 diabetes—e.g., old age, obesity, and family history of diabetes—are also risk factors for diabetes secondary to pancreatic cancer, there is a possibility that increased prevalence of diabetes in pancreatic ductal adenocarcinoma is an artifact of screening for diabetes in an elderly population. However, a study comparing the prevalence of diabetes in common cancers (breast, lung, prostate, and colon) showed no increased prevalence of diabetes compared with age-matched controls, although the high prevalence of diabetes in pancreatic ductal adenocarcinoma, especially recent-onset diabetes, was confirmed.

*Glandular destruction*

If the diabetes observed in pancreatic ductal adenocarcinoma were a consequence of glandular destruction, hyperinsulinemia would be expected; however, diabetes secondary to pancreatic cancer is associated with hyperinsulinemia secondary to insulin resistance. In fact, the median duration of diabetes in pancreatic ductal adenocarcinoma is about 13 months, at a time when imaging studies show no visible tumour. Moreover, 60% of small tumors (<20 mm in size) are associated with glucose intolerance, and more than half of patients with resectable tumors have diabetes. Thus, there is insufficient evidence to support the hypothesis that diabetes secondary to pancreatic cancer is due to local effects of tumor infiltration, ductal obstruction, and consequently glandular destruction.

*Pancreatic ductal adenocarcinoma causes diabetes*

The markedly increased risk of pancreatic ductal adenocarcinoma in new-onset diabetes appears to be due to reverse causality—i.e., pancreatic ductal adenocarcinoma causes hyperglycemia. This notion is supported by a large body of clinical, epidemiological, and experimental evidence. First, there is an exceedingly high prevalence of diabetes in the setting of pancreatic ductal adenocarcinoma, irrespective of the method of diagnosis. Approximately 80% of patients with pancreatic ductal adenocarcinoma have abnormal fasting glucose or glucose intolerance regardless of tumor size or stage. When formally tested with oral glucose tolerance tests, nearly two-thirds of patients with pancreatic ductal adenocarcinoma have diabetes. When screened for diabetes with fasting glucose, the prevalence is about 45%. Second, the onset of diabetes is often temporally related to the diagnosis of pancreatic ductal adenocarcinoma. Most patients (75–88%) reported that diabetes was new onset—i.e., diagnosed less than 24–36 months before diagnosis of pancreatic ductal adenocarcinoma. Third, effective treatment of pancreatic ductal adenocarcinoma often leads to improvement in Hyperglycaemia for those with new-onset diabetes secondary to pancreatic cancer. Resection of the tumor improves or resolves diabetes in many patients with new-onset diabetes, although there is no improvement in those with long-standing diabetes. Similarly, the metabolic defects are improved in those who have a treatment response to chemotherapy. Lastly, pancreatic tumors might indirectly induce hyperglycemia. Addition of conditioned media from pancreatic ductal adenocarcinoma cell lines impairs glucose metabolism in vitro in peripheral tissues and inhibits insulin release from β-cell lines.

**SIGNS / SYMPTOMS**

**What are the symptoms of Type 3c diabetes?**

The symptoms of Type 3c diabetes are the same as other forms of diabetes. They include:

* Increased thirst (polydipsia) and dry mouth.
* Frequent urination.
* Fatigue.
* Blurred vision.
* Unexplained weight loss.
* Numbness or tingling in your hands or feet.
* Slow-healing sores or cuts.
* Frequent skin and/or vaginal yeast infections.

People with Type 3c diabetes typically also have symptoms of exocrine pancreatic insufficiency, which include:

* Abdominal pain, gas and bloating.
* Constipation.
* Diarrhea.
* Fatty stools (pale, oily, foul-smelling poop that floats).
* Unexplained weight loss.

It’s important to see a healthcare provider if you have these symptoms.

## **DIAGNOSIS METHODS**

### **How is Type 3c diabetes diagnosed?**

It can be difficult for healthcare providers to diagnose Type 3c diabetes. This is because it isn’t a very common or well-known type of diabetes. Providers tend to misdiagnose it as Type 2 diabetes, which is a much more common form. If you have a known pancreatic condition, it’s less difficult to diagnose Type 3c.

Providers have to confirm diabetes, confirm damage to your pancreas and rule out other types of diabetes to diagnose Type 3c.

They may order the following tests to do so:

* Fasting blood glucose test: For this test, you don’t eat or drink anything except water (fast) for at least eight hours before the test. A result of 126 mg/dL or higher typically indicates diabetes.
* A1C: This blood test, also called HbA1C or glycated hemoglobin test, provides your average blood glucose level over the past two to three months. A result of 6.5% or higher typically indicates diabetes.
* Imaging tests: Imaging tests, such as a computed tomography (CT) scan, can help your provider see damage to your pancreas.
* Pancreas blood tests: These tests can check pancreas function. They measure the levels of certain digestive enzymes your pancreas produces. If the results are abnormal, they can help confirm pancreas damage.
* Diabetes autoantibody panel: This is a blood test that checks if you have the autoantibodies that cause Type 1 diabetes. Your provider may order this test to rule out Type 1.

## **Management and Treatment**

### **How is Type 3c diabetes treated?**

The treatment for Type 3c diabetes varies based on the underlying cause and how much of your pancreas is damaged (or surgically removed).

People with the condition typically take an oral diabetes medication (such as metformin) and/or take synthetic insulin (with injections or an insulin pump).

Your treatment needs may change over time if your pancreas becomes more damaged. For example, an oral medication may work well to manage your blood sugar at first. But you may eventually need insulin to keep your blood sugar levels in range if your pancreas produces less and less insulin.

Other management strategies for Type 3c diabetes include:

* Blood sugar monitoring: Monitoring your blood sugar (glucose) is key to determining how well your current treatment plan is working. It gives you information on how to manage Type 3c diabetes on a daily — and sometimes even hourly — basis. You can monitor your levels with frequent checks with a glucose meter and finger stick and/or with a continuous glucose monitor (CGM). You and your healthcare provider will determine the best blood sugar range for you.
* Diet: Meal planning and choosing a healthy diet for you are key aspects of diabetes management in general, as food greatly impacts blood sugar. A registered dietitian can help you develop the best eating plan.
* Exercise: Physical activity increases insulin sensitivity (and helps reduce insulin resistance), so regular exercise is an important part of management for all people with diabetes.

Diabetes is a complex condition, so its management involves several strategies. In addition, diabetes affects everyone differently, so management plans are highly individualized. You’ll likely benefit from regular visits with your healthcare team to monitor how well your treatment plan is working.

### **PREVENTION TIPS**

### **Can I prevent Type 3c diabetes?**

The only way to prevent Type 3c diabetes is to try to prevent the underlying conditions that cause it, if possible. Inherited conditions like cystic fibrosis and hereditary pancreatitis aren’t preventable. But there are steps you can take to try to prevent acquired pancreatitis, such as moderating your alcohol consumption and maintaining healthy triglyceride levels.

**OUTLOOK / PROGNOSIS**

The prognosis (outlook) for Type 3c diabetes varies greatly depending on several factors, including:

* The underlying condition that caused it.
* How well you manage Type 3c diabetes over time and your access to diabetes care.
* How well the underlying condition is managed.
* Your age at diagnosis/how long you’ve had diabetes.
* If you have other health conditions.
* If you develop diabetes complications.

Chronic high blood sugar can cause severe complications, which are often irreversible. Several studies have shown that untreated chronic high blood sugar shortens your lifespan and worsens your quality of life.

However, it’s important to know that you can live a healthy life with diabetes. The following are key to a better prognosis:

* Lifestyle changes.
* Regular exercise.
* Dietary changes.
* Regular blood sugar monitoring.

**POSSIBLE COMPLICATIONS**

### **What are the complications of Type 3c diabetes?**

Blood glucose levels that remain high for too long can damage your body’s tissues and organs. This is mainly due to damage to your blood vessels and nerves, which support your body’s tissues.

Cardiovascular (heart and blood vessel) issues are the most common type of long-term diabetes complication. They include:

* Coronary artery disease (CAD).
* Heart attack.
* Stroke.
* Atherosclerosis.

Other diabetes complications include:

* Nerve damage (neuropathy).
* Nephropathy.
* Retinopathy.
* Diabetes-related foot conditions.

**WHEN TO SEE A DOCTOR / RED FLAG**

### **When should I see my healthcare provider about Type 3c diabetes?**

If you have a condition that affects your pancreas, such as chronic pancreatitis or hemochromatosis, talk to your healthcare provider about your risk of developing Type 3c diabetes. They’ll likely order regular tests to monitor for diabetes.

If you have Type 3c diabetes, you’ll need to see your healthcare team regularly to manage both diabetes and the underlying condition that caused it.

**DIFFERENTIAL DIAGNOSIS**

There is no officially recognized type 3 diabetes. However, some researchers and clinicians use the term "type 3 diabetes" to describe diabetes that develops in individuals with Alzheimer's disease, suggesting a link between the two conditions. This usage is not universally accepted and is considered a form of debate within the medical community.

For differential diagnoses related to diabetes, consider the following:

* Type 1 Diabetes: Characterized by the destruction of beta cells in the pancreas, typically secondary to an autoimmune process, leading to the absence or extremely low levels of insulin.
* Type 2 Diabetes: Involves a more insidious onset where an imbalance between insulin levels and insulin sensitivity causes a functional deficit of insulin. Commonly associated with obesity and aging.
* Maturity-Onset Diabetes of the Young (MODY): A heterogeneous disorder identified by non-insulin-dependent diabetes diagnosed at a young age (usually under 25 years), with an autosomal dominant transmission and no involvement of autoantibodies.
* Gestational Diabetes: Diabetes that manifests during pregnancy, though the exact cause is not fully understood.
* Secondary Causes: Including endocrinopathies such as acromegaly, Cushing syndrome, glucagonoma, hyperthyroidism, hyperaldosteronism, and somatostatinomas, which can lead to glucose intolerance and diabetes mellitus due to the glucogenic action of the endogenous hormones excessively secreted in these conditions.

Type 3c diabetes, which is also known as a pancreatogenic diabetes, is a form of diabetes that develops due to damage to the pancreas, which affects its ability to produce insulin.To differentiate Type 3c diabetes from other types of diabetes, healthcare providers need to confirm diabetes, confirm damage to the pancreas, and rule out other types of diabetes.

The differential diagnosis process includes several steps:

* Fasting blood glucose test: A result of 126 mg/dL or higher typically indicates diabetes.
* A1C test: Provides your average blood glucose level over the past two to three months. A result of 6.5% or higher typically indicates diabetes.
* Imaging tests: Such as a computed tomography (CT) scan, can help visualize damage to the pancreas.
* Pancreas blood tests: Measure the levels of certain digestive enzymes produced by the pancreas. Abnormal results can help confirm pancreas damage.
* Diabetes autoantibody panel: Checks for the autoantibodies that cause Type 1 diabetes. This test helps rule out Type 1 diabetes.

Type 3c diabetes is often misdiagnosed as Type 2 diabetes due to a lack of awareness and the term "3c" not being widely used. Therefore, it is crucial to consider Type 3c diabetes in patients with known pancreatic conditions or those experiencing new-onset diabetes along with weight loss, especially in individuals aged 60 and older.

Misclassification of Type 3c diabetes can lead to inappropriate treatment

**What’s the difference between Type 1, Type 2 and Type 3c diabetes?**

The main difference between these types of diabetes is what causes them.

Type 1 diabetes is an autoimmune disease in which your immune system attacks and destroys insulin-producing cells in your pancreas for unknown reasons. People with Type 1 always need insulin to manage the condition.

Type 2 diabetes develops when your body doesn’t make enough insulin and/or your body’s cells don’t respond normally to the insulin (insulin resistance). People with Type 2 diabetes may manage the condition with lifestyle changes, oral medication and/or insulin.

Type 3c diabetes results from damage to your pancreas that isn’t autoimmune. People with Type 3c often also lack the enzymes their pancreas makes for digestion. In this type, the amount of insulin your pancreas makes can vary. Some people take oral diabetes medications and others need insulin to manage the condition.

Initial diagnosis of T3cDM (as for types 1 and 2), includes measurement of fasting glucose and glycated hemoglobin (HbA1c or A1c), repeated annually for those with pancreatitis. Equivocal results should arguably be investigated further by means of an oral glucose tolerance test.12 The ADA guidelines state that fasting plasma glucose of >126 mg/dl (>7 mmol/L) or HbA1c of >48 mmol/mol (6.5%) are diagnostic of DM, while a fasting glucose of 100-125 mg/dl (5.5-6.9mmoL) or HbA1c of 39-46 mmol/mol (5.7- 6.4%) are indicative of prediabetes.1,13 However, differentiating T3cDM from T1DM and T2DM is not always straightforward.14 Destruction of the islet cells by pancreatic inflammation differs from that in T1DM as there is also a loss of glucagon and pancreatic polypeptide (PP) from the islet alpha cells and PP cells (as well as the loss of insulin from the islet beta-cells). Additionally, nutrient maldigestion and malabsorption lead to impaired incretin secretion and therefore diminished release from the remaining beta cells. Although circulating insulin levels are known to be low in T3cDM, along with a compensatory increase in peripheral insulin sensitivity, there is a decrease in hepatic insulin sensitivity (and unsuppressed hepatic glucose production), which drives hyperglycemia. The impairment of hepatic insulin sensitivity and persistent hepatic glucose production is associated with the reduction in pancreatic PP secretion. Therefore, the DM associated with pancreatic disease is erratic in nature, characterized by significant swings in blood glucose from hypoglycemia to hyperglycemia in a manner which is difficult to control.

Pancreatic exocrine insufficiency

2. Pathological pancreatic imaging

3. Absence of T1DM-associated auto-antibodies. The minor criteria were absent PP secretion, impaired incretin secretion, absence of excessive insulin resistance, impaired beta-cell function, and low serum levels of fat-soluble vitamins. Assessment and monitoring of patients with pancreatic disease should include body mass index, diabetes-associated antibodies (to out rule T1DM), and glucose to c-peptide ratio which estimates beta cell area. Insulin resistance is measurable by the homeostasis model assessment, which estimates steady state beta-cell function and insulin sensitivity as percentages of a normal reference range. This is calculated based on fasting plasma glucose and insulin values. Unlike T2DM patients, those with T3cDM will not normally have excess insulin resistance. The absence of (or reduced) PP secretion following ingestion of glucose or a mixed meal may also be indicative of T3cDM.

However, these guides require the measurement of incretin, PP and c-peptide levels, among others, which in everyday practice is unlikely to occur.

**EPIDEMIOLOGY**

Type 3c diabetes, also known as pancreatogenic diabetes, is a condition that develops when the pancreas stops producing sufficient insulin due to an illness or damage affecting the pancreas. It is estimated that **5 to 10 percent of diabetic individuals in Western populations have type 3c diabetes**, indicating its significant prevalence.5 Chronic pancreatitis, which accounts for approximately 79 percent of cases, is the most common cause of type 3c diabetes.3 Additionally, there is a strong association between diabetes and pancreatic cancer, particularly pancreatic ductal adenocarcinoma.

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**GESTATIONAL DIABETES**

ALTERNATIVE NAMES: Gestational diabetes is also known as “**gestational diabetes mellitus** (GDM)”

* **Diabetes mellitus, gestational**: This term emphasizes the nature of the condition as a form of diabetes that occurs during pregnancy.
* **Maternal diabetes**: This name highlights the condition's impact on the mother during pregnancy.

These alternative names refer to the same condition, which is characterized by high blood glucose levels during pregnancy in women who did not have diabetes prior to pregnancy.

**DEFINITION / DESCRIPTION**

This type of diabetes develops during pregnancy and normally disappears post giving birth. It is caused by high blood sugar and can occur at any stage of pregnancy. The reason it occurs is that the individual's body isn't able to produce enough of the hormone insulin to meet their additional needs during pregnancy.

Gestational diabetes is diabetes diagnosed for the first time during pregnancy (gestation). Like other types of diabetes, gestational diabetes affects how your cells use sugar (glucose). Gestational diabetes causes high blood sugar that can affect your pregnancy and your baby's health.

While any pregnancy complication is concerning, there's good news. During pregnancy you can help control gestational diabetes by eating healthy foods, exercising and, if necessary, taking medication. Controlling blood sugar can keep you and your baby healthy and prevent a difficult delivery.

If you have gestational diabetes during pregnancy, generally your blood sugar returns to its usual level soon after delivery. But if you've had gestational diabetes, you have a higher risk of getting type 2 diabetes. You'll need to be tested for changes in blood sugar more often.

**CAUSES**

Researchers don't yet know why some women get gestational diabetes and others don't. Excess weight before pregnancy often plays a role.

Usually, various hormones work to keep blood sugar levels in check. But during pregnancy, hormone levels change, making it harder for the body to process blood sugar efficiently. This makes blood sugar rise.

**RISK FACTORS**

Risk factors for gestational diabetes include:

* Being overweight or obese
* Not being physically active
* Having prediabetes
* Having had gestational diabetes during a previous pregnancy
* Having polycystic ovary syndrome
* Having an immediate family member with diabetes
* Having previously delivered a baby weighing more than 9 pounds (4.1 kilograms)
* Being of a certain race or ethnicity, such as Black, Hispanic, American Indian and Asian American

**SIGNS / SYMPTOMS**

Often, there will not be any symptoms of gestational diabetes, or they may be similar to pregnancy side-effects which can make it difficult to detect. However, if a pregnant woman’s blood sugar levels rise too high, they may experience the following symptoms:

Increased thirst

* Urinating more often than usual
* A dry mouth
* Fatigue

**DIAGNOSIS METHODS**

Certain factors contribute towards a persons' risk of gestational diabetes; having a Body Mass Index over 30, if they have had a baby before who has weighed 10lb or more at birth, have had gestational diabetes before or have a family history of the condition.

The risk of gestational diabetes will be determined during the first antenatal appointment 8 to 12 weeks into a pregnancy. Women who have any of the risk factors of gestational diabetes will be offered a screening test which will determine whether or not they have the condition.

If you're at average risk of gestational diabetes, you'll likely have a screening test during your second trimester — between 24 and 28 weeks of pregnancy.

If you're at high risk of diabetes — for example, if you're overweight or obese before pregnancy; you have a mother, father, sibling or child with diabetes; or you had gestational diabetes during a previous pregnancy — your health care provider may test for diabetes early in pregnancy, likely at your first prenatal visit.

### **Routine screening for gestational diabetes**

Screening tests may vary slightly depending on your healthcare provider, but generally include:

* **Initial glucose challenge test.** You'll drink a syrupy glucose solution. One hour later, you'll have a blood test to measure your blood sugar level. A blood sugar level of 190 milligrams per deciliter (mg/dL), or 10.6 millimoles per liter (mmol/L), indicates gestational diabetes.  
  A blood sugar level below 140 mg/dL (7.8 mmol/L) is usually considered within the standard range on a glucose challenge test, although this may vary by clinic or lab. If your blood sugar level is higher than expected, you'll need another glucose tolerance test to determine if you have gestational diabetes.
* **Follow-up glucose tolerance testing.** This test is similar to the initial test — except the sweet solution will have even more sugar and your blood sugar will be checked every hour for three hours. If at least two of the blood sugar readings are higher than expected, you'll be diagnosed with gestational diabetes.

**TREATMENT METHODS**

Controlling blood sugar levels can help to decrease the chances of there being any problems during and after pregnancy. Anyone with the condition will be provided with a blood sugar testing kit so that they can monitor the effects of the treatment. Simple things such as making diet adjustments or exercising can help to reduce blood sugar levels. If this is not effective, medication will also be provided which could be in tablet form or insulin injection.

**Treatment for gestational diabetes includes:**

* Lifestyle changes
* Blood sugar monitoring
* Medication, if necessary

Managing your blood sugar levels helps keep you and your baby healthy. Close management can also help you avoid complications during pregnancy and delivery.

### **Lifestyle changes**

Your lifestyle — how you eat and move — is an important part of keeping your blood sugar levels in a healthy range. Health care providers usually don't advise losing weight during pregnancy — your body is working hard to support your growing baby. But your health care provider can help you set weight gain goals based on your weight before pregnancy.

**Lifestyle changes include:**

* **Healthy diet.** A healthy diet focuses on fruits, vegetables, whole grains and lean protein — foods that are high in nutrition and fiber and low in fat and calories — and limits highly refined carbohydrates, including sweets. A registered dietitian or a certified diabetes care and education specialist can help you create a meal plan based on your current weight, pregnancy weight gain goals, blood sugar level, exercise habits, food preferences and budget.
* **Staying active.** Regular physical activity plays a key role in every wellness plan before, during and after pregnancy. Exercise lowers your blood sugar. As an added bonus, regular exercise can help relieve some common discomforts of pregnancy, including back pain, muscle cramps, swelling, constipation and trouble sleeping.

With your health care provider's OK, aim for 30 minutes of moderate exercise on most days of the week. If you haven't been active for a while, start slowly and build up gradually. Walking, cycling and swimming are good choices during pregnancy. Everyday activities such as housework and gardening also count.

### **Blood sugar monitoring**

While you're pregnant, your health care team may ask you to check your blood sugar four or more times a day — first thing in the morning and after meals — to make sure your level stays within a healthy range.

### **Medication**

If diet and exercise aren't enough to manage your blood sugar levels, you may need insulin injections to lower your blood sugar. A small number of women with gestational diabetes need insulin to reach their blood sugar goals.

Some health care providers prescribe an oral medication to manage blood sugar levels. Other health care providers believe more research is needed to confirm that oral medications are as safe and as effective as injectable insulin to manage gestational diabetes.

### **Close monitoring of your baby**

An important part of your treatment plan is close observation of your baby. Your health care provider may check your baby's growth and development with repeated ultrasounds or other tests. If you don't go into labor by your due date — or sometimes earlier — your health care provider may induce labor. Delivering after your due date may increase the risk of complications for you and your baby.

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### **Follow-up after delivery**

Your health care provider will check your blood sugar level after delivery and again in 6 to 12 weeks to make sure that your level has returned to within the standard range. If your tests are back in this range — and most are — you'll need to have your diabetes risk assessed at least every three years.

If future tests indicate type 2 diabetes or prediabetes, talk with your health care provider about increasing your prevention efforts or starting a diabetes management plan.

**POSSIBLE COMPLICATIONS**

Maternal and fetal complications are associated with GDM. The fetal complications include macrosomia, neonatal hypoglycemia, polycythemia, shoulder dystocia, hyperbilirubinemia, neonatal respiratory distress syndrome, increased perinatal mortality, and hypocalcemia. Maternal complications include preeclampsia, increased risk of developing diabetes mellitus, and increased risk of Cesarean delivery

Gestational diabetes that's not carefully managed can lead to high blood sugar levels. High blood sugar can cause problems for you and your baby, including an increased likelihood of needing a surgery to deliver (C-section).

**Complications that may affect your baby**

If you have gestational diabetes, your baby may be at increased risk of:

* **Excessive birth weight.** If your blood sugar level is higher than the standard range, it can cause your baby to grow too large. Very large babies — those who weigh 9 pounds or more — are more likely to become wedged in the birth canal, have birth injuries or need a C-section birth.
* **Early (preterm) birth.** High blood sugar may increase the risk of early labor and delivery before the due date. Or early delivery may be recommended because the baby is large.
* **Serious breathing difficulties.** Babies born early may experience respiratory distress syndrome — a condition that makes breathing difficult.
* **Low blood sugar (hypoglycemia).** Sometimes babies have low blood sugar (hypoglycemia) shortly after birth. Severe episodes of hypoglycemia may cause seizures in the baby. Prompt feedings and sometimes an intravenous glucose solution can return the baby's blood sugar level to normal.
* **Obesity and type 2 diabetes later in life.** Babies have a higher risk of developing obesity and type 2 diabetes later in life.
* **Stillbirth.** Untreated gestational diabetes can result in a baby's death either before or shortly after birth.

**Complications that may affect you**

Gestational diabetes may also increase your risk of:

* **High blood pressure and preeclampsia.** Gestational diabetes raises your risk of high blood pressure, as well as preeclampsia — a serious complication of pregnancy that causes high blood pressure and other symptoms that can threaten both your life and your baby's life.
* **Having a surgical delivery (C-section).** You're more likely to have a C-section if you have gestational diabetes.
* **Future diabetes.** If you have gestational diabetes, you're more likely to get it again during a future pregnancy. You also have a higher risk of developing type 2 diabetes as you get older.

**PREVENTION TIPS**

There are no guarantees when it comes to preventing gestational diabetes — but the healthier habits you can adopt before pregnancy, the better. If you've had gestational diabetes, these healthy choices may also reduce your risk of having it again in future pregnancies or developing type 2 diabetes in the future.

* **Eat healthy foods.** Choose foods high in fiber and low in fat and calories. Focus on fruits, vegetables and whole grains. Strive for variety to help you achieve your goals without compromising taste or nutrition. Watch portion sizes.
* **Keep active.** Exercising before and during pregnancy can help protect you from developing gestational diabetes. Aim for 30 minutes of moderate activity on most days of the week. Take a brisk daily walk. Ride your bike. Swim laps. Short bursts of activity — such as parking further away from the store when you run errands or taking a short walk break — all add up.
* **Start pregnancy at a healthy weight.** If you're planning to get pregnant, losing extra weight beforehand may help you have a healthier pregnancy. Focus on making lasting changes to your eating habits that can help you through pregnancy, such as eating more vegetables and fruits.
* **Don't gain more weight than recommended.** Gaining some weight during pregnancy is typical and healthy. But gaining too much weight too quickly can increase your risk of gestational diabetes. Ask your health care provider what a reasonable amount of weight gain is for you.

**OUTLOOK / PROGNOSIS**

Gestational diabetes **typically resolves after birth, but women who have had it are at a higher risk of developing type 2 diabetes later in life**. Postpartum, women should have a blood test to check for diabetes 6 to 13 weeks after giving birth, and should continue to be screened annually if the initial test is normal.

Additionally, babies born to mothers with gestational diabetes may be at a higher risk of becoming obese or developing diabetes later in life.

For ongoing health management, women with a history of gestational diabetes are advised to maintain a healthy weight, eat a balanced diet, and engage in regular physical activity to reduce their risk of developing diabetes or prediabetes.

Proper control of maternal glucose levels significantly reduces GDM risks, including macrosomia and neonatal hypoglycemia. The risk of preeclampsia decreases from 18% to 12% with treatment.If GDM interventions, including dietary modifications or pharmacologic therapy, are implemented early enough, progression to type 2 diabetes in 10 years is reduced by 35% to 40%. Furthermore, even small reductions in BMI can result in a reduced risk for diabetes by 25%.

**How worried should I be about gestational diabetes?**

Gestational diabetes is a common condition and healthcare providers have a good idea of how best to manage and treat it. You’ll still have a healthy pregnancy and a healthy baby if you have gestational diabetes. Work with your healthcare provider to make sure you understand your treatment plan and how you can keep your blood sugar levels healthy.

Take time to understand the possible complications of not managing gestational diabetes. Your baby has a very good chance of being born healthy, but you must take steps to manage the condition. If your blood sugar levels are high several readings in a row, don’t wait to contact your provider. Let them know that your blood sugar levels are repeatedly high so they can adjust your foods or medication and help you. Gestational diabetes is manageable, but there’s a level of responsibility you must take to ensure your pregnancy is healthy.

**Will gestational diabetes go away after pregnancy?**

Your blood sugar levels should come down after you give birth, when your hormone levels return to normal. Your pregnancy care provider will test you for gestational diabetes after your baby is born to confirm it’s gone (usually around six to 12 weeks postpartum).

But about 50% of people with gestational diabetes develop Type 2 diabetes later in life. Eating the right foods for your body and getting physical activity can help lower your risk. Your healthcare provider may recommend blood glucose tests every few years to watch for diabetes, especially if you have one or more risk factors.

**Does having gestational diabetes make a pregnancy high risk?**

Yes, having gestational diabetes may make your pregnancy high risk. Healthcare providers consider a pregnancy high risk when either you or the fetus (or both) has health conditions that increase your chances of having a pregnancy complication.

**Will my baby be healthy if I have gestational diabetes?**

Yes. Most babies are born healthy. There are some steps you can take to manage gestational diabetes during pregnancy to give your child the best start in life. Attending all your prenatal appointments and managing diabetes the best you can during pregnancy are the two best things you can do.

**Living With**

**What can I do to make living with gestational diabetes easier?**

Make diabetes management part of your daily routine. Create a schedule and stick to it. Try to:

* Check your blood glucose levels at the same time each day.
* Choose three days each week to get 30 minutes of light exercise.
* Plan small, balanced meals ahead of time.
* Talk with your healthcare provider or a diabetes educator about other tips for daily diabetes management.

**WHEN TO SEE A DOCTOR / RED FLAG**

If possible, seek healthcare when you start to think about trying to get pregnant. Then your healthcare professional can check your risk of gestational diabetes and your overall wellness. Once you're pregnant, your healthcare professional will check you for gestational diabetes as part of your prenatal care.

If you have gestational diabetes, you'll need checkups more often. These extra checkups are most likely to be during the last three months of pregnancy. Your healthcare professional will check your blood sugar level and your baby's health.

Even if you’re being careful to manage your condition, there may be situations where you need to call your pregnancy care provider. Contact your provider if you have gestational diabetes and:

* **You’re having trouble managing blood sugar levels**. This means your blood sugar levels are higher than the range your provider gave you for several readings in a row. They may want to adjust your diabetes management plan.
* **Your blood sugar is consistently low**. Having low blood sugar can be a bad thing, too. Your provider may have ideas to help your blood sugar stay in a healthier range.
* **You have an illness that prevents you from following your management plan**. For example, you may have food poisoning or be vomiting for another reason. Being unable to eat will affect your blood sugar levels.

**DIFFERENTIAL DIAGNOSIS**

Many women do not receive the appropriate screening for diabetes mellitus before pregnancy, so in some cases, it is challenging to distinguish GDM from preexisting diabetes and maturity-onset diabetes of the young.

Other differential diagnosis for gestational diabetes include:

Acute Renal Failure

Acute Respiratory Distress Syndrome

Acute Tubular Necrosis

Appendicitis

Autoimmune Thyroid Disease and Pregnancy

Cholecystitis

Cholelithiasis

Chronic Renal Failure

Diabetes Mellitus, Type 1

Diabetes Mellitus, Type 2

Diabetic Foot Infections

Diabetic Ketoacidosis

Diabetic Nephropathy

Diabetic Ulcers

Early Pregnancy Loss

Fetal Growth Restriction

Hypertension

Hypoglycemia

Pulmonary Edema, Cardiogenic

**RECENT GUIDELINES OR UPDATES**

***Gestational diabetes in minority populations***

The prevalence of gestational diabetes is strongly related to the patient's race and culture. Prevalence rates are higher in black, Hispanic, Native American, and Asian women than in white women. For example, typically, only 1.5-2% of white women develop gestational diabetes mellitus, whereas Native Americans from the southwestern United States may have rates as high as 15%. In Hispanic, black, and Asian populations, the incidence is 5-8%.

In these high-risk populations, the recurrence risk with future pregnancies has been reported to be as high as 68%.In addition, approximately one-third will develop overt diabetes mellitus within 5 years of delivery, with higher-risk ethnicities having risks nearing 50%.

Race also influences many complications of diabetes mellitus in pregnancy. For instance, black women have been shown to have lower rates of macrosomia, despite similar levels of glycemic control. Conversely, Hispanic women have higher rates of macrosomia and birth injury than women of other ethnicities, even with aggressive management.

***Infants of mothers with maternal hyperglycemia***

Infants of mothers with preexisting diabetes experience double the risk of serious injury at birth, triple the likelihood of cesarean delivery, and quadruple the incidence of newborn intensive care unit (NICU) admission. Studies indicate that the risk of these morbidities is directly proportional to the degree of maternal hyperglycemia.

In gestational diabetes mellitus, OGTT gut glucose absorption is markedly lowered. Thus, hyperglycemia of pregnancy does not result from too rapid or increased glucose absorption.

The excessive fetal and neonatal morbidity attributable to diabetes in pregnancy should be considered preventable with early diagnosis and effective treatment therapies. Guidelines have been established for the screening of pregnant women (see Screening for Diabetes Mellitus during Pregnancy) and for tailoring treatment to the unique needs of pregnancy.

***Maternal education on gestational diabetes***

Education is the cornerstone of effective metabolic management of the patient with diabetes during pregnancy. The American Diabetes Association (ADA) offers educational curricula specific to each type of diabetes encountered during pregnancy (type 1, type 2, gestational), specifically organized around each phase of pregnancy. This information can be transmitted to the patient by office staff and labor/delivery nurses. However, specially trained and certified nurses and dietitians (i.e., certified diabetes educators) are the most effective in this regard.

**EPIDEMIOLOGY**

**Rate of gestational diabetes U.S. and worldwide**

The rate of gestational diabetes in the United States is rising. According to the U.S. Centers for Disease Control and Prevention (CDC), about 8% to 10% of pregnant women will develop GD.

The rate of gestational diabetes worldwide, on average, is between 14% and 17%. Other factors can contribute to rates being higher, such as age, race/ethnicity, access to prenatal care and geography.

GDM is a common complication in pregnancy. The International Diabetes Federation recently estimated that globally, 1 in 6 live births had a GDM diagnosis. In the United States, approximately 7% of pregnancies were complicated by diabetes of any type, with 86% of those cases being pregnancies complicated by GDM. The estimated prevalence of GDM in Europe is 10.9%.

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**MATURITY ONSET DIABETES OF THE YOUNG (MODY)**

*ALTERNATIVE NAMES:* Maturity onset of the young (MODY) is also known as “type 5 diabetes”, or “monogenic diabetes”

**DEFINITION / DESCRIPTION**

MODY is a rare form of diabetes which is more often than not genetic. It occurs due to a mutation in a single gene so if a parent has the gene, their offspring have a 50% chance of inheriting the condition. This type of diabetes is not affected by a persons' weight or lifestyle, and will usually develop before the person is 25 years old. People with MODY experience problems with regulating their blood sugar levels.

**MODY is a rare form of diabetes which is different from both type 1 and type 2 diabetes, and runs strongly in families.**

MODY is caused by a mutation (or change) in a single gene. If a parent has this gene mutation, any child they have, has a 50% chance of inheriting it from them. If a child does inherit the mutation, they will generally go on to develop MODY before they’re 25, whatever their weight, lifestyle, ethnic group etc.

**The key features of MODY are:**

* Being diagnosed with diabetes under the age of 25.
* Having a parent with diabetes, with diabetes in two or more generations.
* Not necessarily needing insulin.

MODY is very rare compared with **type 1** and **type 2 diabetes** – experts estimate that only 1–2% of people with diabetes (20-40,000 people) in the UK have it. But because MODY is so rare, doctors may not be aware of it, so it’s estimated that about 90% of people with it are mistakenly diagnosed with type 1 or type 2 diabetes at first.

**The most common types of MODY are:**

* **HNF1-alpha.** This gene causes about 70 percent of cases of MODY. It causes diabetes by lowering the amount of insulin made by the pancreas. Diabetes usually develops in adolescence or early twenties, and people with HNF1-alpha MODY generally don’t need to take insulin: they can be treated with small doses of a group of tablets called **sulphonyl ureas** (often used in type 2 diabetes).
* **HNF4-alpha.** This isn’t as common as the other forms of MODY. People who have inherited a change in this gene are likely to have had a birth weight of 9lb or more (around 4kg). They may also have had a low blood sugar at, or soon after, birth which might have needed treatment. People with HNF4-alpha are generally treated with a sulphonyl urea tablet but may progress on to needing insulin.
* **HNF1-beta.** People with this type of MODY can have a variety of problems including renal cysts (cysts of the kidneys), uterine abnormalities and gout, as well as diabetes. Often the renal cysts can be detected in the womb before a baby is born. Diabetes tends to develop later and insulin treatment is usually necessary, as well as following a healthy balanced diet and getting regular physical activity. HNF4-beta MODY also carries a risk of complications of diabetes.
* **Glucokinase.** This gene helps the body to recognize how high the blood glucose level is in the body. When this gene isn’t working properly the body allows the level of blood glucose to be higher than it should be. Blood glucose levels in people with glucokinase MODY are typically only slightly higher than normal, generally between 5.5-8 mmol/l. You don’t generally have symptoms of this type of MODY and so it’s often picked up through routine testing (e.g. during pregnancy). You don’t need any treatment for glucokinase MODY.

All types of MODY apart from glucokinase carry a risk of the long-term complications of diabetes so you should follow a healthy balanced diet and keep physically active as this helps to maintain good blood glucose and cholesterol levels which in turn reduce the risk of complications.

**It’s important to know if you’ve got MODY, for the following reasons:**

* To make sure you get the right treatment and advice for your type of diabetes (e.g. stopping insulin).
* As there is a 50% chance of a parent passing on MODY to their child, you can consider and discuss the risk to any children you have/plan to have.
* Genetic testing can be offered to other family members.

If you think you might have MODY you should discuss testing with your doctor.

**Testing for MODY involves:**

* Having blood taken for pancreatic antibodies and blood or urine tested for C-peptide (your doctor/hospital can do this).
* Having blood taken for genetic testing. Your doctor/hospital will take the blood from you, but they will send it on to the specialist center in Exeter for it to be tested, along with details of your diagnosis and treatment.

**CAUSES AND RISK FACTORS**

MODY occurs as a result of genetic changes that affect the function of beta cells in the pancreas. These cells are responsible for monitoring changes in blood sugar and responding with sufficient levels of insulin to regulate a person’s blood sugar levels.

As a monogenic condition, MODY often runs in families. This means that if a person has a family member with MODY, they have a higher risk of developing the condition.

Several different gene changes can cause MODY, all of which limit the ability of the pancreas to produce insulin. At present, data suggest that variations in at least 14 genes cause MODY. However, some genetic variations are more prevalent than others.

The four most common types of MODY involve changes in the following genes:

* *HNF1-alpha* gene: Also known as MODY 3, this type results from the most common genetic change responsible for MODY. This change affects the function of HNF1-alpha protein, which alters the development of beta cells in the pancreas, making them less capable of producing insulin to help regulate blood sugar.
* *HNF4-alpha* gene: Also known as MODY 1, this type impacts a different HNF protein, called HNF4-alpha. Children with this gene change are often have a high birth weight and low blood sugar at birth. As with MODY 3, the changes in this protein affect the development of beta cells and reduce the ability to produce insulin.
* *HNF1-beta* gene: This type is also known as MODY 5 or renal cysts and diabetes syndrome. This type affects the beta protein. Individuals with this genetic change often develop kidney problems in addition to diabetes. This change affects beta cell development and results in the formation of cysts in the kidneys.
* *GCK* gene: Also known as MODY 2, this type alters the function of the glucokinase protein, which helps beta cells in the pancreas detect blood sugar changes. As a result, the body is less able to produce a suitable amount of insulin to manage blood sugar levels.

## Vs. other types of diabetes

Type 1 and type 2 diabetes are the most common types of the condition. They are polygenic conditions, which means they occur as a result of changes in multiple genes. In contrast, MODY occurs because of a change in a single gene.

MODY is a rare condition and may present with slightly different symptoms depending on which type a person has. Therefore, doctors may misdiagnose MODY as either type 1 or type 2 diabetes. A doctor can diagnose diabetes by measuring a person’s blood sugar levels. However, for an accurate diagnosis of MODY, genetic testing is often necessary

**SIGNS / SYMPTOMS**

People living with MODY may experience mild diabetes symptoms. Symptoms of MODY tend to develop gradually and may include:

* frequent urination
* increased thirst
* dehydration
* blurry vision
* recurring infections, such as skin and yeast infections

MODY also has clinical features, which help distinguish it from other types of diabetes:

* It often develops before age 25.
* It typically carries from one generation to the next within families.
* Treatment often involves diet or medication and does not necessarily require insulin.
* Individuals with the condition often have a moderate, healthy weight.

**DIAGNOSIS METHODS**

A GP can complete a blood test to examine blood sugar levels, or a genetic test can be carried out which will determine the exact type of MODY.

The diagnosis of Maturity-Onset Diabetes of the Young (MODY) involves a combination of **clinical evaluation, family history assessment, and genetic testing**. Here are the key methods used for diagnosing MODY:

* **Clinical Evaluation**: MODY should be suspected in individuals with a strong family history of diabetes, especially if the diabetes onset occurs before the age of 25 years. Features inconsistent with type 1 diabetes, such as lack of insulin resistance and its markers (e.g., acanthosis nigricans, central obesity, hypertension, and dyslipidaemia), may also point towards MODY.
* **Family History**: A family history of diabetes in successive generations is highly suggestive of MODY. However, some mutations in MODY-associated genes can occur at high frequencies in individuals without a family history of diabetes, highlighting the importance of genetic testing even in such cases.
* **Blood Sugar Tests**: A blood sugar test is the first step toward diagnosing MODY. If the results indicate diabetes, additional tests may be conducted to determine if the condition is MODY or another type of diabetes, such as type 1 or type 2.
* **Genetic Testing**: Genetic testing is crucial for confirming the diagnosis of MODY. It can identify the exact type of MODY by detecting mutations in specific genes. Direct sequencing with sensitivity close to 100% and next-generation sequencing methods can be successfully used to identify MODY gene mutations.3 Genetic testing is recommended for individuals diagnosed with diabetes at a young age (25 years), those with a familial history of diabetes, evidence of endogenous insulin secretion, detectable levels of C-peptide, and negative antibody results.
* **C-Peptide Test**: The C-peptide test measures the level of C-peptide, a marker of endogenous insulin production. In MODY, C-peptide levels are typically in the normal range, whereas in type 1 diabetes, C-peptide levels are low or undetectable.
* **Autoantibody Testing**: Beta-cell antibodies, such as glutamic acid decarboxylase (GAD) antibodies, are usually negative in MODY, whereas they are positive in type 1 diabetes.
* **Age of Onset**: The age of onset is another important factor. MODY is typically diagnosed before the age of 25 years, although some subtypes may present later in life.

These methods collectively help in accurately diagnosing MODY, which is essential for determining the appropriate treatment and management strategies.

**TREATMENT OPTIONS**

MODY is usually treated by medication, and eventually insulin injections. Treatment will be more effective for those who are a healthy weight.

MANAGEMENT

At presentation of diabetes, if the differential diagnosis includes T1DM, close monitoring of blood glucose with ketones and regular contact is required. Insulin may be commenced for safety while investigation results are awaited. A referral to a monogenic diabetes clinic should be made early (for example, once antibodies are known to be negative) as only a genetic test gives a definitive diagnosis and allows firm treatment decisions to be made.

A small dose of a SU is the recommended first-line treatment in HNF1A-/HNF4A-MODY. The typical starting dose close to onset of diabetes is 20 mg of gliclazide or 1.25 mg of glibenclamide once a day. Most patients respond well to this treatment, with HbA1c remaining at target for many years. There is no evidence base for second-line treatment, but metformin is a sensible choice, followed by other oral agents for T2DM. The only exception for HNF1A-MODY would be to avoid sodium/glucose cotransporter 2 (SGLT2) inhibitors such as dapagliflozin, as HNF1A deficiency already decreases SGLT2 expression. Patients with HNF1B-MODY are not sensitive to SUs and usually require insulin earlier than other subtypes of MODY. No specific treatment is recommended for GCK-MODY, and treatment that has been previously commenced can be stopped. Observational studies have shown that those with GCK-MODY do not develop diabetic complications and HbA1c does not change with pharmacological treatment.

In any type of MODY, diabetic relatives should be offered genetic testing for the same mutation as they could also benefit from treatment changes. Unaffected first-degree family members should be offered diabetes screening.

**POSSIBLE COMPLICATIONS**

Maturity-onset diabetes of the young (***MODY***) can lead to various complications, similar to those seen in other forms of diabetes, including type 1 and type 2 diabetes. These complications arise due to chronic hyperglycemia and can affect multiple organs and systems in the body. The specific complications may vary depending on the subtype of MODY and the individual's overall health.

Common complications associated with MODY include:

* **Diabetic retinopathy**: Damage to the light-sensitive tissue at the back of the eye, which can lead to vision loss and eventual blindness.
* **Diabetic nephropathy**: Kidney damage that can progress to kidney failure and end-stage renal disease (ESRD).
* **Neuropathy**: Nerve damage that can cause pain, tingling, or numbness, particularly in the extremities.
* **Cardiovascular disease**: Increased risk of heart disease, stroke, and other cardiovascular complications due to damage to blood vessels.

Some subtypes of MODY, such as HNF1A-MODY (MODY 3), are associated with a higher risk of developing noncancerous liver tumors known as hepatocellular adenomas. Additionally, individuals with certain subtypes of MODY, such as HNF1-beta MODY, may experience renal cysts, uterine abnormalities, and gout.

It is important to note that the risk and severity of complications can vary depending on the specific genetic mutation causing MODY and the individual's ability to maintain good glycemic control. Regular monitoring and appropriate management of blood glucose levels are essential to minimize the risk of these complications.

**What Are the Complications?**

Like other types of diabetes, MODY causes high blood sugar levels. If you don't get treatment, over time it can lead to complications like:

* Nerve damage
* Heart disease
* Eye damage, including blindness
* Foot problems
* Skin problems such as infections

**PREVENTION TIPS**

Maturity-onset diabetes of the young (MODY) is a type of monogenic diabetes caused by mutations in specific genes, and while it cannot be completely prevented, certain measures can help manage the condition and reduce the risk of complications. One of the key strategies is maintaining a healthy lifestyle, particularly focusing on weight management. Obesity can exacerbate the symptoms of MODY, and an obese individual with a MODY gene mutation may develop diabetes symptoms sooner than someone of normal weight. Therefore, adopting a healthy diet and regular physical activity can help delay the onset of symptoms and improve overall health.

Additionally, early diagnosis and appropriate treatment are crucial. Genetic testing can identify MODY, allowing for tailored management strategies. For instance, some forms of MODY, such as HNF1A-MODY, are highly responsive to sulfonylureas, which can effectively control blood glucose levels without the need for insulin. **Regular monitoring of blood glucose levels and adherence to prescribed treatments** can also help in maintaining good glycemic control and preventing long-term complications such as kidney disease, retinopathy, and cardiovascular issues.

In summary, while MODY cannot be entirely prevented due to its genetic nature, **maintaining a healthy lifestyle, managing weight, and seeking early diagnosis and treatment** can significantly help in managing the condition and reducing the risk of complications.

**OUTLOOK / PROGNOSIS**

MODY 2 (GCK) patients generally have a good prognosis as a result of the relatively mild hyperglycemia and low complication rates.

MODY 3 (HNF1A) patients have similar complication rates and prognosis to type 1 and type 2 diabetes mellitus. This is the case with most subtypes of MODY, with the exception of MODY 2, which has the best prognosis.

MODY 5 (HNF1B) patients have a propensity of developing end-stage kidney disease requiring renal replacement therapy independent of diabetic nephropathy. This is because the affected gene is involved in the organogenesis of multiple organs, including the kidneys.

**WHEN TO SEE A DOCTOR / RED FLAG**

Symptoms of MODY may develop gradually. If you have the symptoms described above, make an appointment with your primary care provider. You may also need to see an endocrinologist who specializes in diabetes.

**DIFFERENTIAL DIAGNOSIS**

* Type 1 diabetes mellitus
* Type 2 diabetes mellitus
* Chronic pancreatitis
* Cystic fibrosis
* Diabetic ketoacidosis (DKA)
* Diabetic nephropathy
* Disorders of target tissues
* Endocrine disorders
* Glucocorticoids
* Insulin resistance
* Lead nephropathy
* Non-Diabetic glycosuria
* Renal glycosuria
* Secondary hyperglycemia

**Type 1 Diabetes Mellitus**: An autoimmune disorder characterized by destruction of insulin-producing pancreatic beta cells, leading to absolute insulin deficiency, hyperglycemia, and symptoms such as polyuria, polydipsia, polyphagia, weight loss, and risk of diabetic ketoacidosis. It typically presents in childhood or young adulthood and requires lifelong insulin therapy

**Type 2 Diabetes Mellitus**: A metabolic disorder characterized by insulin resistance and relative insulin deficiency, leading to chronic hyperglycemia. It is associated with obesity, sedentary lifestyle, and genetic predisposition, often presenting in adulthood with symptoms like fatigue, blurred vision, and slow-healing wounds

**Chronic Pancreatiti**s: A progressive inflammatory disease of the pancreas causing irreversible damage, leading to fibrosis, exocrine insufficiency, and often diabetes due to destruction of islet cells.

**Cystic Fibrosis**: A genetic disorder causing thick, sticky mucus production affecting lungs and pancreas, leading to recurrent infections and pancreatic insufficiency, including diabetes due to islet cell damage.

**Diabetic Ketoacidosis** (DKA): An acute, life-threatening complication of diabetes (mostly type 1) characterized by hyperglycemia, ketosis, metabolic acidosis, dehydration, and electrolyte imbalance, presenting with nausea, vomiting, abdominal pain, and altered consciousness

**Diabetic Nephropathy**: A microvascular complication of diabetes causing progressive kidney damage, proteinuria, hypertension, and eventual chronic kidney disease.

**Disorders of Target Tissues**: Conditions where insulin resistance or hormone dysfunction affects tissues such as muscle, fat, and liver, impairing glucose uptake and metabolism.

**Endocrine Disorders**: Diseases involving hormone-producing glands, including diabetes, thyroid diseases, adrenal disorders, and pituitary dysfunction.

**Glucocorticoid**s: Steroid hormones that regulate metabolism and immune response; excess glucocorticoids can induce insulin resistance and hyperglycemia.

**Insulin Resistance**: A pathological condition where target tissues have reduced responsiveness to insulin, leading to impaired glucose uptake and hyperglycemia, often preceding type 2 diabetes.

**Lead Nephropathy**: Kidney damage caused by chronic lead exposure, leading to tubular dysfunction and possible secondary effects on glucose metabolism.

**Non-Diabetic Glycosuria**: The presence of glucose in urine despite normal blood glucose levels, often due to renal tubular dysfunction.

**Renal Glycosuria**: A benign condition caused by impaired renal tubular glucose reabsorption, resulting in glucose excretion in urine without hyperglycemia.

**Secondary Hyperglycemia**: Elevated blood glucose levels due to causes other than primary diabetes, such as endocrine disorders (e.g., Cushing's syndrome), medications, or pancreatic diseases.

**EPIDEMIOLOGY**

MODY accounts for less than 5.0% of all patients with diabetes mellitus (DM). It is now thought that 6.5% of children with antibody-negative diabetes have a form of MODY. The onset of MODY is typically between the ages of 10 to 40 years old. Patients with MODY share genotypic features of both type 1 and type 2 diabetes and are often misdiagnosed as having either type 1 diabetes or type 2 diabetes. Therefore, as the frequency of MODY diagnosis increases, the prevalence may prove to be higher. While MODY has been described predominantly in Caucasian populations, it has also been reported in other races, such as Asian Indians in South Africa by Jialal et a

MODY is estimated to account for 1 to 3 percent of all cases of diabetes.

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**DIABETIC MYOPATHY**

**DEFINITION / DESCRIPTION**

Diabetic myopathy is a condition that affects people with diabetes, specifically those with type 2 diabetes. It is characterized by muscle weakness, wasting, and pain. This condition can affect any muscle group in the body, but it is most commonly seen in the hips, legs, and feet. In this article, we will explore the causes, symptoms, and treatment options for diabetic myopathy.

## **CAUSES OF DIABETIC MYOPATHY**

The exact cause of diabetic myopathy is not fully understood. However, it is believed to be a result of long-term high blood sugar levels. High blood sugar levels can damage the blood vessels that supply the muscles with oxygen and nutrients. This damage can lead to muscle weakness, wasting, and pain.

In addition to high blood sugar levels, other factors can contribute to diabetic myopathy. These include:

1. Poor blood circulation: High blood sugar levels can damage the blood vessels that supply the muscles with oxygen and nutrients. This can lead to poor circulation, which can contribute to muscle weakness and wasting.
2. Neuropathy: Diabetes can cause nerve damage, which can lead to muscle weakness and wasting. This is known as diabetic neuropathy.
3. Inactivity: People with diabetes may be less active due to pain or other symptoms, which can contribute to muscle weakness and wasting.

**RISK FACTORS**

Diabetic myopathy is a complication of diabetes that affects skeletal muscle, and several risk factors have been identified. **Poor glycemic control** is a significant risk factor, as elevated hemoglobin A1C levels (greater than 7%) are commonly associated with the development of diabetic myopathy. The longer a person has diabetes, especially if blood sugar is not well controlled, the higher the risk of developing this condition. Additionally, the presence of other diabetes-related complications, such as nephropathy, neuropathy, and retinopathy, increases the likelihood of diabetic myopathy.

Other risk factors include **being overweight, having a high body mass index (BMI) of 25 or more, smoking, and having high blood pressure or high cholesterol**. These factors contribute to the overall burden of diabetes and its complications, including muscle damage.

In addition, studies have shown that skeletal muscle dysfunction and type 2 diabetes share common factors such as oxidative stress and dyslipidemia, which further increase the risk of developing diabetic myopathy. The impact of diabetes on skeletal muscle progenitor cells, which are essential for muscle repair and regeneration, also plays a role in the development of this condition.

Overall, the risk factors for diabetic myopathy are closely linked to the management of diabetes and the presence of related comorbidities.

## **SYMPTOMS OF DIABETIC MYOPATHY**

The symptoms of diabetic myopathy can vary from person to person. However, some common symptoms include:

### **Dysarthria:**

This is a motor speech disorder that is primarily characterized by difficulty expressing and forming words. It is mainly a result of pathology or injury of the nervous system due to diabetes myopathy. The muscles of the respiratory system, face, and mouth move very slowly or do not move at all.

However, severity depends on the areas of the muscular and nervous systems that have been affected. Symptoms include; a slow or rapid rate of speech with a mumbling quality, limited lip, jaw, and tongue movement, changes in vocal quality, abnormal intonation, drooling, and chewing or swallowing difficulty.

### **Muscle weakness:**

This is the most common symptom of diabetic myopathy. Muscle weakness occurs at any age and it can either affect the entire portion or just a portion of the body. Diabetic myopathy affects the nervous system resulting in muscle weakness. It occurs in conjunction with symptoms such as paresthesia, pain, or fever-like symptoms. Complications of muscle weakness vary depending on the stage of diabetic myopathy and they include contractures and muscle atrophy.

### **Muscle wasting:**

Diabetic myopathy can lead to muscle wasting, also known as muscle atrophy. Muscle atrophy is the gradual loss of muscle tissue, which can result in decreased muscle strength and mobility.

### **Muscle pain:**

Diabetic myopathy might also cause pain and aches in the muscles. This may be due to muscle cramps, muscle strains, injury, fatigue, circulatory disorders, and stress. The changes in muscle can be detected with biochemical or molecular techniques or with functional testing mainly because this condition is primarily associated with loss of strength and muscle mass.

### **Ataxia:**

As diabetes progresses, sufferers may also experience failure of voluntary muscle coordination. It implies dysfunction of some parts of the nervous system that usually coordinate movement. Ataxia can cause a person to have difficulty with balance, walking, and other movements that require precise coordination of muscle activity.

## **Foot drop:**

Foot drop is a condition where a person is unable to lift the front part of their foot, which can cause difficulty in walking and increase the risk of falling. A Foot drop due to diabetic myopathy is a condition caused by nerve damage that affects the muscles responsible for lifting the front part of the foot.

### **TREATMENT OPTIONS FOR DIABETIC MYOPATHY**

There are several treatment options available for diabetic myopathy. The most effective treatment will depend on the severity of the condition and the individual’s overall health.

1. Blood sugar control: The most important treatment for diabetic myopathy is to control blood sugar levels. This can be done through lifestyle changes such as diet and exercise, and medications such as insulin or oral hypoglycemic agents.
2. Exercise: Exercise can help improve muscle strength and flexibility. People with diabetic myopathy should engage in regular physical activity, such as walking, swimming, or resistance training.
3. Physical therapy: Physical therapy can help improve muscle strength, flexibility, and coordination. It may also include stretches and massages to help alleviate muscle pain.
4. Pain management: Pain medication may be prescribed to help manage muscle pain and cramping.
5. Surgery: In some cases, surgery may be necessary to repair or replace damaged muscles.

### **How can you help prevent diabetic leg pain?**

Prevention of diabetic myopathy involves maintaining good blood sugar control and keeping active with regular physical activity. People with diabetes should aim to keep their blood sugar levels within a healthy range, as this can help prevent muscle damage and other complications.

Good blood sugar levels for the average person with diabetes should be between 60.8 mg/dl and 120.4 mg/dl ( 3.4 to 6.7mmol/L) depending on the time of day and amount eaten at the last meal.

They should also engage in regular physical activity, such as walking, swimming, or resistance training. This can help improve muscle strength, flexibility, and coordination.

In addition to these lifestyle changes, people with diabetes should have regular check-ups with their healthcare provider. This can help detect and treat any complications early on, including diabetic myopathy.

Diabetic myopathy is one of the leading causes of disability among diabetics. Therefore, regardless of how mild these signs and symptoms of diabetic myopathy are, they should never be ignored. In addition to the blood glucose control measures, interventions to improve strength and muscle mass in these patients should also be undertaken.

**PREVENTION TIPS**

Diabetic myopathy refers to the muscle weakness and dysfunction that can occur in individuals with diabetes. Prevention of diabetic myopathy involves managing underlying risk factors and adopting lifestyle changes that can help maintain muscle mass and function. Tightly managing blood sugar levels and leading a healthy lifestyle are key to preventing diabetic myopathy. Additionally, physical training has been identified as an important component in improving insulin sensitivity and muscle glucose uptake, which can help prevent the development of diabetic myopathy. Regular exercise, including moderate strength training, can contribute to the gain of peripheral muscle strength and improve overall metabolic capacity. Furthermore, maintaining a healthy weight, avoiding smoking, and managing blood pressure and cholesterol levels are also important in preventing diabetic myopathy. It is also important to note that chronic hyperglycemia can lead to lung functional changes, which can influence exercise tolerance, highlighting the importance of comprehensive management of diabetes to prevent complications such as diabetic myopathy

**POSSIBLE COMPLICATIONS**

Diabetic myopathy, a complication of diabetes mellitus, can lead to various serious health issues. It is characterized by reduced physical capacity, strength, and muscle mass. The condition can contribute to the progression of additional diabetic complications due to the vital importance of skeletal muscle for physical and metabolic well-being.

Complications associated with diabetic myopathy include **muscle inflammation, ischemia, hemorrhage, infarction, necrosis, fibrosis, and fatty atrophy**. Diabetic muscle infarction, a specific form of diabetic myopathy, is generally self-limiting, but its occurrence can portend a poor disease prognosis due to macrovascular complications associated with diabetes, including myocardial infarction and stroke.

Moreover, diabetic myopathy often coexists with other diabetic complications such as nephropathy and neuropathy, which are significantly more prevalent among patients with diabetic myopathy compared to the general diabetic population. These complications can lead to further health deterioration, including the risk of limb amputation due to poor wound healing and increased susceptibility to infections.

In addition, the impact of diabetic myopathy on skeletal muscle progenitor cells can **impair muscle repair and regeneration, exacerbating the overall decline in muscle function**. This can result in a reduced quality of life and increased morbidity for individuals affected by the condition.

**OUTLOOK / PROGNOSIS**

Diabetic myopathy refers to the deterioration of muscle mass and function in individuals with diabetes, and its prognosis is influenced by various factors. The condition is often associated with reduced mitochondrial function, impaired lipid oxidation, and excessive production of reactive oxygen species, which contribute to muscle weakness and functional decline.

The prognosis of diabetic myopathy can be improved through non-pharmacological interventions such as cardiopulmonary rehabilitation involving combined exercise programs. These programs have been shown to improve antioxidant capacity, attenuate oxidative stress, and enhance functional improvements, making them a cornerstone of treatment strategies.3 Additionally, moderate strength training in type 2 diabetes mellitus (T2DM) can contribute to the gain of peripheral muscle strength, although further research is needed to fully understand the impact on functional capacity and the optimal prescription of physical exercise for this condition.

Despite these interventions, the prognosis remains challenging, as diabetic myopathy can lead to additional complications due to the key role of skeletal muscle in locomotion and glucose homeostasis. Large-scale studies have shown that elderly individuals with long-term T2DM experience accelerated loss of muscle mass and strength compared to healthy counterparts.

In summary, while the prognosis of diabetic myopathy is complex, early intervention with exercise and rehabilitation can significantly improve outcomes. However, more research is needed to develop targeted therapies and better understand the underlying mechanisms.

**DIFFERENTIAL DIAGNOSIS**

* Necrotizing Fasciitis: A life-threatening soft tissue infection characterized by rapidly progressing inflammation and systemic signs such as fever and elevated white blood cell count. Unlike diabetic myopathy, it often presents with severe cellulitis and systemic toxicity
* Pyomyositis: Bacterial infection of muscle causing abscess formation. It usually presents with localized muscle swelling, pain, and systemic infection signs, which may help differentiate it from diabetic myopathy
* Muscle Abscess: Localized collection of pus within muscle, often with systemic infection signs, distinguishable by imaging and clinical presentation.
* Hemorrhage into Muscle: May mimic diabetic muscle infarction but usually has a history of trauma or bleeding disorders.
* Other Forms of Myositis: Inflammatory muscle diseases such as polymyositis or dermatomyositis can resemble diabetic myopathy but have distinct clinical and laboratory features
* Diabetic Amyotrophy: A diabetic neuropathic syndrome causing proximal muscle weakness and pain, but primarily due to nerve involvement rather than primary muscle pathology
* Muscle Infarction (Diabetic Muscle Infarction): Often considered a manifestation of diabetic myopathy, characterized by spontaneous muscle infarction and necrosis, typically in the thigh or calf muscles

**EPIDEMIOLOGY**

Diabetic myopathy is a condition that affects the muscles of individuals with diabetes, and its epidemiology shows varying prevalence rates. **Reported prevalence varies around 10–90%**, which is marked variable and unreliable. In a study, it was found that diabetic myopathy may occur more frequently in patients with type 2 diabetes than previously reported. Specifically, in a population studied, 14 (88%) patients had type 2 diabetes, and two (12%) had type 1 diabetes. Additionally, the condition is often associated with other complications such as nephropathy, neuropathy, and retinopathy, which were present in 50%, 50%, and 38% of cases, respectively.

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**HYPOGLYCEMIA**

*ALTERNATIVE NAMES*: Hypoglycemia is also known as “Hypoglycaemia”, “hypoglycæmia”, “low blood sugar”, and “low blood glucose”.

**DEFINITION /DESCRIPTION**

Hypoglycemia is a condition in which your blood sugar (glucose) level is lower than the standard range. Glucose is your body's main energy source.

Hypoglycemia is often related to diabetes treatment. But other drugs and a variety of conditions — many rare — can cause low blood sugar in people who don't have diabetes.

Hypoglycemia needs immediate treatment. For many people, a fasting blood sugar of 70 milligrams per deciliter (mg/dL), or 3.9 millimoles per liter (mmol/L), or below should serve as an alert for hypoglycemia. But your numbers might be different. Ask your healthcare provider.

Treatment involves quickly getting your blood sugar back to within the standard range either with a high-sugar food or drink or with medication. Long-term treatment requires identifying and treating the cause of hypoglycemia.

**CAUSES**

Hypoglycemia occurs when your blood sugar (glucose) level falls too low for bodily functions to continue. There are several reasons why this can happen. The most common reason for low blood sugar is a side effect of medications used to treat diabetes.

### **Blood sugar regulation**

When you eat, your body breaks down foods into glucose. Glucose, the main energy source for your body, enters the cells with the help of insulin — a hormone produced by your pancreas. Insulin allows the glucose to enter the cells and provide the fuel your cells need. Extra glucose is stored in your liver and muscles in the form of glycogen.

When you haven't eaten for several hours and your blood sugar level drops, you will stop producing insulin. Another hormone from your pancreas called glucagon signals your liver to break down the stored glycogen and release glucose into your bloodstream. This keeps your blood sugar within a standard range until you eat again.

Your body also has the ability to make glucose. This process occurs mainly in your liver, but also in your kidneys. With prolonged fasting, the body can break down fat stores and use products of fat breakdown as an alternative fuel.

### **Possible causes, with diabetes**

If you have diabetes, you might not make insulin (type 1 diabetes) or you might be less responsive to it (type 2 diabetes). As a result, glucose builds up in the bloodstream and can reach dangerously high levels. To correct this problem, you might take insulin or other medications to lower blood sugar levels.

But too much insulin or other diabetes medications may cause your blood sugar level to drop too much, causing hypoglycemia. Hypoglycemia can also occur if you eat less than usual after taking your regular dose of diabetes medication, or if you exercise more than you typically do.

### **Possible causes, without diabetes**

Hypoglycemia in people without diabetes is much less common. Causes can include:

* **Medications.** Taking someone else's oral diabetes medication accidentally is a possible cause of hypoglycemia. Other medications can cause hypoglycemia, especially in children or in people with kidney failure. One example is quinine (Qualaquin), used to treat malaria.
* **Excessive alcohol drinking.** Drinking heavily without eating can keep the liver from releasing glucose from its glycogen stores into the bloodstream. This can lead to hypoglycemia.
* **Some critical illnesses.** Severe liver illnesses such as severe hepatitis or cirrhosis, severe infection, kidney disease, and advanced heart disease can cause hypoglycemia. Kidney disorders also can keep your body from properly excreting medications. This can affect glucose levels due to a buildup of medications that lower blood sugar levels.
* **Long-term starvation.** Hypoglycemia can occur with malnutrition and starvation when you don't get enough food, and the glycogen stores your body needs to create glucose are used up. An eating disorder called anorexia nervosa is one example of a condition that can cause hypoglycemia and result in long-term starvation.
* **Insulin overproduction.** A rare tumor of the pancreas (insulinoma) can cause you to produce too much insulin, resulting in hypoglycemia. Other tumors also can result in too much production of insulin-like substances. Unusual cells of the pancreas that produce insulin can result in excessive insulin release, causing hypoglycemia.
* **Hormone deficiencies.** Certain adrenal gland and pituitary tumor disorders can result in an inadequate number of certain hormones that regulate glucose production or metabolism. Children can have hypoglycemia if they have too little growth hormone.

### **Hypoglycemia after meals**

Hypoglycemia usually occurs when you haven't eaten, but not always. Sometimes hypoglycemia symptoms occur after certain meals, but exactly why this happens is uncertain.

This type of hypoglycemia, called reactive hypoglycemia or postprandial hypoglycemia, can occur in people who have had surgeries that interfere with the usual function of the stomach. The surgery most commonly associated with this is stomach bypass surgery, but it can also occur in people who have had other surgeries.

**RISK FACTORS**

Hypoglycemia, or low blood sugar, has several risk factors that vary depending on the population and context. In adults with diabetes, risk factors include the use of medications such as insulin or sulfonylureas, which can cause hypoglycemia if overused or improperly dosed. Impaired awareness of hypoglycemia due to repeated episodes, dietary issues such as skipping meals or having insufficient carbohydrate intake, and physical activity that is increased or unplanned without adjusting food intake or medication are also significant risk factors.5 Alcohol consumption can further impair the liver's ability to produce glucose, contributing to hypoglycemia.

In inpatient settings, risk factors for hypoglycemia include **advanced age, comorbid diseases, type of diabetes, a previous history of hypoglycemia, body mass index, and the type of hyperglycemia therapy administered**. Other factors such as inadequate glucose monitoring, unclear or unreadable physician instructions, limited health personnel, limited facilities, prolonged fasting, and incompatibility between nutritional intake and therapy administered can also contribute to inpatient hypoglycemia. Additionally, unexpected nutritional interruption, prior hypoglycemia during a hospital visit, and asynchrony of nutrition delivery and insulin administration are powerful risk factors.

For neonates, risk factors for hypoglycemia include caesarean section, small gestational age, gestational diabetes, gestational hypertension, and respiratory distress syndrome. In the general population, causes of hypoglycemia include consuming too few carbohydrates, fasting, or drinking too much alcohol.

**SIGNS / SYMPTOMS**

If blood sugar levels become too low, hypoglycemia signs and symptoms can include:

* Looking pale
* Shakiness
* Sweating
* Headache
* Hunger or nausea
* An irregular or fast heartbeat
* Fatigue
* Irritability or anxiety
* Difficulty concentrating
* Dizziness or lightheadedness
* Tingling or numbness of the lips, tongue or cheek

As hypoglycemia worsens, signs and symptoms can include:

* Confusion, unusual behavior or both, such as the inability to complete routine tasks
* Loss of coordination
* Slurred speech
* Blurry vision or tunnel vision
* Nightmares, if asleep

Severe hypoglycemia may cause:

* Unresponsiveness (loss of consciousness)
* Seizures

**DIAGNOSIS METHODS**

If you have hypoglycemia symptoms, your health care provider will likely conduct a physical exam and review your medical history.

If you use insulin or another diabetes medication to lower your blood sugar, and you have signs and symptoms of hypoglycemia, test your blood sugar levels with a blood glucose meter. If the result shows low blood sugar (under 70 mg/dL), treat according to your diabetes treatment plan.

Keep a record of your blood sugar testing results and how you treated low blood sugar levels so that your healthcare provider can review the information to help adjust your diabetes treatment plan.

If you don't use medications known to cause hypoglycemia, your health care provider will want to know:

* **What were your signs and symptoms?** If you don't have signs and symptoms of hypoglycemia during your initial visit with your healthcare provider, he or she might have you fast overnight or longer. This will allow low blood sugar symptoms to occur so that a diagnosis can be made. It's also possible that you'll need to do an extended fast — up to 72 hours — in a hospital setting.
* **What is your blood sugar level when you're having symptoms?** Your health care provider will draw a blood sample to be analyzed in the lab. If your symptoms occur after a meal, the blood sugar tests may be done after you eat.
* **Do your symptoms disappear when blood sugar levels increase?**

**TREATMENT METHODS**

### **Immediate hypoglycemia treatment**

If you have hypoglycemia symptoms, do the following:

* **Eat or drink 15 to 20 grams of fast-acting carbohydrates.** These are sugary foods or drinks without protein or fat that are easily converted to sugar in the body. Try glucose tablets or gel, fruit juice, regular (not diet) soda, honey, or sugary candy.
* **Recheck blood sugar levels 15 minutes after treatment.** If blood sugar levels are still under 70 mg/dL (3.9 mmol/L), eat or drink another 15 to 20 grams of fast-acting carbohydrate, and recheck your blood sugar level again in 15 minutes. Repeat these steps until the blood sugar is above 70 mg/dL (3.9 mmol/L).
* **Have a snack or meal.** Once your blood sugar is back in the standard range, eating a healthy snack or meal can help prevent another drop in blood sugar and replenish your body's glycogen stores.

### **Immediate treatment of severe hypoglycemia**

Hypoglycemia is considered severe if you need help from someone to recover. For example, if you can't eat, you might need a glucagon injection or intravenous glucose.

In general, people with diabetes who are treated with insulin should have a glucagon kit for emergencies. Family and friends need to know where to find the kit and how to use it in case of emergency.

If you're helping someone who is unconscious, don't try to give the person food or drink. If there's no glucagon kit available or you don't know how to use it, call for emergency medical help.

### **Treatment of an underlying condition**

Preventing recurrent hypoglycemia requires your health care provider to identify the condition causing hypoglycemia and treat it. Depending on the cause, treatment may involve:

* **Nutrition counseling.** A review of eating habits and food planning with a registered dietitian may help reduce hypoglycemia.
* **Medications.** If a medication is the cause of your hypoglycemia, your health care provider will likely suggest adding, changing or stopping the medication or adjusting the dosage.
* **Tumor treatment.** A tumor in your pancreas is typically treated by surgical removal of the tumor. In some cases, medication to control hypoglycemia or partial removal of the pancreas is necessary.

**POSSIBLE COMPLICATION**

Untreated hypoglycemia can lead to:

* Seizure
* Coma
* Death

Hypoglycemia can also cause:

* Dizziness and weakness
* Falls
* Injuries
* Motor vehicle accidents
* Greater risk of dementia in older adults

### **Hypoglycemia unawareness**

Over time, repeated episodes of hypoglycemia can lead to hypoglycemia unawareness. The body and brain no longer produce signs and symptoms that warn of a low blood sugar, such as shakiness or irregular heartbeats (palpitations). When this happens, the risk of severe, life-threatening hypoglycemia increases.

If you have diabetes, recurring episodes of hypoglycemia and hypoglycemia unawareness, your health care provider might modify your treatment, raise your blood sugar level goals and recommend blood glucose awareness training.

A continuous glucose monitor (CGM) is an option for some people with hypoglycemia unawareness. The device can alert you when your blood sugar is too low.

### **Undertreated diabetes**

If you have diabetes, episodes of low blood sugar are uncomfortable and can be frightening. Fear of hypoglycemia can cause you to take less insulin to ensure that your blood sugar level doesn't go too low. This can lead to uncontrolled diabetes. Talk to your health care provider about your fear, and don't change your diabetes medication dose without discussing changes with your healthcare provider.

**PREVENTION TIPS**

Follow the diabetes management plan you and your health care provider have developed. If you're taking new medications, changing your eating or medication schedules, or adding new exercise, talk to your health care provider about how these changes might affect your diabetes management and your risk of low blood sugar.

Learn the signs and symptoms you experience with low blood sugar. This can help you identify and treat hypoglycemia before it gets too low. Frequently checking your blood sugar level lets you know when your blood sugar is getting low.

A continuous glucose monitor (CGM) is a good option for some people. A CGM has a tiny wire that's inserted under the skin that can send blood glucose readings to a receiver. If blood sugar levels are dropping too low, some CGM models will alert you with an alarm.

Some insulin pumps are now integrated with CGMs and can shut off insulin delivery when blood sugar levels are dropping too quickly to help prevent hypoglycemia.

Be sure to always have a fast-acting carbohydrate with you, such as juice, hard candy or glucose tablets so that you can treat a falling blood sugar level before it dips dangerously low.

### **If you don't have diabetes**

For recurring episodes of hypoglycemia, eating frequent small meals throughout the day is a stopgap measure to help prevent blood sugar levels from getting too low. However, this approach isn't advised as a long-term strategy. Work with your health care provider to identify and treat the cause of hypoglycemia.

**OUTLOOK / PROGNOSIS**

Hypoglycemia, or low blood sugar, can have varying prognoses depending on the underlying cause and the severity of the condition. In patients with diabetes, hypoglycemia is associated with increased short- and long-term mortality, particularly when it is severe or recurrent. A study found that patients with hypoglycemia, whether related to insulin use or not, had higher mortality rates compared to non-insulin-treated controls. For example, the all-cause mortality at the end of follow-up was 31.9%, with higher rates observed in patients with severe hypoglycemia.

In contrast, reactive hypoglycemia, which is often linked to dietary factors, **typically has a very good prognosis**, with symptoms often improving over time and minimal long-term complications. Treatment usually involves dietary changes, and mortality is not observed in these cases.

For individuals with diabetes, recognizing and managing hypoglycemia is crucial. Symptoms such as fast heartbeat, nervousness, irritability, and confusion are common, and prompt treatment with fast-acting carbohydrates is essential to prevent severe hypoglycemia. Severe hypoglycemia can be life-threatening and may require the use of a glucagon injection.

Overall, the prognosis for hypoglycemia depends on the underlying cause, the frequency and severity of episodes, and the effectiveness of management strategies.

The prognosis of hypoglycemia depends on the cause of this condition, its severity, and its duration. If the cause of fasting hypoglycemia is identified and treated early, the prognosis is excellent.

If the cause of hypoglycemia is not curable, such as an inoperable malignant tumor, the long-term prognosis is poor. However, note that these tumors may progress rather slowly. Severe and prolonged hypoglycemia can be life threatening and may be associated with increased mortality in patients with diabetes.

If the patient has reactive hypoglycemia, symptoms often spontaneously improve over time, and the long-term prognosis is very good. Reactive hypoglycemia is often treated successfully with dietary changes and is associated with minimal morbidity. Mortality is not observed. Untreated reactive hypoglycemia may cause significant discomfort to the patient, but long-term sequelae are not likely.

A study by Boucai et al found that drug-associated hypoglycemia was not associated with increased mortality risk among patients admitted to general wards. This suggests that hypoglycemia may be a marker of disease burden and not a direct cause of death.

**DIFFERENTIAL DIAGNOSIS**

If hypoglycemia is confirmed, the focus should be on correcting the hypoglycemia and identifying the underlying cause. In the workup of hypoglycemia, history should include medication and dietary adherence, medication changes, suspicion for acute kidney injury, or intentional/unintentional weight changes, especially weight loss.

Hypoglycemia, defined as a venous blood glucose level of less than 55 mg/dl (3 mmol/L), can be classified into insulin-mediated and insulin-independent causes. The differential diagnosis of hypoglycemia includes a wide range of conditions, both diabetic and non-diabetic.

In diabetic patients, hypoglycemia is commonly due to iatrogenic causes such as exogenous insulin or insulin secretagogues (e.g., sulphonylureas and glinides). In non-diabetic patients, hypoglycemia can be caused by various factors, including:

1. **Insulin-mediated (hyperinsulinism)**:
   * **Insulinoma**: A rare pancreatic tumor that secretes excess insulin.
   * **Islet cell hyperplasia (nesidioblastosis)**: A condition characterized by excessive proliferation of insulin-secreting cells.
   * **Iatrogenic hyperinsulinism**: Caused by the use of exogenous insulin or insulin secretagogues.
2. **Insulin-independent hypoglycemia**:
   * **Alcohol consumption**: Inhibits gluconeogenesis and glycogenolysis, leading to hypoglycemia.
   * **Visceral failure**: Conditions such as liver or renal failure can impair glucose metabolism.
   * **Critical illness**: Severe infections, sepsis, or other critical conditions can lead to hypoglycemia.
   * **Primary adrenal failure**: Deficiency in cortisol can impair glucose regulation.
   * **Anterior pituitary failure**: Deficiency in growth hormone or ACTH can affect glucose homeostasis.
   * **Severe sepsis**: Can lead to hypoglycemia due to altered metabolism.
   * **Cerebral malaria**: A severe form of malaria that can cause hypoglycemia.
   * **Anorexia nervosa**: Malnutrition and altered metabolism can lead to hypoglycemia.
   * **Glycogen storage disease**: Genetic disorders affecting glycogen metabolism.
   * **Post-bariatric surgery**: Conditions such as Roux-en-Y gastric bypass can lead to reactive hypoglycemia.
   * **Mesenchymal tumors with elevated IGF-2 levels**: Tumors that secrete insulin-like growth factor 2 (IGF-2).
   * **Autoimmune hypoglycemia**: Caused by anti-insulin or anti-insulin receptor antibodies.
   * **Drugs**: Many medications, including quinolones, antimalarials, glucagon, lithium, ACE inhibitors, ARBs, and non-selective beta-blockers, can cause hypoglycemia.

In children, hypoglycemia is often due to inborn errors of metabolism (IEM), such as **glycogen storage disease, fatty acid oxidation defects, ketogenesis defects, and gluconeogenesis disorders**. Genetic disorders like galactosaemia and hereditary fructose intolerance can also cause hypoglycemia.

The diagnosis of hypoglycemia is typically based on Whipple's triad: symptoms consistent with hypoglycemia, low blood glucose levels, and resolution of symptoms after glucose administration. Additional diagnostic tests may include measuring insulin and C-peptide levels, assessing for the presence of sulphonylureas, and evaluating for underlying conditions such as insulinoma or other tumors.

In summary, the differential diagnosis of hypoglycemia is broad and includes both diabetic and non-diabetic causes, with a focus on identifying the underlying etiology to guide appropriate management.

**Diagnostic Considerations**

Because the consequences of hypoglycemia can be devastating and an antidote is readily available, diagnosis and treatment must be rapid in any patient with suspected hypoglycemia, regardless of the cause. Patients with no previous history of hypoglycemia require a complete workup to find a potentially treatable disease.

Careful consideration should be given to all patients with diabetes who present with hypoglycemia. New medications, activity changes, and infection should be considered. Early in the course of non–insulin-dependent diabetes, patients may experience episodes of hypoglycemia several hours after meals. The symptoms generally are brief and respond spontaneously.

Conditions such as Jamaican vomiting sickness, ingestion of ethanol-containing mouthwash or cologne (children), gastric surgery, potassium administration during periodic attacks of paralysis, excessive muscular activity, and diarrhea (childhood) can also cause hypoglycemia.

The following should also be considered when evaluating a patient with hypoglycemia:

* Hepatic disease (e.g., hepatic failure, cirrhosis, galactose intolerance, fructose intolerance, glycogen storage diseases)[[25](about:blank)]
* Transient ischemic attacks
* Cardiac dysrhythmia
* Endocrine disorders (e.g., pheochromocytoma, Addison disease, glucagon deficiency, carcinomas, extrahepatic tumors)
* Substance abuse (e.g., cocaine, ethanol, salicylates, beta blockers, pentamidine)
* Hypoglycemic agents (e.g., insulin, oral hypoglycemic agents)
* Nutritional disorders (e.g., prolonged starvation before anesthesia, protein calorie malnutrition, L-leucine-sensitive hypoglycemic defect in children, low-calorie ketogenic diet, renal disease)

**RECENT GUIDELINES OR UPDATES**

#### **Recommendations**

Review history of hypoglycemia at every clinical encounter for all individuals at risk for hypoglycemia, and evaluate hypoglycemic events as indicated.

Screen individuals at risk for hypoglycemia for impaired hypoglycemia awareness at least annually and when clinically appropriate. Refer to a trained health care professional for evidence-based intervention to improve hypoglycemia awareness.

Screen individuals at high risk for hypoglycemia or with severe and/or frequent hypoglycemia for fear of hypoglycemia at least annually and when clinically appropriate. Refer to a trained health care professional for evidence-based intervention.

Clinicians should consider an individual’s risk for hypoglycemia when selecting diabetes medications and glycemic goals.

Use of CGM is beneficial and recommended for individuals at high risk for hypoglycemia.

Glucose is the preferred treatment for the conscious individual with glucose <70 mg/dL (<3.9 mmol/L), although any form of carbohydrate that contains glucose may be used. Avoid using foods or beverages high in fat and/or protein for initial treatment of hypoglycemia. Fifteen minutes after initial treatment, repeat the treatment if hypoglycemia persists.

Glucagon should be prescribed for all individuals taking insulin or at high risk for hypoglycemia. Family, caregivers, school personnel, and others providing support to these individuals should know its location and be educated on how to administer it. Glucagon preparations that do not have to be reconstituted are preferred.

All individuals taking insulin or at risk for hypoglycemia should receive structured education for hypoglycemia prevention and treatment, with ongoing education for those who experience hypoglycemic events.

One or more episodes of level 2 or 3 hypoglycemia should prompt reevaluation of the treatment plan, including de intensifying or switching diabetes medications if appropriate.

Regularly assess cognitive function; if impaired or declining cognition is found, the clinician, person with diabetes, and caregiver should increase vigilance for hypoglycemia.

### **Hypoglycemia Definitions and Event Rates**

Hypoglycemia is often the major limiting factor in the glycemic management of type 1 and type 2 diabetes. Level 1 hypoglycemia is defined as a measurable glucose concentration <70 mg/dL (<3.9 mmol/L) and ≥54 mg/dL (≥3.0 mmol/L). A blood glucose concentration of 70 mg/dL (3.9 mmol/L) has been recognized as a threshold for adrenergic responses to falling glucose in people without diabetes. Symptoms of hypoglycemia include, but are not limited to, shakiness, irritability, confusion, tachycardia, sweating, and hunger . Because many people with diabetes demonstrate impaired counterregulatory responses to hypoglycemia and/or experience impaired hypoglycemia awareness, a measured glucose level <70 mg/dL (<3.9 mmol/L) is considered clinically important, regardless of symptoms. Level 2 hypoglycemia (defined as a blood glucose concentration <54 mg/dL [<3.0 mmol/L]) is the threshold at which neuroglycopenic symptoms begin to occur and requires immediate action to resolve the hypoglycemic event. If an individual has level 2 hypoglycemia without adrenergic or neuroglycopenic symptoms, they likely have impaired hypoglycemia awareness This clinical scenario warrants investigation and review of the treatment plan. Lastly, level 3 hypoglycemia is defined as a severe event characterized by altered mental and/or physical functioning that requires assistance from another person for recovery, irrespective of glucose level.

**EPIDEMIOLOGY**

Hypoglycemia is common with type 1 diabetes, particularly in those patients receiving intensive insulin therapy. Severe hypoglycemic events have reportedly been anywhere between 62 to 320 episodes per 100 patient-years in type 1 diabetes. As opposed to patients who have type 1 diabetes and require insulin therapy exclusively, patients with type 2 diabetes experience hypoglycemia relatively less frequently compared to patients with type 1 diabetes. This can be, in part, due to pharmacotherapies that do not induce hypoglycemia, like metformin. The incidence of hypoglycemia in patients with type 2 diabetes has been reportedly approximately 35 episodes for 100 patient years. There are no reported disparities in incidents based on gender.

Hypoglycemia was observed in 7.7% of admissions. In multivariable analysis, each additional day with hypoglycemia was associated with an increase of 85.3% in the odds of inpatient death (*P* = 0.009) and 65.8% (*P* = 0.0003) in the odds of death within 1 year from discharge. The odds of inpatient death also rose threefold for every 10 mg/dl decrease in the lowest blood glucose during hospitalization (*P* = 0.0058). LOS increased by 2.5 days for each day with hypoglycemia (*P* < 0.0001).

**Frequency of hypoglycemia and patient mortality**

In univariate analysis, inpatient mortality was 2.96% for patients who had at least one hypoglycemic episode during the hospital stay vs. 0.82% for patients who had none (*P* = 0.0013). In a multivariable analysis adjusted for the patients' demographics, expected LOS, Charlson Comorbidity Index, GFR, complications of diabetes, and average blood glucose, the odds of inpatient mortality rose by 85.3% for each additional day with a hypoglycemic episode (*P* = 0.009). The odds of inpatient mortality also increased by 24.8% for each additional point of the Charlson Comorbidity Index (*P* < 0.0001). Patient age, GFR, and insulin secretagogue use during the admission had no significant relationship with inpatient mortality.

Mortality 1 year after discharge was 27.8% for patients who had at least one hypoglycemic episode vs. 14.1% for patients who had no hypoglycemic episodes (*P* < 0.0001). Univariate analysis showed a progressive increase in 1-year mortality from 14.1% for patients with no hypoglycemic episodes to 33.3% for patients with more than two hypoglycemic episodes. Multivariable analysis of this dataset showed a 65.8% increase in mortality 1 year after discharge for each day with a hypoglycemic episode during the admission (*P* = 0.0003) and a 41.8% decrease for patients given insulin secretagogues during their hospitalization (*P* = 0.0007).

The incidence of hypoglycemia in a population is difficult to ascertain. Patients and physicians frequently attribute symptoms (e.g., anxiety, irritability, hunger) to hypoglycemia without documenting the presence of low blood sugar. The true prevalence of hypoglycemia, with blood sugar levels below 50 mg/dL, is generally 5-10% of people presenting with symptoms suggestive of hypoglycemia.

A study by Heidenreich et al of more than 500,000 patients with type 2 diabetes who were hospitalized in the Veterans Affairs health care system found that the rate of patients who had an episode of hypoglycemia fell by 17% between 2016 and 2022 (from 7.4% to 6.3%).

A Brazilian study, by Lamounier et al, found that during a 4-week prospective evaluation period, at least one hypoglycemic event occurred in 91.7% of study patients with type 1 diabetes and in 61.8% of those with type 2 diabetes. This included nocturnal hypoglycemia in 54.0% and 27.4% of patients, respectively; asymptomatic hypoglycemia in 20.6% and 10.6% of patients, respectively; and severe hypoglycemic events in 20.0% and 10.3% of patients, respectively.

Hypoglycemia is a known complication of several medications, and the incidence is difficult to determine with any certainty. In addition, this condition is a known complication of many therapies for diabetes; therefore, the incidence of hypoglycemia in a population of people with diabetes is very different from that in a population of people without diabetes.

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**INSULINOMA**

*ALTERNATIVE NAMES*: insulinoma is also referred to as a “**pancreatic neuroendocrine tumor** (pNET)”.

Some other alternative names include: Insulinoma; Islet cell adenoma; Pancreatic neuroendocrine tumor; Hypoglycemia – insulinoma.

**DEFINITION / DESCRIPTION**

Insulinoma is a rare tumor in your pancreas that releases excess insulin. Insulin is the hormone that helps keep your blood sugar (glucose) at healthy levels.

Insulinoma is one of several pancreatic neuroendocrine tumors (pNETs). These are rare tumors that start in your pancreas’s endocrine cells.

About 85% to 90% of insulinomas are nonmetastatic (“indolent”). This means they don’t spread outside of your pancreas (metastasize). Metastatic (“aggressive”) insulinomas are very rare. Metastatic insulinomas are most likely to spread to your lymph nodes and/or liver.

Insulinomas release insulin. If you have insulinoma, it typically floods your body with insulin. This results in low blood sugar (hypoglycemia). When that happens, you may feel shaky. You may also feel like your heart is racing. In extreme circumstances, you may faint or have seizures.

Your symptoms should improve if you consume something that has sugar (carbohydrates). This could include apple juice, regular soda or a banana.

Experiencing low blood sugar can be scary, especially when you don’t know why it’s happening or when it’ll strike again. Keep snacks on hand and see your healthcare provider as soon as possible.

**CAUSES**

**What causes insulinoma?**

Insulinomas happen when the cells in your pancreas that create insulin multiply uncontrollably. Researchers aren’t sure why that happens.

But they do know that insulinoma can happen alongside multiple endocrine neoplasia type 1 (MEN1). This is an inherited condition in which multiple tumors affect different parts of your endocrine system. About 5% to 10% of insulinoma cases affect people with MEN1.

If one of your first-degree relatives (biological parents and siblings) has a MEN1 diagnosis, talk to your healthcare provider. They can recommend genetic testing that can screen for the condition. If you have MEN1, genetic testing could help detect tumors in their early phases.

**RISK FACTORS**

## **Who is at risk for an insulinoma?**

There are few risk factors for an insulinoma. But women seem to be affected more often than men. Most often, it starts between ages 40 and 60. Some genetic diseases can raise your chance of getting an insulinoma. They are:

* Multiple endocrine neoplasia type 1, which is abnormal tissue growth in the endocrine system
* Von Hippel-Lindau syndrome, an inherited disease that causes tumors and cysts throughout your body
* Other genetic syndromes, such as neurofibromatosis type 1 and tuberous sclerosis
* These tumors are rare.
* They tend to affect people assigned female at birth more often than people assigned male at birth. They most commonly develop in people ages 40 to 60 years.
* Around 10%Trusted Source of insulinomas are cancerous. Cancerous tumors tend to occur more often in people who have multiple endocrine neoplasia type 1. This inherited disease causes tumors in one or more hormonal glands.
* The risk of insulinoma may also be higher for those with Von Hippel-Lindau disease, an inherited condition that causes tumors and cysts to form throughout the body.

## **SIGNS / SYMPTOMS**

Insulinomas mainly cause low blood sugar (hypoglycemia) episodes. Symptoms of low blood sugar include:

* Confusion or difficulty concentrating
* Sweating
* Rapid heartbeat
* Anxiety or irritability

Symptoms of severe low blood sugar include:

* Vision changes, like blurred vision
* Slurred speech
* Clumsiness or difficulty with coordination
* Seizures
* Loss of consciousness

Most people with insulinoma experience low blood sugar when fasting — usually in the morning when they wake up. Some people with insulinoma experience low blood sugar episodes after meals.

Persistent hypoglycemia can interfere with daily activities and cause irreversible brain damage. It can even lead to coma and death. It’s very important to see your healthcare provider if you have low blood sugar symptoms.

Mild symptoms include:

* double vision or blurred vision
* dizziness or lightheadedness
* weakness
* sweating
* hunger
* sudden weight gain
* mood changes
* anxiety and irritability
* confusion
* tremors

**Severe symptoms**

More severe symptoms of an insulinoma can affect the brain. Sometimes, symptoms seem similar to those of the neurological disorder epilepsy.

Symptoms that are seen in more serious cases may include:

* convulsions or seizures
* a rapid heart rate
* difficulty concentrating
* loss of consciousness or coma

**Symptoms of a metastatic insulinoma**

In some cases, insulinomas can get bigger and metastasize (spread) to other parts of the body. When this occurs, you may have the following symptoms:

* abdominal pain
* back pain
* diarrhea
* jaundice

Metastatic insulinomas are considered malignant, or cancerous.

**DIAGNOSIS METHODS**

Insulinomas are rare and can be hard to diagnose. Some data show the average time from the start of symptoms to diagnosis is about a year and a half.

If your healthcare provider thinks you have an insulinoma, you may stay in the hospital for a few days. This is so your healthcare provider can watch your blood sugar and other substances in your blood while you fast. You will not be able to eat or drink anything except water during this time. If you have an insulinoma, you will probably have very low blood sugar levels within 48 hours of starting this test. If your symptoms of low blood sugar have been after meals, you may have a test of your blood sugar and insulin for several hours after a meal.

You may also have imaging tests. These can help find out how big your tumor is and where it's located. A transabdominal ultrasound study is sometimes the first test done. Other tests include endoscopic ultrasound, CT scan, or MRI. If the insulinoma is too small to be seen with these imaging tests, you may need tests that sample blood from multiple areas of your pancreas. These will find where the extra insulin is being released into your bloodstream.

Your healthcare provider will likely suspect you have insulinoma if you have the following signs (called Whipple’s triad):

* Symptoms of low blood sugar
* A documented low blood sugar test result (a fingerstick blood sugar result at least less than 55 mg/dL)
* Improvement of your symptoms when you eat or drink sugar (carbohydrates)

They’ll then recommend some tests to help diagnose insulinoma.

#### **72-hour fast**

Your provider may recommend fasting up to 72 hours to bring on a low blood sugar episode. This is the gold-standard test for diagnosing insulinoma. But you won’t be alone. A provider will monitor you during your fast.

Once you develop low blood sugar symptoms, you’ll get blood tests that check your:

* Blood sugar level
* Insulin level
* Proinsulin level
* C-peptide level
* Beta-hydroxybutyrate level
* Sulfonylurea level

After the blood draw, a provider will give you treatment for the low blood sugar.

The results of these tests can show if too much insulin (hyperinsulinemia) is causing your low blood sugar episodes.

#### **Imaging tests**

If the 72-hour fast points to insulinoma, your provider may suggest one or more of the following imaging tests:

* CT scan
* MRI scan
* Abdominal ultrasound
* Endoscopic ultrasound (EUS)

These tests can assess the tumor’s size and its location in your pancreas. If imaging tests don’t provide enough information, your provider may recommend a selective arterial calcium stimulation test. For this test, a provider measures insulin levels in your hepatic (liver) vein after stimulating arteries in various parts of your pancreas.

**TREATMENT OPTIONS**

How is an insulinoma treated?

Most insulinomas are not cancerous. A surgeon can usually remove it and cure the condition. This may be done using a laparoscope. In laparoscopy, the surgeon makes small incisions and uses special small tools to remove the tumor. If your healthcare provider thinks that surgery would not be a good option for you, there are other options. These would help the symptoms of hypoglycemia. For example, you may need to eat small, frequent meals and take certain medicines to fight the effects of the excess insulin.

While you are waiting for your surgery, you may stay in the hospital and get intravenous (IV) solutions to keep you from becoming hypoglycemic.

**Management and Treatment**

Surgery is the main treatment for nonmetastatic (indolent) insulinomas. Surgical options include:

* Enucleation. Your surgeon removes the insulinoma without cutting into it. This is kind of like the way you might remove the yolk from a hard-boiled egg.
* Partial pancreatectomy. As the name sounds, this surgery involves removing part of your pancreas. In this case, it’s the part where the insulinoma is.
* Whipple surgery. Your surgeon removes part of your pancreas and other nearby tissues. You may need this surgery if the insulinoma is metastatic.

Each of these surgeries has different risks. Your provider will go over the risks and which surgery would be best for you.

#### **Prevention and treatment of low blood sugar (hypoglycemia)**

In the time leading up to surgery (or if surgery isn’t possible), it’s important to prevent and treat low blood sugar episodes. Your provider may recommend getting a continuous glucose monitoring (CGM) system. A CGM can help you catch low blood sugar episodes before they get too severe, especially during the night.

It’s important to remember that you shouldn’t use a CGM to diagnose insulinoma or other low blood sugar conditions. They’re for monitoring conditions after a diagnosis.

Your provider may recommend one or more of the following treatments for low blood sugar:

* Dietary changes. Regular meals or snacks rich in complex carbohydrates can help prevent low blood sugar. A bedtime or late-night meal may also help.
* IV glucose. If you experience frequent severe episodes of hypoglycemia, you may need to receive IV glucose.
* Diazoxide. This medication can help control how much insulin your pancreas releases. It may also increase how much glucagon your liver releases. Glucagon raises your blood sugar.
* Octreotide and lanreotide. These medications may help reduce the release of insulin from certain types of insulinoma tumors.

It’s important to wear medical identification that states that you experience low blood sugar. This way, someone can get you help as soon as possible if you have a severe episode. Also, tell people close to you about your low blood sugar episodes and how they can help.

#### **Treatment of metastatic insulinoma**

Your provider may recommend combining surgery with other treatments for metastatic (aggressive) insulinoma. Or they may use medical treatments when surgery isn’t an option. Your provider might recommend:

* Peptide receptor radionuclide therapy (PRRT)
* Targeted therapy
* Chemotherapy

**PREVENTION TIPS**

There are no known ways to prevent an insulinoma. You may want to be checked for an insulinoma if any of your family members have any of the genetic conditions that increase risk.

Doctors don’t know why insulinomas form, so there’s no known way to prevent them.

However, if you develop an insulinoma, you can reduce your risk of hypoglycemia by maintaining a balanced diet. This diet should largely consist of fruits, vegetables, and lean protein.

You can also keep your pancreas healthy by eating less red meat and quitting smoking if you smoke.

**Living with an insulinoma**

Almost all insulinomas are not cancerous. Removing the tumor cures the condition. Usually, symptoms don't recur. You are unlikely to get diabetes unless your surgeon has to remove a large part of your pancreas.

A small number of insulinomas are cancer. Your surgeon may not be able to remove them entirely. If this happens, you may need to take medicine to help prevent hypoglycemia. You may also need chemotherapy to help control the size of the tumor.

**POSSIBLE COMPLICATIONS**

After surgery to remove an insulinoma, some people develop a pancreatic fistula. This causes pancreatic fluid to leak. You may be given medicine and extra fluids to help your fistula heal. Most close without the need for more surgery.

In general, complications are more likely in people with cancerous insulinomas.

This is particularly true when the tumors have spread to other organs. The surgeon may not be able to remove all of the tumors completely. In this case, additional treatment and follow-up care will be necessary.

Keep in mind that insulinomas are rare in general, and only a small percentage of them are cancerous.

A very small number of people with insulinomas may develop diabetes after surgery. This usually only occurs when the entire pancreas or a large portion of the pancreas is removed.

Complications may include:

* Severe hypoglycemic reaction
* Spread of a cancerous tumor (metastasis)
* Diabetes if the entire pancreas is removed (rare), or food not being absorbed if too much of the pancreas is removed
* Inflammation and swelling of the pancreas

## **OUTLOOK / PROGNOSIS**

### In most cases, the tumor is non-cancerous (benign), and surgery can cure the disease. But a severe hypoglycemic reaction or the spread of a cancerous tumor to other organs can be life threatening.

### **Can insulinoma be cured?**

Yes, most insulinomas can be cured with surgery. One study showed that 87% of people who had surgery for nonmetastatic insulinoma were alive 10 years after diagnosis. Your healthcare provider will consider factors like the tumor’s size and location before recommending a specific surgery.

The 10-year survival rate for metastatic insulinomas was 33%. It’s important to remember this is just an estimate. Your healthcare team will be able to give you a better idea of what to expect based on your unique situation.

The long-term outlook for people with insulinomas is very good if the tumor is removed. After surgery, most people recover completely without complications.

An insulinoma may return in the future, though. Recurrence is more common in people who have multiple tumors.

**WHEN TO SEE A DOCTOR / RED FLAG**

If you have an insulinoma, you may have symptoms of low blood sugar. These include sweating, confusion, and double vision. You may notice these symptoms more when you’re hungry or after exercise. If you have these symptoms several times in 1 week, talk to your healthcare provider right away.

Contact your health care provider if you develop any symptoms of insulinoma. Seizures and losing consciousness are an emergency. Call 911 or the local emergency number right away.

**EPIDEMIOLOGY**

Insulinomas have an incidence of approximately 1 to 32 cases per million persons per year, with a slight female preponderance. Despite their rarity, they represent the most common type of functional pancreatic neuroendocrine tumors. Insulinomas are associated with MEN1 syndrome in approximately 6% to 7% of cases

**MEDICAL MANAGEMENT OF BENIGN INSULINOMAS**

Most patients with benign insulinomas can be cured with surgery, although other techniques for the management of insulinomas, including injection of octreotide, EUS-guided alcohol ablation, radiofrequency ablation (RFA), or embolization of an insulinoma of the pancreas, have been described.

After identification of an insulinoma, surgery is indicated for all localized tumors. The choice of procedure will depend on the features of the tumor mass, such as type, size, and localization. Atypical resection, including enucleation, partial pancreatectomy, or middle pancreatectomy, has the advantage of preserving the pancreatic parenchyma as much as possible, thereby reducing the risk of late exocrine/endocrine insufficiency. To date, laparoscopic resection has often been performed for insulinomas that are benign, small, and/or located in the body or tail of the pancreas. Radical resection should be considered for patients in whom the lesion is not single, not well-encapsulated, > 4 cm in diameter, and involves or is near the main pancreatic duct. Lymphadenectomy is not usually performed. Although the cure rate after resection for insulinoma is very high, it is necessary to be aware of the potential for postoperative complications after pancreatic surgery, especially postoperative pancreatic fistula.

However, there is a considerable risk of morbidity and mortality associated with the surgical management of insulinomas, which precludes surgery in high-risk patients. Alcohol ablation and RFA have been established as minimally invasive procedures in the treatment of primary liver tumors and hepatic metastases. Recently, successful EUS-guided alcohol ablation and CT-guided RFA of pancreatic insulinomas have been reported in humans. These two patients were in poor general condition and were experiencing recurrent symptomatic episodes of hypoglycemia. Because it was considered that surgical management for benign insulinoma of the pancreas was impossible in both cases, ablation of the solitary mass was performed. Both patients were discharged without any complications and reported no further hypoglycemic episodes. Embolization of an insulinoma of the pancreas is another non-surgical alternative. Because angiographically the insulinoma is demonstrated in the arterial phase as a hypervasculated mass, embolization could be performed using flow to direct particles exclusively into the tumor. Although it remains contentious as to whether these procedures are a viable treatment for patients with an insulinoma, they may be offered as an alternative for certain patients, such as those who refuse surgery, those who are of advanced age, those with a poor general condition, those who have already undergone multiple abdominal surgeries, or those with an increased risk of postoperative complications due to other reasons.

Insulinomas are rare endocrine tumors, most of which can be cured by surgery. Medical treatment to normalize blood glucose is useful during the preoperative period, as well as for patients who cannot be cured by surgery, such as those with diffuse β-cell disease, multiple insulinomas, unresectable malignant insulinoma, those in whom surgery is contraindicated, or patients who refuse surgery. Octreotide is a somatostatin analog that inhibits insulin secretion and the peripheral action of many gastrointestinal hormones, primarily *via* activation of somatostatin sst2 receptors. Octreotide has been used for the treatment of insulinoma, with successful control of blood glucose levels. In addition, ocreotide may have an antiproliferative effect, as well as a moderate antitumoral action, on pancreatic endocrine tumors. Therapy may be initiated with short-acting ocreotide two to four times daily, or 20-30 mg long-acting ocreotide every 4 wk. Initiation of therapy with short-acting ocreotide can be used to assess systemic tolerability, particularly any gastrointestinal side-effects. Thus, pharmacotherapy with somatostatin to control hypoglycemia represents a feasible option for the non-surgical management of insulinomas.

**MEDICAL MANAGEMENT OF MALIGNANT INSULINOMAS**

To be considered malignant, insulinomas must show evidence of local invasion into the surrounding soft tissue or there must be verification of lymph node or liver metastasis. The reported incidence of malignant insulinomas ranges between 7% and 10%, and the 10-year survival has been reported to be 29%. The major sites of metastasis or recurrence are the liver and regional lymph nodes. Aggressive surgical resection is recommended because these tumors are much less virulent than their malignant ductal exocrine counterparts, in which there are severe hormonal symptoms that cannot be controlled by medical treatment. RFA can be used to reduce the tumor mass in the liver, thereby reducing hormonal symptoms. Selective embolization alone or in combination with intra-arterial chemotherapy is an established procedure to reduce both hormonal symptoms and liver metastases. Although experience is limited, liver transplantation for multiple liver metastases of malignant insulinomas may be considered in patients with no extrahepatic metastases. Aggressive sequential multimodal therapy (chemoembolization, RFA, liver resection, liver transplantation) can prolong the survival of patients with sporadic malignant insulinoma, even in the presence of liver metastases.

Malignant insulinomas remain extremely rare tumors. In many patients with malignant insulinomas, the tumors are unresectable and medical treatment therapy is limited in its ability to prevent hypoglycemic episodes. Continuous glucose monitoring in patients with insulinomas can detect hypoglycemia, monitor responses to medical therapy, and confirm a cure postoperatively. In the literature, continuous glucose monitoring has been reported using a Dexcom Seven System continuous glucose monitor . Continuous glucose monitoring is a useful addition to the armamentarium for the prevention of hypoglycemia. These techniques are considered an effective adjunct to therapy to reduce hypoglycemic episodes by alerting patients to low glucose concentrations before they develop neuroglycopenic symptoms; however, patients should respond promptly to oral glucose intake after hypoglycemia has been detected by these machines. In patients with a poorer general condition, malignant insulinomas that are unresectable, and uncontrolled hypoglycemia, it is proposed that blood glucose concentrations are monitored using the STG-22. The STG-22 is a reliable and accurate device for the measurement of blood glucose concentrations compared with the ABL 800FLEX machine that is recommended by the National Committee for Clinical Laboratory Standards. The STG-22 closed-loop glycemic control system is composed of a glucose sensor for the detection and/or monitoring of glucose and pumps for infusing an appropriate amount of insulin or glucose. The insulin and glucose pumps are computer regulated based on a target blood glucose value that is defined prior to initiation of the system. It is has been proven clinically that the STG-22 device is safe and beneficial for maintaining glycemic control without hypoglycemic episodes in surgical patients

In patients who have unresectable or uncontrollable malignant insulinomas of the pancreas, several strategies need to be considered to both control hypoglycemic episodes and improve quality of life, including administration of ocreotide and continuous glucose monitoring. RFA: Radiofrequency ablation; LN: Lymph node.

**DIFFERENTIAL DIAGNOSIS**

Differential diagnoses that should also be considered when evaluating insulinomas include:

* Persistent hyperinsulinemic hypoglycemia of infancy
* Noninsulinoma pancreatogenous hypoglycemia syndrome
* Post-gastric bypass hypoglycemia
* Factitious use of insulin
* Sulfonylurea-induced hypoglycemia
* Insulin autoimmune hypoglycemia
* Non-islet-cell tumors that secrete insulin-like growth factors
* Nesidioblastosis
* Persistent Hyperinsulinemic Hypoglycemia of Infancy (PHHI): A congenital disorder characterized by inappropriate and excessive insulin secretion from pancreatic beta cells in neonates and infants, causing severe hypoglycemia. It is often due to genetic mutations affecting insulin regulation or beta-cell hyperplasia (nesidioblastosis).
* Noninsulinoma Pancreatogenous Hypoglycemia Syndrome (NIPHS): A rare adult disorder marked by postprandial hypoglycemia caused by diffuse beta-cell hyperplasia or nesidioblastosis without a discrete insulinoma tumor, leading to inappropriate insulin secretion.
* Post-Gastric Bypass Hypoglycemia (PBH): A complication occurring after Roux-en-Y gastric bypass surgery characterized by exaggerated postprandial insulin secretion and hypoglycemia. It results from rapid nutrient transit, enhanced incretin hormone (especially GLP-1) secretion, beta-cell hyperplasia (nesidioblastosis), and altered glucose metabolism.
* Factitious Use of Insulin: Hypoglycemia caused by surreptitious or inappropriate administration of exogenous insulin, often seen in patients with diabetes or factitious disorder. Characterized by elevated insulin levels but low C-peptide.
* Sulfonylurea-Induced Hypoglycemia: Hypoglycemia caused by oral hypoglycemic agents (sulfonylureas) that stimulate pancreatic beta cells to secrete insulin, leading to elevated insulin and C-peptide levels.
* Insulin Autoimmune Hypoglycemia: A rare condition caused by autoantibodies to endogenous insulin, leading to hypoglycemia due to unpredictable insulin binding and release.
* Non-Islet-Cell Tumors Secreting Insulin-Like Growth Factors: Certain tumors produce insulin-like growth factors (IGF-1 or IGF-2) that mimic insulin action, causing hypoglycemia without elevated insulin levels.
* Nesidioblastosis: A histopathological term describing diffuse proliferation and hyperplasia of pancreatic islet beta cells, leading to excessive insulin secretion; seen in infants (PHHI) and adults (NIPHS and PBH).

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**NEONATAL DIABETES**

*ALTERNATIVE NAMES*: Neonatal diabetes mellitus (NDM) is also referred to as congenital diabetes or diabetes of infancy.

* Congenital Diabetes: This term refers to diabetes that is present at birth.
* Diabetes of Infancy: This describes diabetes that occurs within the first 6 months of life.
* PNDM

These alternative names are used interchangeably to describe the condition characterized by the body's inability to produce sufficient insulin in infants.

**DEFINITION / DESCRIPTION**

Neonatal diabetes is a very rare type of diabetes that can occur in babies under the age of 9 months. It is caused by a change in a gene which affects an infant’s insulin production leading to their levels of blood sugar to rise dramatically. There are two types of neonatal diabetes, transient and permanent. Transient neonatal diabetes can resolve and then reoccur in later life, whilst permanent neonatal diabetes never goes away.

Permanent neonatal diabetes mellitus can have different inheritance patterns.

When this condition is caused by mutations in the *KCNJ11* or *INS* gene it is inherited in an autosomal dominant pattern, which means one copy of the altered gene in each cell is sufficient to cause the disorder. In about 90 percent of these cases, the condition results from new mutations in the gene and occurs in people with no history of the disorder in their family. In the remaining cases, an affected person inherits the mutation from one affected parent.

When permanent neonatal diabetes mellitus is caused by mutations in the *ABCC8* gene, it may be inherited in either an autosomal dominant or autosomal recessive pattern. In autosomal recessive inheritance, both copies of the gene in each cell have mutations. The parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but they typically do not show signs and symptoms of the condition.

Less commonly the condition is caused by mutations in other genes, and in these cases, it is also inherited in an autosomal recessive pattern.

**Types of neonatal diabetes**

There are two main types of neonatal diabetes:

* Transient Neonatal Diabetes Mellitus
* Permanent Neonatal Diabetes Mellitus

Transient neonatal diabetes is so called because it usually disappears within a year of birth but can come back again typically during adolescence

Permanent neonatal diabetes, once diagnosed, stays for the rest of life.

**CAUSES OF NEONATAL DIABETES**

Neonatal diabetes is a rare form of diabetes that occurs in the first six months of life and requires lifelong management and treatment. The causes of neonatal diabetes can be attributed to both genetic and non-genetic factors. Let's delve into the various causes of neonatal diabetes in detail.

### Genetic Causes

Genetic mutations are a primary cause of neonatal diabetes. According to the [Diabetes UK](https://www.diabetes.org.uk/guide-to-diabetes/types-of-diabetes/neonatal-diabetes), mutations in specific genes such as KCNJ11, ABCC8, and INS can lead to the development of neonatal diabetes. These mutations affect the function of pancreatic beta cells, which are responsible for producing insulin. As a result, infants with these genetic mutations are unable to regulate their blood sugar levels effectively, leading to the onset of diabetes at such a young age.

### Non-Genetic Causes

While genetic factors play a significant role, non-genetic causes also contribute to neonatal diabetes. One of the non-genetic causes is intrauterine growth restriction (IUGR). Babies born with IUGR have a higher risk of developing neonatal diabetes due to impaired pancreatic development and function. Additionally, maternal gestational diabetes can also predispose infants to neonatal diabetes, as it can affect the baby's insulin production and glucose metabolism.

### Transient Neonatal Diabetes

It's important to note that not all cases of neonatal diabetes are lifelong. Transient neonatal diabetes is a rare form of the condition that typically resolves within the first 18 months of life. This type of neonatal diabetes is often caused by abnormalities in chromosome 6, specifically the 6q24 region. According to the [National Center for Biotechnology Information](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3232502/), around 60% of transient neonatal diabetes cases are due to abnormalities in this chromosomal region.

**RISK FACTORS**

Neonatal Diabetes Mellitus is a rare form of diabetes that occurs in newborns and infants. Certain factors can increase the risk of developing this condition. Understanding these risk factors is crucial for early detection and management.

* Genetic mutations
* Family history of diabetes
* Autoimmune disorders
* Certain medications
* Exposure to certain viruses during pregnancy
* Low birth weight

**SIGNS / SYMPTOMS**

Neonatal diabetes is a rare form of diabetes that is usually diagnosed in children under 6 months of age. The symptoms of neonatal diabetes include **persistent thirst, frequent urination and dehydration**. The first sign of neonatal diabetes is often slowed fetal growth, followed by unusually low birthweight. At some point within the first six months of life, infants with neonatal diabetes tend to experience the classic symptoms of type 1 diabetes: thirst, frequent urination, and signs of dehydration. The timing of symptom onset varies with the type of neonatal diabetes. Those with transient neonatal diabetes tend to have symptoms in the first few days or weeks of life, with affected children showing weight loss and signs of dehydration, along with high levels of sugar in the blood and urine. Some children also have high levels of ketones in the blood and urine, or signs of metabolic acidosis. Permanent neonatal diabetes starts slightly later, typically around six weeks of age. Preterm infants tend to experience symptoms earlier, typically around one week of age.

Some other symptoms of neonatal diabetes include:

* Excessive thirst
* Urinating more than usual
* Dehydration
* Weight loss
* Fatigue
* Dehydration
* Irritability
* Delayed growth and development

**DIAGNOSIS METHODS**

Neonatal diabetes is often diagnosed via genetic testing. Neonatal Diabetes Mellitus is typically diagnosed through a series of tests that help healthcare providers determine if a newborn or young infant has this condition. These tests often involve evaluating the baby's blood sugar levels, genetic factors, and other relevant medical information. By analyzing these factors, doctors can make an accurate diagnosis of Neonatal Diabetes Mellitus.

* Genetic testing
* Blood glucose monitoring
* Insulin and C Peptide levels testing
* HbA1c testing
* Urine tests for ketones and glucose
* Imaging studies like ultrasound or MRI for pancreatic abnormalities

**TREATMENT OPTIONS**

Neonatal Diabetes Mellitus is a rare form of diabetes that occurs in infants. Treatment options for this condition typically involve a combination of medication, diet management, and close monitoring of blood sugar levels. Insulin therapy is often a key component of treatment for neonatal diabetes, along with medications that help regulate blood sugar levels. Additionally, dietary changes may be recommended to help control blood sugar levels and promote overall health. Regular monitoring of blood sugar levels is essential to ensure that treatment is effective and adjusted as needed. In some cases, genetic testing may also be recommended to determine the underlying cause of neonatal diabetes and guide treatment decisions.

**Insulin Therapy:** Neonatal diabetes mellitus is typically managed with insulin therapy to regulate blood sugar levels in newborns.

**Genetic Testing:** Identifying the specific genetic mutation causing neonatal diabetes can help tailor treatment and management strategies for better outcomes.

**Continuous Glucose Monitoring:** Monitoring blood glucose levels continuously can help healthcare providers adjust insulin doses more effectively in neonates with diabetes.

**Nutritional Management**: A carefully planned diet with the right balance of nutrients is crucial in managing neonatal diabetes and supporting overall health.

**Regular FollowUp Care:** Close monitoring by healthcare providers is essential to ensure proper management of neonatal diabetes and early detection of any complications.

Half the time, insulin is not needed to treat neonatal diabetes and instead can be treated with a tablet which is called Glibenclamide.

**Glibenclamide for Neonatal Diabetes**

In summary, glibenclamide is a valuable treatment option for neonatal diabetes, offering metabolic benefits and potential neuroprotective effects, particularly when treatment is initiated early.

**Treatment of neonatal diabetes**

The mainstay of the management of NDM in the immediate newborn period is insulin, regardless of the etiology. Another available treatment option is oral sulfonylurea, which is administered based on the genetic diagnosis of KATP channel mutations. Treatment with insulin should be started immediately after diabetes is diagnosed by persistent hyperglycemia or elevated glycated hemoglobin (HbA1c).

**Management of acute hyperglycemia**

Neonates with diabetes mellitus can present with significant hyperglycemia, electrolyte disturbance, dehydration, and ketoacidosis. The initial management includes fluid resuscitation with isotonic electrolyte solutions, to treat the dehydration that results from osmotic diuresis. The appropriate fluid therapy is calculated on an individual basis and administered slowly over a period of 24−48 hours to avoid cerebral edema that results from too rapid correction. Neonates and infants presenting with diabetic ketoacidosis should be managed in an intensive care unit, under the supervision of a pediatric endocrinologist, with frequent monitoring of blood glucose, electrolytes, and neurological status. Neonatal diabetic ketoacidosis is managed according to the same principles guiding the therapy for children and adolescents with diabetes mellitus. Insulin therapy should be started with careful attention as newborns are very sensitive to insulin and therefore in danger of severe hypoglycemia. A continuous intravenous infusion of regular insulin is started at 0.05−0.1 U/kg/hr and titrated up or down as needed based on the blood glucose levels. The goal of therapy is to allow normal energy utilization by tissues as well as to replace fluids and electrolytes.

**Insulin therapy**

Insulin therapy is crucial to obtain satisfactory weight gain and growth, especially in babies with IUGR, but the treatment of NDM is complex due to the paucity of subcutaneous fat and the need for the low doses of insulin. Insulin is administered as an intravenous infusion, intermittent subcutaneous therapy, or as continuous subcutaneous insulin infusion (CSII). It is often delivered initially by an intravenous infusion as this enables better titration of doses based on the blood glucose levels. After the initial treatment of the diabetic ketoacidosis, the intravenous infusion of regular insulin should be continued in infants with persistent hyperglycemia, despite reductions in glucose infusion rates, and in those with persistent glucose excursions, while others are transitioned to an appropriate regimen of subcutaneous insulin. Finding a suitable regimen is usually not an easy task as few data are available on the most appropriate insulin preparations for young infants. Patients are transitioned to injections of basal insulin or a combination basal/bolus insulin regimen.

**Basal insulin**

Basal insulin may be intermediate-acting insulin, like NPH (isophane) insulin or long-acting insulin, like insulin glargine or insulin detemir. Intermediate-acting insulin, like NPH, does not provide insulin delivery profiles that complement the feeding patterns and results in significant swings in glucose levels and hypoglycemia. Insulin glargine, with an almost flat action profile and 24-hour action, would overcome the problems of intermediate acting insulin, but the safety and effectiveness of glargine insulin have not been established in patients less than 6 years of age. However, it is being used in the treatment of toddlers and children with type 1 diabetes mellitus and has shown to be suited for treating newborns and infants, with better glucose control and less hypoglycemia. Glargine is started at a dose of 0.5−1 U/day and is often divided into twice-daily dosing to provide an adequate basal effect. Another long-acting insulin analogue that has been used in NDM is insulin detemir. Unlike insulin glargine, insulin detemir has a peak, which results in hypoglycemia. The prolonged action of detemir is due to the binding of fatty acid residues to serum albumin, and the lack of subcutaneous fat and low albumin in many newborns also affects the pharmacokinetics of this insulin. Another long-acting insulin, ultralente, provides good control of blood glucose, but is not available in the USA. Some infants can maintain an appropriate blood glucose level on just small doses of basal insulin without requiring any bolus insulin.

**Bolus insulin**

Bolus is given with either short-acting insulin, like regular insulin, or rapid-acting insulin, like insulin lispro or insulin aspart. The groups of insulins should be used cautiously as their peak action can result in significant hypoglycemia, even in very small doses. As in children with type 1 diabetes, an insulin to carbohydrate ratio and a ratio of insulin to blood glucose level (insulin sensitivity factor) can be used in newborns and infants to give the bolus for carbohydrate and the high-blood glucose correction.

**Diluted insulin**

Newborns and infants usually require very small doses of insulin, with gradations in fractions of a unit, which can be difficult to measure with a standard insulin syringe, hence there is a need to use diluted insulin. Diluents appropriate for each insulin are provided by the pharmaceutical companies.. Dilute insulin should be prepared under aseptic conditions by a pharmacist who is familiar with the dilution technique. Usually insulin is diluted to a concentration of 1:10 (equivalent to U-10) or 1:2 (equivalent to U-50). Due to instability issues, diluted insulin loses its potency more quickly than standard insulin and should be discarded 30 days after preparation or earlier, based on the manufacturer’s recommendation. Diluted insulin should be used with caution in newborns or infants with impaired liver function due to the presence of some preservatives. The long-acting insulins glargine and detemir usually should not be diluted due to the risk of alteration of the pharmacokinetic profile. However, due to the requirement of very small doses in newborns, these insulin preparations may need to be diluted with normal saline. But studies have not evaluated the efficacy or stability of diluted long-acting insulin products. Extreme caution should be observed when using diluted insulin preparation, in order to avoid dose errors.

**Continuous subcutaneous insulin infusion**

The delivery of small doses of insulin and variable insulin requirements, together with the frequent monitoring of blood glucose, remains a major challenge in NDM. CSII allows for low rates of insulin delivery that are suited for newborns with diabetes. In addition, CSII provides greater flexibility, to adjust for the variability in oral intake as well as changes in energy expenditure as the child grows. When compared with subcutaneous insulin injections, CSII therapy has also been effective in reducing both HbA1c and hypoglycemic episodes, in patients managing it appropriately. In children on continuous enteral or parenteral nutrition, the total insulin dose is administered as a basal rate, while in orally fed neonates, basal rates combined with boluses can better mimic physiological insulin delivery. Some centers recommend CSII for young infants as it is safe, more physiological, easier to manage than injections, and offers the possibility of very low rates of insulin delivery.[1](https://www.dovepress.com/neonatal-diabetes-mellitus-current-perspective-peer-reviewed-fulltext-article-RRN#ref1)

**Continuous glucose monitoring sensor**

A continuous glucose monitoring sensor (CGMS) consists of an electrode sensor that catalyzes glucose oxidation, generating an electric current that is recorded by a monitor. The CGMS is inserted subcutaneously and allows continuous measurement of glucose in the interstitial fluid. The sensor is especially useful in preterm babies and in small gestational age babies who are at risk for wide excursions in blood glucose levels. The CGMS is programmed to give alerts when glucose levels are either lower or higher than acceptable limits, and this feature enables the caregiver to respond promptly. The prompt care is clinically important as both hypoglycemia and hyperglycemia are associated with acute neurophysiological abnormalities and later neurodevelopmental impairment. However, despite its proposed advantages for continuous blood glucose measurement, there is limited experience with its use, or accuracy in newborns..

**Oral sulfonylurea**

Patients with NDM were previously believed to require lifelong insulin treatment as they have little or no endogenous insulin. The identification of KATP channel mutations in these patients has revolutionized the treatment of NDM. The oral sulfonylureas commonly used in adults with type 2 diabetes mellitus have been used with success in cases of NDM caused by mutations in the *KCNJ11* and *ABCC8* genes. Sulfonylurea binds to the SUR1 subunits of the KATP channel and closes the channel in an ATP-independent manner, causing membrane depolarization and insulin secretion. In the same way, sulfonylurea causes insulin secretion in the mutated KATP channels by binding to the SUR subunits. Of the known genetic subtypes of NDM, only patients with activating *KCNJ11* or *ABCC8* gene mutations respond to treatment with a sulfonylurea. Sulfonylurea can be started in a patient as soon as the genetic diagnosis is established, and a trial of sulfonylurea in NDM without a genetic diagnosis is not recommended. Patients on insulin can transition to oral sulfonylurea over a period of a few weeks to months as an outpatient or over a few days as an inpatient, based on specific protocols. In both settings, the dose of sulfonylurea is increased with a concomitant reduction in insulin dose, based on the blood glucose levels. About 90% of patients with *KCNJ11* gene mutations and 85% of patients with *ABCC8* gene mutations can successfully transition from insulin to sulfonylurea. It has been shown that patients with *ABCC8* gene mutation require lower doses of sulfonylurea than those with *KCNJ11* gene mutation and hence, require a different treatment protocol. Infants as young as 1 month have been successfully transitioned to sulfonylurea therapy. Long-term insulin therapy is required for all other causes of PNDM, although a mild beneficial effect of oral sulfonylurea has been reported in patients with *GCK* gene mutations.

Treatment with sulfonylurea reduces fluctuations in blood glucose and improves the glycemic control by reducing HbA1c levels without concomitant hypoglycemia.This improvement in glycemic control reduces the risk of diabetic complications. In addition to diabetes control, nonspecific sulfonylurea drugs, like glibenclamide (glyburide), improves neurological function by improving both muscle strength and cognitive function. Improved neurodevelopmental outcome has been reported in children with intermediate and complete DEND syndrome treated with sulfonylurea, but the best outcome is seen if transition occurs early in the first 6 months of life.

A small group (10%−15%) of patients with *KCNJ11* and *ABCC8* gene mutations do not respond to sulfonylurea therapy. This is attributed to the characteristic of the specific mutation, to B-cell glucotoxicity from prolonged poor control before transfer, or to noncompliance. In fact, patients should be given a trial of sulfonylurea for a period of at least 3 months, with a dose as high as 1.5 mg/kg/day, before considering it as a treatment failure as B-cell function improves with time on sulfonylureas. Sometimes, even identical mutations within the same family can produce a variable clinical picture and different responses to treatment.

Most patients with KATP channel mutations are treated with glibenclamide. Other first and second generation sulfonylurea drugs, like tolbutamide, glipizide, gliclazide, and glimepiride, have been used with success in patients with KATP channel mutation. The doses required in the treatment of NDM are usually higher than those used in patients with type 2 diabetes mellitus. With time, many patients have been able to reduce their doses of sulphonylureas and maintain excellent glycemic control. Despite the requirement of high doses, the side effects of sulfonylurea are mild and transitory. The most common side effects are diarrhea, nausea, vomiting, and abdominal pain. Hypoglycemia, transient allergic skin reactions, and tooth discoloration are some of the less common side effects. Also, the unknown interactions of sulfonylurea with the extrapancreatic KATP channels found in the cardiac, smooth and skeletal muscles, adipocytes, and brain are of concern for long-term use in children.

Follow up of patients on sulfonylurea for more than 68 months has showed that chronic sulfonylurea therapy retains its efficacy in patients with PNDM, contrary to the findings reported in type 2 diabetes, where secondary sulfonylurea failure has been reported. Capillary blood glucose monitoring and close follow up is needed in all patients treated with sulfonylurea. Parents and patients should understand that the risk of hypo- and hyperglycemia exists on sulfonylurea treatment, and education in their prevention and treatment should be given. Parents should also be cautioned that insulin may be needed, at times, for eg, to control high blood sugars during illness.

**Diet**

All newborns with NDM should receive a high caloric diet along with an adequate amount of insulin to promote satisfactory weight gain and growth. Any reduction of glucose and calories to improve hyperglycemia in these babies significantly affects their weight gain. A high caloric diet can be achieved with the help of the dietician, who can assist in calculating the calories and in determining the carbohydrate content of breast milk or formula. The carbohydrate content of human milk and the standard infant formula are similar (approximately 70−75 g/L), and the carbohydrate content of human milk fortifiers is negligible (<0.1 g/packet). Dietary management requires a team approach to address the caloric needs and carbohydrate counting.

**PREVENTION TIPS**

Neonatal diabetes is a rare form of diabetes that is usually diagnosed in children under 6 months of age. Unfortunately, **there is no known prevention for neonatal diabetes as it is a genetic disorder**. However, early recognition and urgent genetic testing are important for predicting the clinical course and raising awareness of possible additional features. It is also important to distinguish neonatal diabetes mellitus from other causes of hyperglycemia in the newborn. If you suspect your infant has neonatal diabetes, talk to his or her health care provider as soon as possible. Genetic testing for neonatal diabetes is offered free of charge for all people diagnosed with diabetes before 9 months of age. Confirming the diagnosis by molecular genetic testing is essential before considering any change to treatment.

**POSSIBLE COMPLICATIONS**

Neonatal diabetes is a rare form of diabetes that occurs within the first six months of life and can lead to various complications. The condition is often mistaken for type 1 diabetes, but it is caused by genetic mutations and can be classified into two main types: permanent neonatal diabetes mellitus (PNDM) and transient neonatal diabetes mellitus (TNDM).

Complications associated with neonatal diabetes can vary depending on the specific genetic mutation involved. For instance, infants with neonatal diabetes may experience **intrauterine growth restriction, leading to low birth weight**. Additionally, neonatal diabetes can result in developmental delays, such as muscle weakness and learning disabilities.

In some cases, neonatal diabetes may be managed with insulin, but in others, oral medications like glibenclamide may be effective. However, even with treatment, individuals with neonatal diabetes may face long-term challenges, including the risk of diabetes reoccurring later in life.

Moreover, neonatal diabetes can be part of syndromic conditions, such as IPEX syndrome, Wolcott-Rallison syndrome, and Wolfram syndrome, which can lead to additional health issues. The prognosis for neonatal diabetes depends on the severity of the disease, the speed of diagnosis and treatment, and the presence of associated abnormalities.

In summary, neonatal diabetes can lead to a range of complications, including **intrauterine growth restriction, developmental delays, and the potential for diabetes to reoccur later in life**. Early diagnosis and appropriate management are crucial for improving outcomes.

**OUTLOOK / PROGNOSIS**

In the neonatal period, the prognosis is linked to the severity of the disease, the degree of dehydration and acidosis, as well the rapidity with which the disease is recognized and treated. In the following period, the prognosis is determined by the associated malformations and lesions. For example, in the case of potassium channel anomalies, neuropsychological and neuromuscular disturbances can be present. Finally, the prognosis relies on metabolic control, as in all the forms of diabetes mellitus, which will determine the timing of appearance of the long-standing diabetes complications.

**WHEN TO SEE A DOCTOR / RED FLAG**

If you suspect your infant has neonatal diabetes, it is important to talk to his or her health care provider as soon as possible. Neonatal diabetes is a rare form of diabetes that occurs within the first 6 months of life, and it is often mistaken for type 1 diabetes. Symptoms of neonatal diabetes include persistent thirst, frequent urination, and dehydration. If your infant is diagnosed with diabetes before 6 months of age, it is crucial to seek medical attention to determine if it is neonatal diabetes, as the treatment and management differ from type 1 diabetes. Additionally, if your infant shows signs of high blood glucose levels, such as increased urination, dehydration, or weight loss, you should consult a healthcare professional immediately. Early diagnosis and treatment are essential for managing neonatal diabetes effectively.

**DIFFERENTIAL DIAGNOSIS**

Neonatal diabetes needs to be distinguished from autoimmune type 1 diabetes. Most patients diagnosed with diabetes after 6 months of age, and especially after 12 months of age will have autoimmune type 1 diabetes. In a study of children with diabetes onset before 13 months of age, the median age for diagnosis for infants with type 1 diabetes was 42.6 weeks (IQR 37.4–50.4) and 87.5% presented in DKA. Most of these patients will test positive for at least one of the specific diabetes-related autoantibodies.

**EPIDEMIOLOGY**

neonatal diabetes is very rare, occurring in around **1 in 300,000** to **1 in 400,000 births**

out of the two types of neonatal diabetes, the transient type is slightly more common affecting 50-60% of cases of neonatal diabetes.

About 1 in 400,000 infants are diagnosed with diabetes mellitus in the first few months of life. However, in about half of these babies the condition is transient and goes away on its own by age 18 months. The remainder are considered to have permanent neonatal diabetes mellitus.

incidence of neonatal dm is thought to range from 1:90,000 to 1:160,000 live births. hyperglycemia in a neonate is not an uncommon occurrence. Therefore, making the diagnosis of neonatal dm can be difficult. neonatal hyperglycemia is more common to develop in the first 3–5 days of life and resolve within 2–3 days of onset but can persist up to 10 days.

The difficulty in diagnosis is especially true in the preterm population or low birth weight infants. the prevalence of hyperglycemia in preterm infants can vary from 25% to 75%. common reasons for hyperglycemia in these patients include: sepsis, increased counter-regulatory hormones due to stress, parenteral glucose administration and medications such as steroids and beta-adrenergic agents. also in critically ill preterm neonates, there is evidence that shows this population has some degree of pancreatic insulin secretion insufficiency and relative insulin resistance. however, in a study of 750 patients with diabetes diagnosed before 6 months of age (146 preterm patients born <37 weeks and 604 born ≥37 weeks), a genetic etiology was found in 97/146 (66%) preterm infants compared with 501/604 (83%) born ≥37 weeks. genetic etiology was noted less frequently in early preterm infants (<32 weeks, 31%) than those born between 32–<37 weeks (81%) and ≥37 weeks of gestation (83%). there was no difference in the age at presentation between preterm and term infants (1 week vs 0.7 weeks). the diagnosis of neonatal dm, therefore, should be considered in the presence of insulin-dependent hyperglycemia without an alternative causative factor in both preterm infants and in term infants.

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**WOLFRAM SYNDROME**

**DEFINITION / DESCRIPTION**

Wolfram syndrome is a rare genetic disease. It’s a progressive, neurodegenerative disorder that damages your brain and other tissues in your body. A series of symptoms usually appear during childhood and into adulthood. Diabetes and vision changes before age 15 are usually the first symptoms. Eventually, impaired brain function can lead to early death.

**Types of Wolfram syndrome**

Healthcare providers have identified two genes involved in Wolfram syndrome. Genes are sequences of DNA that carry genetic information.

People with Wolfram syndrome have changes (mutations) in their genes. Healthcare providers classify Wolfram syndrome based on the affected genes:

* Wolfram syndrome type 1 is the result of a mutation of the *WFS1* gene.
* Wolfram syndrome type 2 is the result of a mutation of the *WFS2* (*CISD2*) gene.

**How is Wolfram syndrome inherited?**

To pass on Wolfram syndrome, usually both biological parents must carry the same gene mutation. But in some cases, a person can inherit Wolfram syndrome type 1 when only one parent has the mutation.

Because Wolfram syndrome is so rare, healthcare providers don’t know exactly how often it occurs. One study estimated that Wolfram syndrome affects 1 in 770,000 people in the United Kingdom. Studies from other countries suggest it may be more common in areas where people who are close relatives marry and have children.

Wolfram syndrome type 2 is extremely rare. Healthcare providers have reported cases in only a few families worldwide.

**SIGNS / SYMPTOMS**

***What are the four most common features of Wolfram syndrome type 1?***

Symptoms of Wolfram syndrome type 1 may vary from person to person. But often, they appear in a predictable order during childhood and adolescence. This is the typical sequence and average age that symptoms appear:

1. ***Diabetes mellitus (age 6):*** Diabetes mellitus is a problem with your body’s ability to absorb sugar (glucose) from the food you eat. Normally, your pancreas makes insulin, which helps your cells absorb sugars (glucose) from your bloodstream. If you don’t make enough insulin or if your cells don’t respond to insulin, your blood sugar can rise too high. Wolfram syndrome-related diabetes is similar to Type 1 diabetes, but it’s not an autoimmune disease. Diabetes symptoms include frequent urination, increased thirst, blurred vision and unexplained weight loss.
2. ***Optic atrophy (age 11):*** Optic atrophy is the degeneration of your optic nerve, which carries signals from your eyes to your brain. Symptoms include blurred, dulled or reduced peripheral (side) vision.
3. ***Sensorineural hearing loss (age 13):*** Sensorineural hearing loss occurs due to damage in your inner ear. This type of hearing loss usually gets worse as you get older and can lead to deafness.
4. ***Diabetes insipidus (age 14):*** Diabetes insipidus isn’t related to diabetes mellitus. It’s an issue with the production of an antidiuretic hormone that controls the amount of water in your urine (pee). People with diabetes insipidus have large amounts of watery urine. This excess urination can cause dehydration, electrolyte disturbance, weakness, dry mouth and constipation.

An outdated name for Wolfram syndrome is DIDMOAD. This acronym incorporates the primary symptoms:

* Diabetes insipidus (DI).
* Diabetes mellitus (DM).
* Optic atrophy (OA).
* Deafness (D).

**Symptoms of Wolfram syndrome type 1**

Less common symptoms include:

* Hormone disorders: Hypopituitarism, low sex drive (hypogonadism), growth delays and delayed start of menstrual periods.
* Neurological symptoms: Problems with movement and coordination (ataxia), dementia, headaches, central sleep apnea, epilepsy and decreased sense of taste and smell.
* Psychiatric conditions: Depression, anxiety, panic attacks, mood swings and aggressive behavior.
* Urinary tract abnormalities: Urinary tract infections, urinary incontinence and incomplete emptying of your bladder.

**Symptoms of Wolfram syndrome type 2**

Symptoms of Wolfram syndrome type 2 are similar to type 1, but may also include:

* Abnormal bleeding.
* Gastrointestinal ulcers.

People with Wolfram syndrome type 2 usually don’t have diabetes insipidus or psychiatric conditions.

**CAUSES**

Wolfram syndrome is primarily caused by mutations in the WFS1 gene, which encodes a protein called wolframin. These mutations are responsible for more than 90% of Wolfram syndrome type 1 cases.

The WFS1 gene is located on chromosome 4p and plays a role in regulating calcium balance within cells, which is crucial for various cellular functions. Mutations in the WFS1 gene can lead to a variety of symptoms, including diabetes mellitus, optic atrophy, diabetes insipidus, and sensorineural hearing loss.

Additionally, mutations in the CISD2 gene can cause Wolfram syndrome 2 (WS2), which is characterized by the absence of diabetes insipidus and psychiatric disorders, along with other features such as bleeding upper intestinal ulcers and defective platelet aggregation.

Variants (also known as mutations) in the *WFS1* gene cause more than 90 percent of Wolfram syndrome type 1 cases. This gene provides instructions for producing a protein called wolframin that is thought to regulate the amount of calcium in cells. A proper calcium balance is important for many different cellular functions, including cell-to-cell communication, the tensing (contraction) of muscles, and protein processing. The wolframin protein is found in many different tissues, such as the pancreas, brain, heart, bones, muscles, lung, liver, and kidneys. Within cells, wolframin is located in the membrane of a cell structure called the endoplasmic reticulum that is involved in protein production, processing, and transport. Wolframin's function is important in the pancreas, where the protein is thought to help process a protein called proinsulin into the mature hormone insulin. This hormone helps control blood glucose levels.

*WFS1* gene variants lead to the production of a wolframin protein that has reduced or absent function. As a result, calcium levels within cells are not regulated and the endoplasmic reticulum does not work correctly. When the endoplasmic reticulum does not have enough functional wolframin, the cell triggers its own cell death (apoptosis). The death of cells in the pancreas, specifically cells that make insulin (beta cells), causes diabetes mellitus in people with Wolfram syndrome. The gradual loss of cells along the optic nerve eventually leads to blindness in affected individuals. The death of cells in other body systems likely causes the various signs and symptoms of Wolfram syndrome type 1.

A certain variant in the *CISD2* gene was found to cause Wolfram syndrome type 2. The *CISD2* gene provides instructions for making a protein that is located in the outer membrane of cell structures called mitochondria. Mitochondria are the energy-producing centers of cells. The exact function of the CISD2 protein is unknown, but it is thought to help keep mitochondria functioning normally.

The *CISD2* gene variant that causes Wolfram syndrome type 2 results in an abnormally small, nonfunctional CISD2 protein. As a result, mitochondria are not properly maintained, and they eventually break down. Since the mitochondria provide energy to cells, the loss of mitochondria results in decreased energy for cells. Cells that do not have enough energy to function will eventually die. Cells with high energy demands such as nerve cells in the brain, eye, or gastrointestinal tract are most susceptible to cell death due to reduced energy. It is unknown why people with *CISD2* gene variants have ulcers and bleeding problems in addition to the usual Wolfram syndrome features.

Some people with Wolfram syndrome do not have an identified variant in either the *WFS1* or *CISD2* gene. The cause of the condition in these individuals is unknown.

**What causes Wolfram syndrome?**

Wolfram syndrome occurs when biological parents pass on changes (mutations) in the *WFS1* or *WFS2* (*CISD2*) genes to their children.

**RISK FACTORS**

Wolfram syndrome is a rare genetic disorder primarily caused by mutations in the WFS1 or WFS2 genes, which are inherited in an autosomal recessive pattern.

This means that both copies of the gene in each cell are altered, and the parents of an individual with Wolfram syndrome each carry one copy of the altered gene but typically do not show symptoms.

**DIAGNOSIS METHODS AND TESTS**

Diagnosing Wolfram syndrome can be challenging. Healthcare providers may diagnose individual conditions but not make the connection between them. Often, diagnosis occurs after multiple symptoms develop.

If your provider suspects Wolfram syndrome, they’ll recommend genetic testing. This test detects mutations in the *WFS1* and *WFS2* (*CISD2*) genes and can confirm your diagnosis.

**MANAGEMENT AND TREATMENT OPTIONS**

Currently, there aren’t any standard treatments to stop or slow the progression of Wolfram syndrome. Treatment focuses on managing related symptoms. For example, healthcare providers treat diabetes mellitus with insulin to help manage blood sugar levels. Hearing aids can help people with hearing loss.

**Are other treatments under investigation?**

Researchers are studying therapies that may improve the outlook for people with Wolfram syndrome. Leading treatment strategies include:

* Drugs to reduce cell damage caused by disruption of proteins.
* Gene therapy to repair or replace mutated *WFS1* and *WFS2* (*CISD2*) genes.
* Regenerative therapy to heal or replace damaged tissues.

Some treatments are now available through clinical trials. Others are still in development. Talk to your healthcare provider about emerging treatments and whether they might be an option for you or your child.

**Outlook / Prognosis**

People with Wolfram syndrome have a poor prognosis. In one study of 45 patients, life expectancy ranged from 25 to 49 years with an average of 30. The most common cause of death was due to deterioration of the brainstem that controls vital functions like breathing and heart rate.

Improved diagnosis and management and the prospect of new therapies are improving the outlook.

Prevention

You can’t prevent genetic conditions such as Wolfram syndrome.

Living With

When should I talk to a healthcare provider about genetic testing?

If you have a family history of Wolfram syndrome, talk to your provider about genetic testing. With a simple blood or saliva test, you can:

* Determine your risk of having a child with the disorder.
* Learn whether your child has Wolfram syndrome before they develop symptoms.

**Differential Diagnosis of Wolfram Syndrome (WFS)**

Wolfram syndrome, a rare genetic disorder characterized primarily by juvenile-onset diabetes mellitus and optic atrophy, has a broad differential diagnosis due to overlapping features with other genetic, mitochondrial, and neurodegenerative disorders. Key differential diagnoses include:

* Mitochondrial Disorders
  + Maternally Inherited Diabetes and Deafness (MIDD)
  + Leber Hereditary Optic Neuropathy (LHON)
  + Kearns-Sayre Syndrome
  + Mohr-Tranebjaerg Syndrome  
    These disorders share features such as diabetes, optic atrophy, and sensorineural hearing loss.
* Autosomal Dominant Optic Atrophy  
  Presents with optic nerve atrophy and may have hearing loss, resembling Wolfram syndrome but with different inheritance patterns.
* Thiamine-Responsive Megaloblastic Anemia (TRMA) Syndrome  
  Includes diabetes and optic atrophy among its features.
* Wolfram-like Syndrome  
  An autosomal dominant disorder with adult-onset diabetes and juvenile optic atrophy, sometimes with hearing impairment.
* Friedreich Ataxia  
  A neurodegenerative disorder that can mimic neurological signs seen in Wolfram syndrome.
* Bardet-Biedl Syndrome and Alström Syndrome  
  Multisystem disorders with overlapping features such as diabetes and sensory deficits.
* X-linked Charcot-Marie-Tooth Disease Type 5 (CMTX5)  
  Characterized by neuropathy, optic atrophy, and hearing loss.
* Deafness-Dystonia-Optic Neuropathy (DDON) Syndrome  
  Shares sensorineural deafness and optic neuropathy features.
* Diabetic Papillopathy  
  Can present with optic nerve head swelling in diabetic patients, potentially confused with optic atrophy.

**EPIDEMIOLOGY**

The estimated prevalence of Wolfram syndrome (WS) worldwide ranges between about 1 in 770,000 and 1 in 100,000, depending on the population studied. More specifically:

* In the United Kingdom, prevalence is estimated at approximately 1 in 770,000 people.
* In North America, it is higher, around 1 in 100,000.
* In Japan, the prevalence is about 1 in 710,000.
* In Lebanon and certain Sicilian populations, prevalence is notably higher, reaching as high as 1 in 68,000 and even 1 in 54,478 in a small Sicilian district, likely due to higher rates of consanguinity.
* In India, estimates suggest a prevalence near 1 in 805,000.

Wolfram syndrome type 1 (WS1) is the most common form, with juvenile-onset diabetes mellitus and optic atrophy as hallmark features. The carrier frequency of WS1 mutations can be as high as 1% in some populations, with a heterozygous carrier rate of about 1 in 354 in the UK. The syndrome is autosomal recessive.

Among patients with juvenile-onset insulin-dependent diabetes mellitus, the prevalence of Wolfram syndrome varies between approximately 1 in 148 and 1 in 175, indicating it is an important but rare cause of diabetes in youth.

WS2, caused by mutations in a different gene, is much rarer, with only a few families described.

The syndrome is associated with significant morbidity and early mortality, with a median age of death around 39 years, often due to neurological complications.

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**ALSTROM SYNDROME**

*ALTERNATIVE NAMES:* Alstrom syndrome is also known as “Alström–Hallgren syndrome”, “ALMS”, “Alstrom syndrome”, or “Alstrom-Hallgren syndrome”.

**DEFINITION / DESCRIPTION**

Alstrom syndrome is a rare repressively inherited genetic disorder. This means that both parents will carry the gene, but are unlikely to be affected themselves.

Alström syndrome is a rare condition that affects many body systems. Many of the signs and symptoms of this condition begin in infancy or early childhood, although some appear later in life.

Alström syndrome is characterized by a progressive loss of vision and hearing, a form of heart disease that enlarges and weakens the heart muscle (dilated cardiomyopathy), obesity, type 2 diabetes (the most common form of diabetes), and short stature. This disorder can also cause serious or life-threatening medical problems involving the liver, kidneys, bladder, and lungs. Some individuals with Alström syndrome have a skin condition called acanthosis nigricans, which causes the skin in body folds and creases to become thick, dark, and velvety. The signs and symptoms of Alström syndrome vary in severity, and not all affected individuals have all of the characteristic features of the disorder.

## **Types Of Alström Syndrome**

Alström Syndrome has several types that affect various parts of the body. These types include cardiac, ocular, renal, hepatic, and neurological involvement. Each type presents unique symptoms and challenges for individuals with the condition, impacting their overall health and quality of life.

It is important for healthcare providers to understand the different types of Alström Syndrome to provide appropriate care and support.

* Cardiomyopathy: Alström Syndrome can manifest with cardiomyopathy, a condition where the heart muscle becomes weakened, leading to inefficient pumping of blood and potential heart failure.
* Retinal Degeneration: Individuals with Alström Syndrome may experience progressive retinal degeneration, which can result in severe vision impairment or blindness over time.
* Obesity: Obesity is a common feature of Alström Syndrome, with affected individuals often developing excessive weight gain during childhood, which can contribute to various health complications.
* Sensorineural Hearing Loss: Sensorineural hearing loss is another characteristic of Alström Syndrome, where the individual may experience difficulty hearing due to damage to the inner ear structures responsible for transmitting sound signals to the brain or due to nerve damage affecting auditory processing.

## **Risk Factors**

The risk factors for Alström Syndrome include inheriting a mutated ALMS1 gene from both parents, which is a rare autosomal recessive pattern. The condition can affect individuals of any ethnic background.

Early diagnosis and management are crucial to improve outcomes and quality of life for those with Alström Syndrome. Regular monitoring and specialized care are essential to address the wide-ranging symptoms of the condition.

* Family history of Alström Syndrome increases the risk of inheriting the condition.
* Obesity in childhood or adolescence is a significant risk factor for developing Alström Syndrome.
* Having diabetes mellitus at a young age is associated with an increased risk of Alström Syndrome.
* Vision problems such as nystagmus or photophobia can be early indicators of Alström Syndrome.
* Cardiac abnormalities, including hypertrophic cardiomyopathy, are common risk factors for Alström Syndrome.

## **Causes of Alström Syndrome**

This gene provides instructions for making a protein that plays a role in the structure and function of cell cilia. Mutations in the ALMS1 gene disrupt cilia function, leading to the various symptoms and complications associated with Alström Syndrome.

* Alström Syndrome is primarily caused by mutations in the ALMS1 gene, which is responsible for encoding a protein essential for various cellular functions.
* Inheritance of the mutated ALMS1 gene in an autosomal recessive pattern from both parents is a major cause of developing Alström Syndrome.
* Certain environmental factors and epigenetic influences may contribute to the development of Alström Syndrome in individuals with a genetic predisposition.
* Rarely, de novo mutations in the ALMS1 gene can occur, leading to the manifestation of Alström Syndrome in individuals without a family history of the condition.
* Alström Syndrome can also arise due to genetic mosaicism, where some cells in the body carry mutations in the ALMS1 gene while others do not, potentially leading to a milder or more variable presentation of the syndrome in affected individuals.

**SIGNS / SYMPTOMS**

Alström Syndrome can cause a range of symptoms, including vision problems, hearing loss, obesity, heart issues, and insulin resistance. People with this condition may also experience breathing difficulties, liver abnormalities, and kidney disease.

Additionally, individuals with Alström Syndrome may develop problems with their bones and joints. Early diagnosis and management are essential for improving quality of life.

* Vision problems: People with Alström Syndrome may experience difficulties with their vision, including blindness or severe impairment over time.
* Hearing loss: Individuals with Alström Syndrome may suffer from progressive hearing loss, which can affect their ability to communicate and interact with others.
* Heart issues: Alström Syndrome can lead to heart problems such as cardiomyopathy, which can cause symptoms like fatigue, shortness of breath, and chest pain.
* Obesity: Many individuals with Alström Syndrome have a tendency to gain weight easily, leading to obesity, which can increase the risk of other health complications.
* Diabetes: Alström Syndrome is associated with early-onset type 2 diabetes, characterized by high blood sugar levels and insulin resistance.

## **Diagnosis of Alström Syndrome**

**Doctors may also conduct specific tests to assess the functioning of various organs** like the heart and eyes. By analyzing the symptoms and test results, healthcare providers can identify the presence of Alström Syndrome and create a treatment plan tailored to the individual's needs.

* Genetic testing is the primary diagnostic method for Alström Syndrome, involving the analysis of the ALMS1 gene for mutations.
* Clinical evaluation, including a detailed medical history and physical examination, can help identify characteristic features of Alström Syndrome.
* Electrocardiogram (ECG) and echocardiogram are utilized to assess cardiac abnormalities commonly associated with Alström Syndrome.
* Ophthalmologic examination is essential to detect retinal degeneration, a hallmark sign of Alström Syndrome.
* Audiologic testing is performed to evaluate hearing impairment, which is another prominent symptom of Alström Syndrome.

**TREATMENT OPTIONS**

Treatment for Alström Syndrome focuses on managing symptoms and complications. This may include medications to control heart problems, diabetes, and vision issues. Regular monitoring by a team of healthcare providers is crucial.

Lifestyle modifications like a healthy diet and exercise can also help improve quality of life. In some cases, surgeries or organ transplants may be necessary for certain complications.

* Management of symptoms: Treatment for Alström Syndrome focuses on managing individual symptoms such as heart disease, diabetes, and vision problems through a multidisciplinary approach involving specialists like cardiologists, endocrinologists, and ophthalmologists.
* Genetic counseling and testing: Individuals with Alström Syndrome and their families benefit from genetic counseling and testing to understand the inheritance pattern of the condition, make informed reproductive decisions, and access appropriate support services.
* Regular monitoring and screenings: Regular medical check-ups, monitoring of heart function, blood sugar levels, and vision screenings are essential to detect and address any complications early on in individuals with Alström Syndrome.

**EPIDEMIOLOGY**

Alström syndrome is a very rare autosomal recessive multisystem disorder with an estimated prevalence of about 1 in 1,000,000 individuals in Europe and North America. Worldwide, more than 950 to approximately 1,200 cases have been documented to date. The incidence estimates vary, ranging broadly from 1 in 100,000 to 1 in 1,000,000, reflecting underdiagnosis and phenotypic variability.

Certain populations with high rates of consanguinity or geographic isolation show a notably higher frequency of Alström syndrome. For example, it is more common among French Acadians in Nova Scotia and Louisiana. The syndrome affects males and females equally.

Because of its rarity and the gradual onset of diverse clinical features, many cases may go unrecognized or misdiagnosed, contributing to uncertainty about its true prevalence. The variability in clinical severity and delayed manifestation of some symptoms also complicate diagnosis.

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**LATENT AUTOIMMUNE DIABETES IN ADULTS(LADA)**

ALTERNATIVE NAMES: Latent autoimmune diabetes in adults is also known as “type 1.5 diabetes”, “adult-onset autoimmune diabetes”, “latent autoimmune diabetes of adulthood”, and “slowly progressive insulin-dependent type 1 diabetes mellitus” (mostly in Japan).

**DEFINITION / DESCRIPTION**

*Latent autoimmune diabetes in adults (LADA) is a type of diabetes that features elements of both Type 1 and Type 2 diabetes. That’s why it’s also known as Type 1.5 diabetes. Healthcare providers believe an autoimmune condition causes LADA (like Type 1 diabetes). But a diagnosis typically comes in adulthood and happens gradually (like Type 2 diabetes). For this reason, it’s often misdiagnosed as Type 2.*

*Healthcare providers diagnose it in adults between ages 30 and 50.*

#### **How rare is LADA diabetes?**

*Even though many people haven’t heard of it, LADA is fairly common. Studies suggest that between 4% and 12% of people who initially receive a Type 2 diabetes diagnosis end up having LADA. To put that in perspective, about 530 million adults worldwide have Type 2. This means several million people potentially have LADA diabetes.*

## ***Symptoms and Causes***

*The symptoms of Type 1.5 diabetes are like those of other forms of diabetes. Some of the most common are:*

* *Being very thirsty (polydipsia).*
* *Needing to pee more often.*
* *Losing weight unexpectedly.*
* *Blurred vision.*
* *Fatigue.*
* *Itchy, dry skin.*

### ***What causes it?***

*Researchers suspect LADA happens when antibodies mistakenly attack and destroy cells in your pancreas that make insulin. When you can’t release insulin, sugar (glucose) builds up in your bloodstream. In this way, it’s like Type 1 diabetes. People with Type 1 need insulin injections to survive. Many people with Type 1 are diagnosed as a child or in their teens.*

*But, like Type 2 diabetes, a LADA diagnosis happens more often in adults with symptoms beginning slowly. This is because your pancreas stops making insulin gradually, which can make it hard to notice symptoms. You may not need insulin injections for months or years. This is why some providers initially suspect Type 2 and not LADA diabetes.*

#### **What triggers LADA diabetes?**

*There aren’t any triggers for LADA because it’s something your immune system does without your control. LADA diabetes can go unnoticed because your pancreas still releases enough insulin not to cause symptoms.*

#### **What are the risk factors?**

*LADA has a strong genetic component, which means you may be susceptible to it if your biological parents or grandparents have it. There’s also evidence that environmental and lifestyle factors play a role in developing LADA. These include things like obesity.*

### ***What are the complications?***

*The biggest complication comes from not receiving the right treatment for the condition. Because it can appear to be Type 2 diabetes, you may not get treatment with insulin as early as you need it. This can increase your risk for health complications like kidney damage.*

*Diabetes-related ketoacidosis (DKA) is a life-threatening complication of LADA diabetes. It happens when your liver starts breaking down body fat for energy because you don’t have enough glucose (blood sugar) in your cells to use for energy.*

## ***Diagnosis and Tests***

### ***How is LADA diabetes diagnosed?***

*LADA usually affects adults who initially receive a Type 2 diabetes diagnosis. But, once you’re unable to manage your blood sugar with oral medications (like metformin) and lifestyle modifications (like eating nutritious foods), healthcare providers may suspect Type 1.5 diabetes.*

*Your healthcare provider will diagnose LADA with a blood test called a GAD Antibodies Test (glutamic acid decarboxylase antibodies). It looks for autoantibodies that target glutamic acid decarboxylase (GAD). If your provider finds signs of these autoantibodies in your blood, it can mean you have an autoimmune disorder that affects your pancreas. If you’re an adult, that likely means you have LADA.*

*Your provider may also order a C-peptide test, which measures how much C-peptide is in your blood. C-peptides tell your provider how much insulin your pancreas is making.*

## ***Management and Treatment***

*Treating LADA is tricky because, initially, you may respond to oral diabetes medications. They may help you manage your blood sugar levels temporarily. But as the condition worsens, your body will respond less. You’ll need to switch to insulin injections to manage your blood sugar because your pancreas will completely lose its ability to create its own insulin. This can happen after a few months or a few years.*

*There isn’t one agreed-upon treatment for LADA. Some experts believe treatment with insulin from the get-go is best, while others may wait to start you on insulin injections.*

*The dosage and amount of insulin you need can vary, so you’ll still need to monitor your blood sugar levels.*

## ***Outlook / Prognosis***

*There’s no cure for Type 1.5 diabetes, but your healthcare provider will help you find treatments to manage it. Once you begin taking insulin, you’ll be better able to manage your blood sugar levels.*

#### **What is the life expectancy of someone with LADA diabetes?**

*Your life expectancy depends on several factors. Having Type 1.5 diabetes alone doesn’t decrease your lifespan. But if you have LADA diabetes and can’t manage your glucose levels, you’re at risk for health complications that can shorten your life expectancy. This is mainly because chronic high blood sugar levels can lead to issues like heart disease, which can impact lifespan.*

## ***Prevention***

*There’s no way to prevent LADA diabetes, because you can’t control or prevent the autoimmune condition that causes it. Getting an early diagnosis and starting treatment right away is the best way to prevent complications from the condition.*

## ***Living With***

### ***How do I take care of myself if I have type 1.5 diabetes?***

*The best way to take care of yourself is to manage your blood sugar. LADA diabetes is often misdiagnosed. It can be frustrating to think you’re doing everything right, only to find that your blood sugar is still hard to manage. If you receive a LADA diagnosis, follow the treatment plan your provider helps you create. Be sure to attend all your follow-up appointments. These visits help your provider check on your pancreas and overall health. They’ll also adjust how much insulin you need.*

### ***When should I see my healthcare provider?***

*Contact a healthcare provider if you have symptoms of diabetes like excessive thirst and frequent urination. Be sure to share your complete health history with your healthcare provider.*

*If you receive a Type 2 diabetes diagnosis and find that your symptoms aren’t getting better after treatment, ask your provider about testing for Type 1.5 diabetes.*

***EPIDEMIOLOGY***

*Latent autoimmune disease in adults is the most frequent form of adult-onset autoimmune DM. Geographic and ethnic differences are apparent in the incidence. In the multicentric 'Action LADA' study from Europe, 9.6% of 6156 adults with adult-onset DM had islet cell autoantibodies. In the United Kingdom Prospective Diabetes Study, the antibody positivity among those with a presumptive diagnosis of T2DM in adults was 15%. Similarly, studies from Norway showed a 10% incidence, whereas studies from the Middle East, Korea, and China showed between 4% and 9%.*

*Most patients with LADA are positive for a single islet autoantibody; glutamic acid decarboxylase antibody is the most predominant. Some population groups have a varying prevalence of different autoantibodies, and measuring just one may underestimate the prevalence of LADA. Autoantibodies appear and disappear during longitudinal follow-up. In these situations, the role of assay interference from anti-idiotype antibodies should be considered. A form of latent autoimmune diabetes in the young has been described.*

**DIFFERENTIAL DIAGNOSIS**

The main challenge is to distinguish patients with LADA from those with T2DM. By definition, patients with T2DM have absent autoantibodies to islet cell antigens, normal or elevated fasting, and stimulated C-peptide and usually do not require insulin for an extended period. Clinicians should consider screening for LADA in patients with T2DM who do not achieve adequate glycemic control within a reasonable period after compliance with therapy. This is particularly true if they are not obese, lack the features of the MetS, or they, or their first-degree relatives, have other autoimmune disorders, including Hashimoto thyroiditis, Graves disease, celiac disease, rheumatoid arthritis, or pernicious anemia.

Patients with classic T1DM present dramatically with ketoacidosis, need insulin at the time of presentation and are easily differentiated from LADA. At times, a young adult with maturity-onset diabetes of the young is mistakenly diagnosed as T1DM, T2DM, or LADA. MODY is rare, has a strong family history, residual C-peptide, and absent humoral and cellular immunity to islet cell antigens. It can be distinguished from LADA.

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**GLUCAGONOMA**

*ALTERNATIVE NAMES*: Glucagonoma is also known as “glucagon-secreting pancreatic neuroendocrine tumor”, “glucagon-secreting pancreatic islet cell tumor”, “pancreatic islet alpha cell tumor”, “endocrine-secreting islet cell tumor - glucagonoma”, and “glucagonoma syndrome”. Another term used is “4D syndrome”.

**DEFINITION / DESCRIPTION**

A glucagonoma is a rare pancreatic tumor that releases glucagon, a hormone. It’s a type of pancreatic neuroendocrine tumor (islet cell tumor).

Glucagon is a natural hormone your body makes that helps manage blood glucose (sugar) levels. Specific cells in your pancreas called alpha cells make glucagon. Glucagon triggers your liver to release stored glucose (glycogen) to raise your blood sugar. Your body normally releases glucagon in response to a drop in blood sugar, prolonged fasting, exercise and protein-rich meals.

A glucagonoma can release excess glucagon. This leads to glucagonoma syndrome, which involves several symptoms and complications, like a painful skin rash and diabetes.

Most glucagonomas begin in the tail or body of your pancreas.

#### Is glucagonoma a cancer?

A glucagonoma is usually cancerous. About 50% of people have metastasis (the cancer has spread) when they receive a diagnosis. It most commonly spreads to your liver.

#### How common is glucagonoma?

Glucagonoma is very rare. There’s less than 1 new case per 1 million people a year. It mostly affects people who are 50 to 70 years old.

## **Symptoms and Causes**

Glucagonomas tend to grow slowly. If you have one that isn’t releasing enough excess glucagon to cause issues for your body, you likely won’t have any symptoms.

If a glucagonoma releases excess glucagon that your body can’t keep up with, it triggers glucagonoma syndrome. This condition has noticeable symptoms. If you develop these symptoms, it’s important to see a healthcare provider as soon as possible.

#### Glucagonoma skin rash

The most common symptom of glucagonoma syndrome is a widespread skin rash called necrolytic migratory erythema (NME). It affects about 90% of people with the syndrome.

The rash can be on any part of your body, but it most often starts in your genital and anal regions, buttocks and lower legs. Other features of NME include:

* It may come and go and move around your body.
* It’s often itchy and painful in the beginning.
* It starts as a ring-shaped reddish area that blisters and crusts over. As the area heals, it may leave behind a brownish mark.
* It can cause a sore smooth tongue (glossitis), a sore mouth, cracked dry lips and angular cheilitis.
* It can cause inflamed eyelids (blepharitis), hair loss and issues with your nails.

#### Diabetes symptoms

The syndrome can lead to high blood sugar (hyperglycemia), which causes diabetes. Symptoms of diabetes include:

* Unexplained weight loss.
* Excessive thirst (polydipsia).
* Frequent urination (polyuria), especially overnight.
* Increased appetite or intense hunger (polyphagia).

#### Other symptoms of glucagonoma syndrome

Other symptoms of glucagonoma syndrome include:

* Chronic diarrhea.
* Anemia, which can cause fatigue, dizziness and other symptoms.
* Blood clots, especially deep vein thrombosis.

It can cause neurological and psychiatric symptoms, including:

* Depression.
* Dementia.
* Agitation.
* Hyperreflexia.
* Ataxia.
* Psychosis.
* Paranoid delusions.

### **What causes glucagonoma?**

In most cases, healthcare providers don’t know the cause of glucagonoma. In about 10% of cases, the tumor is linked to an inherited condition called multiple endocrine neoplasia type (MEN) type 1.

However, even among people with MEN type 1, only a very small percentage will develop a glucagonoma.

## **Diagnosis and Tests**

If you have necrolytic migratory erythema (NME), a healthcare provider will likely suspect glucagonoma and order tests. These tests may include:

* Fasting blood sugar test: An elevated level helps point to glucagonoma and can help confirm diabetes related to glucagonoma.
* Fasting glucagon blood test: With glucagonoma, glucagon levels are abnormally elevated — usually greater than 500 picograms per milliliter (pg/mL). Normal fasting blood glucagon levels are less than 150 pg/mL.
* Amino acid blood test: Glucagonoma usually causes hypoaminoacidemia (low levels of amino acids).
* Complete blood count: This test checks for anemia, which can happen with glucagonoma.

Imaging tests can confirm the presence of a tumor. They may include:

* CT scan.
* MRI scan.
* Endoscopic ultrasound.

## **Management and Treatment**

The treatment for glucagonoma largely depends on whether the tumor is localized (just in your pancreas) or has metastasized (spread to other parts of your body).

Initial treatment for glucagonoma involves managing the symptoms and complications related to excess glucagon. Treatments include:

* Medications to manage glucagon excess: Octreotide and lanreotide injections can help reverse the effects of glucagon excess, as well as prevent the release of glucagon. These medications may also slow down the tumor’s growth. They can also help treat NME, diabetes, diarrhea and neurological symptoms.
* Management of diabetes: You may need oral diabetes medications or insulin injections to keep your blood sugar levels in a healthy range.
* Nutritional support: This may include total parenteral nutrition (TPN) and supplementation of amino acids and zinc to reverse the effects of malnutrition.
* Management of NME: Antibiotics and corticosteroids may help improve NME.
* Anticoagulant therapy: Blood-thinning medication (like heparin) can help prevent deep vein thrombosis.

#### Treatment for localized glucagonoma

If the tumor is only in your pancreas, surgery is the main treatment. If your surgeon can completely remove the tumor, then it’s usually cured. Once the glucagonoma is gone, your glucagon levels should return to normal. Your symptoms should also go away.

#### Treatment for metastasized glucagonoma

When possible, your healthcare provider will recommend surgery to remove tumors. This may include tumors in your pancreas, nearby lymph nodes and liver.

If your surgeon can’t remove any or all of the tumor(s), your healthcare team will likely recommend one or more of the following:

* Chemotherapy: This treatment aims to destroy cancer cells and prevent them from multiplying.
* Radiofrequency ablation: This treatment uses heat from radio waves to kill tumor cells.
* Cryosurgical ablation: This treatment uses extremely cold chemicals, like liquid nitrogen, to destroy cancerous cells.
* Chemoembolization: This treatment blocks a tumor’s blood supply.

## **Outlook / Prognosis**

The prognosis (outlook) for people with glucagonoma depends on several factors, including:

* Your age and overall health.
* The tumor size.
* If the tumor has spread or not.

The outlook is usually good if the tumor is contained within your pancreas. Surgery to remove the tumor typically cures these cases. But this represents only about 20% of glucagonoma cases.

Glucagonomas are very rare, so there’s not much data that can predict survival rates and outcomes for metastasis. Your healthcare team will be able to provide more information based on your unique situation.

## **Prevention**

As scientists don’t know the cause of most cases of glucagonoma, there’s nothing you can do to prevent it.

If one of your first-degree relatives (biological parents and siblings) has a multiple endocrine neoplasia (MEN) diagnosis, talk to your healthcare provider about genetic testing that can screen for the condition. If you do have MEN, genetic testing could help detect tumors in their early phases.

**DIFFERENTIAL DIAGNOSIS**

Glucagonoma is a rare pancreatic neuroendocrine tumor characterized by excessive glucagon secretion, leading to a syndrome with necrolytic migratory erythema (NME), diabetes mellitus, weight loss, anemia, and other systemic symptoms. Because many symptoms overlap with other conditions, several differential diagnoses should be considered:

*1. Skin Rash Differential Diagnoses (Necrolytic Migratory Erythema Mimics)*

* Cirrhosis-associated skin changes
* Chronic pancreatitis-related rash
* Celiac disease (gluten-sensitive enteropathy)
* Psoriasis
* Paraneoplastic syndromes
* Vitamin and mineral deficiency syndromes (e.g., pellagra [niacin deficiency], zinc deficiency)
* Toxic epidermal necrolysis (e.g., associated with hepatitis B)
* Immunobullous diseases (e.g., pemphigus, bullous pemphigoid)
* Herpes simplex virus infections
* Seborrheic dermatitis or contact dermatitis

*2. Metabolic and Endocrine Conditions*

* Diabetes mellitus (type 1 or type 2) causing hyperglycemia without glucagonoma
* Prolonged fasting or malnutrition causing metabolic disturbances
* Familial hyperglucagonemia (benign elevation of glucagon without tumor)
* Pancreatitis (acute or chronic) causing elevated glucagon or skin changes
* Renal failure causing moderate glucagon elevation and skin manifestations

*3. Other Neoplastic or Paraneoplastic Syndromes*

* Pancreatic adenocarcinoma (non-functioning tumor)
* Other pancreatic neuroendocrine tumors (PNETs) with different hormone secretion
* Multiple endocrine neoplasia type 1 (MEN1) associated tumors (rarely glucagonoma)

*4. Nutritional Deficiency Syndromes*

* Acrodermatitis enteropathica (zinc deficiency)
* Pellagra (niacin deficiency)
* Essential fatty acid deficiency

1. *Other Causes of Hyperglycemia and Weight Loss*

* Chronic infections or malignancies causing cachexia
* Malabsorption syndromes
* Chronic liver disease

The following differential diagnoses should also be considered when evaluating glucagonomas:

* Fasting plasma glucagon levels can be elevated in several conditions, including acute trauma, diabetes mellitus, burn injuries, sepsis, renal failure, cirrhosis, pancreatitis, and Cushing syndrome. While glucagon levels may rise in these situations, they typically remain below 500 pg/mL. One rare disorder characterized by an inactivation mutation in the glucagon receptor gene is known as Mahvash disease. This condition leads to pancreatic alpha cell hyperplasia and an increase in glucagon levels, but without accompanying symptoms.
* NME is not specific to glucagonoma and can also be seen in chronic liver disease, inflammatory bowel disease, pancreatitis, heroin abuse, jejunal and rectal adenocarcinoma, and myelodysplastic syndrome.
* NME-like lesions have been associated with essential fatty acid deficiency, zinc deficiency (acrodermatitis enteropathica), and dermatosis associated with protein-calorie malnutrition.

**GUIDELINES**

**Diagnosis**

The NCCN guidelines recommend the following testing for the diagnosis of glucagonoma:

* Glucagon and blood glucose
* Multiphasic computed tomography (CT) or magnetic resonance imaging (MRI) of the abdomen with or without the pelvis

The following testing may be appropriate:

* Somatostatin receptor (SSTR) positron emission tomography (PET)/CT or SSTR-PET/MRI
* Chest CT with or without contrast
* Endoscopic ultrasound
* Biochemical evaluation when clinically indicated
* Consider genetic testing and counseling for inherited genetic syndromes

Overall, the NANETS guidelines concur with the recommendations above. With regard to screening patients for inherited genetic syndromes, NANETS guidelines recommend that patients with glucagonoma undergo a thorough history (including family history) and physical examination (including skin examination) to identify symptoms and signs of multiple endocrine neoplasia type 1 (MEN1), von Hippel-Lindau (VHL) syndrome, neurofibromatosis type 1 (NF1), or tuberous sclerosis complex type 1 and 2 (TSC1-2). If any of those syndromes is suggested, the patient should be referred to a medical geneticist for further evaluation.

Testing for MEN1 is indicated in patients who have any other MEN1-associated tumors such as the following:

* Pa parathyroid adenoma or multigland hyperplasia
* Thymic or bronchial neuroendocrine tumor
* Pituitary adenoma
* Adrenal nodule

**Treatment**

The NCCN's recommended treatment for symptoms and/or tumor control in locoregional disease includes octreotide long-acting release (LAR) 20–30 mg IM or lanreotide 120 mg SC every 4 weeks. For added symptom control, octreotide 100–250 mcg SC TID can be considered. Diabetes and hyperglycemia should be treated as appropriate. The recommended surgical intervention is distal pancreatectomy, peripancreatic lymphadenectomy, and splenectomy.

NANETS also recommends the somatostatin analogues octreotide or lanreotide as first-line treatment of glucagonoma and glucagonoma syndrome.Localized, biochemically confirmed glucagonoma should be resected for control of the tumor and management of glucagonoma syndrome.

For metastatic disease, NCCN guidelines recommend resection of metastases and primary tumor, if complete resection is possible.The NANETS guideline conference reached no consensus on the benefit of resection of primary tumors in patients with metastases. The guidelines do suggest that factors to be considered in individual cases include the following:

* Location of the tumor
* Patient age and morbidities
* Ability to treat or avoid local complications
* Possibility of improved response to peptide receptor radionuclide therapy (PRRT)

For progressive disease, the NCCN guidelines recommend managing clinically significant symptoms as appropriate. Octreotide LAR or lanreotide (if the patient is not already receiving it) should be considered. Alternative options for disease progression include the following:

* Clinical trial
* Everolimus
* Sunitinib
* Temozolomide with capecitabine
* PRRT with 177Lu-dotatate (if SSTR-positive and progression on octreotide LAR or lanreotide)
* Other cytotoxic chemotherapy
* Consider belzutifan in the setting of germline *VHL* alteration
* Consider liver-directed therapy for liver-predominant disease
* Palliative radiation therapy for symptomatic bone metastases

**EPIDEMIOLOGY**

Glucagonoma is very rare. There’s less than 1 new case per 1 million people a year. It mostly affects people who are 50 to 70 years old.

A study by Yao and colleagues, based on an analysis of the Surveillance, Epidemiology, and End Results (SEER) program database between 1973–2003, reported the occurrence of a total of 2705 cases of endocrine pancreatic tumors in the United States. According to these authors, the incidence of glucagonoma is very low, with islet cell neoplasms accounting for 1.3% of pancreatic cancers.

Glucagonoma probably accounts for 1% of all neuroendocrine tumors. The annual incidence rate is estimated at 1 case per 20 million population, but that is probably an underestimation because of the relative lack of specificity of the symptoms. Autopsy studies have reported the incidence of islet cell tumors with glucagon-expressing cells at approximately 1%, supporting the assertion that many of these tumors are undiagnosed and may be associated with subclinical disease.

No race prevalence is known for glucagonoma. The frequency of glucagonoma in males and females is nearly equal, although a greater incidence has been reported in females. Most patients with glucagonoma are in the sixth decade of life, with a mean age of 55 years and an age range of 19-84 years.

Glucagonomas are exceedingly rare neoplasms, with an estimated annual incidence ranging from 0.01 to 0.1 new cases per 100,000 individuals. These tumors most commonly present in individuals between the fifth and sixth decades of life, with no significant difference in incidence between males and females.

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**MONOGENIC DIABETES**

**DEFINITION / DESCRIPTION**

Monogenic diabetes is a rare condition resulting from mutations (changes) in a single gene. In contrast, the most common types of diabetes—**type 1 and type 2**—are caused by multiple genes (and in type 2 diabetes, lifestyle factors such as obesity). Most cases of monogenic diabetes are inherited from a parent who also has the disorder. It accounts for 2-5 % of all diabetes mellitus.   
  
Monogenic diabetes appears in several forms and most often affects young people, mostly 25 years or younger. In most forms of the disease, the body is less able to make **insulin**, a hormone that helps the body use glucose (sugar) for energy. Rarely, the problem is severe insulin resistance, a condition in which the body cannot use insulin properly. The specific form of monogenic diabetes may also be called MODY (formerly, maturity onset diabetes of the young) or neonatal diabetes, depending on when it develops.

#### **Endocrine Connection**

People typically have two copies of most genes, with one gene inherited from each parent. Genes are instrumental for making proteins within cells. If a gene has mutated, the protein may not function properly, affecting the body’s ability to produce or regulate insulin properly.

The hormone insulin allows the cells in the muscles, fat and liver to absorb glucose that is in the blood. The glucose serves as energy to these cells, or it can be converted into fat when needed. Insulin also affects other metabolic processes, such as the breakdown of fat or protein.   
  
Some patients with monogenic diabetes are misdiagnosed as having type 1 or 2 diabetes. The genes control the development, function, and regulation of the insulin-producing (islet, or beta) cells of the pancreas. The monogenic diabetes conditions were previously numbered (see below), related to timing of discovery of the genetic problem, but now are referred to by their genetic mutations.   
  
The most common mutations are related to genes hepatocyte nuclear factor-1-alpha (HNF1A, MODY3) and glucokinase (GCK, MODY2) genes in 50-60% and 15-30% of people with monogenic diabetes, respectively.   
  
Some genes causing monogenic diabetes can also cause a more severe form of diabetes, presenting as a baby (neonatal diabetes). The genes are categorized based on whether they cause abnormal insulin production and secretion, islet cell destruction, or abnormal pancreas development.

**CAUSES**

A variant, or change, in a single gene causes monogenic diabetes.

You inherited genes—which determine things like your hair color, eye color, and height—from each of your parents. In most cases of MODY forms of diabetes, you inherit a gene from one or both parents that causes the disease.

Babies with NDM forms of diabetes rarely have a family history of the disease. Most cases of NDM are caused by a gene change that happens while a baby develops in the womb.

Most people with MODY forms of diabetes have inherited a gene for the disease from a parent who also had the disease. Diseases caused by a gene from one parent are called autosomal dominant. If you have a form of NDM or MODY that is autosomal dominant, your child has a 50% chance of having the disease.

Some forms of NDM or MODY occur only if a child inherits a gene for the disease from both parents. In most cases, neither of the child’s parents had the disease. Diseases that occur only if you inherit a gene from both parents who don’t have the disease are called autosomal recessive. If you inherit a gene for a recessive form of NDM or MODY from only one parent, you won’t have the disease. However, you can pass that gene to future generations.

Different gene variants cause monogenic diabetes in different ways. For example, gene variants may

* affect how the pancreas develops
* cause the pancreas to produce insulin that does not work well
* destroy cells in the pancreas that produce insulin

**SIGNS / SYMPTOMS**

#### **MODY (formerly Maturity-Onset Diabetes of the Young)**

MODY is the most common form of monogenic diabetes. It usually first occurs in children or teenagers but sometimes is not found until adulthood. MODY can be mild or severe, depending on which gene is involved. Researchers have found at least nine different genes responsible for MODY, and new genetic causes are still being discovered.

Some of the most common are:   
  
**MODY1, hepatocyte nuclear factor-4-alpha (HNF4A)**: This gene mutation causes decreased insulin secretion in response to glucose in diet which gets progressively worse during adolescence. Patients may initially do well with oral medications (sulfonylureas) but eventually may need insulin, and are at risk for complications of diabetes.   
  
**MODY2, glucokinase (GCK)**: This gene mutation causes problems converting glucose into a signal for the pancreas to make insulin. Therefore, insulin is not made until higher glucose levels are reached in the blood. Usually, this form of monogenic diabetes is mild, stable, and not associated with complications. It can be controlled with diet, if needed.   
  
**MODY3, hepatocyte nuclear factor-1-alpha (HNF1A)**: This gene mutation can cause decreased insulin secretion and glucose wasting in the urine. Patients can often be treated with oral medication (sulfonylureas), even if they were previously taking insulin. Patient are at risk for complications of diabetes, including cardiovascular mortality.   
  
**MODY4, insulin promoter factor 1 (IPF1)**: This gene defect reduces the body’s ability to tell insulin to be made. It can be seen in different ways in individuals, from needing insulin, to having late-onset type 2-like diabetes, to having slightly higher blood glucose levels. Treatment is based on severity in the individual.   
  
**MODY5, hepatocyte nuclear factor-1-beta (HNF1B)**: This gene defect can cause a multitude of problems besides diabetes, including small pancreas size, abnormal kidney development, slowly progressive kidney disease, low magnesium levels, elevated liver tests, and genital anomalies.   
  
**MODY6, neurogenic differentiation factor 1 (NEUROD1)**: This gene defect causes problems with the development of insulin-producing cells of the pancreas and requires insulin treatment.

#### **Neonatal Diabetes**

This rare condition occurs in the first 6 months of life. Many infants with neonatal diabetes don’t grow well before birth and are born small for their age. The gene mutations can present in the following ways:

* Permanent neonatal diabetes, a lifelong condition
* Responsive to oral medication (sulfonylureas), 40% of cases
* Requiring lifelong insulin, 10% of cases
* Requiring insulin due to a syndrome also having other features (skeletal, liver, eye, hearing, cardiac, kidney, immune, neurologic), 10% of cases
* No genetic cause, 20% of cases
* Transient neonatal diabetes, 20% of cases: goes away during infancy but can return later in life, especially during puberty or pregnancy, is treated with oral medication or insulin depending on the gene defect

**DIAGNOSIS METHODS**

A correct diagnosis can help people get the right treatment. For example, some children with monogenic diabetes are misdiagnosed with type 1 diabetes and are given insulin. When correctly diagnosed, some of these children can take diabetes pills instead, with even better glucose control. A correct diagnosis may also benefit family members, who might have monogenic diabetes themselves without knowing it.

Because monogenic diabetes is rare, this diagnosis is often not considered in people with diabetes. However, certain factors (see below) can make doctors suspect that a diagnosis of type 1 or type 2 diabetes is not correct. A combination of tests and clinical factors help rule out type 1 or type 2 diabetes and identify MODY or neonatal diabetes.   
  
**Blood Tests:** Blood glucose and insulin levels help with diagnosis. Doctors might also check for the presence of certain autoimmune antibodies (substances made by the body that work against one’s own healthy tissues), which suggests type 1 diabetes.   
  
**Clinical Factors:** Doctors consider factors that may suggest monogenic diabetes:

* Being diagnosed in the first six months of life
* Having other conditions caused by a specific gene mutation, such as cysts in the kidneys, deafness, or genital abnormalities
* Not being overweight or obese with negative autoimmune antibodies for type 1 diabetes mellitus
* Having a family history of diabetes, especially when a parent or other first-degree relative (sibling or child) is affected, or when at least 3 generations have diabetes, or when family members with diabetes have normal weights
* Belonging to certain ethnic groups (since European Caucasians are less affected by type 2 diabetes)
* Having a mild form of diabetes as a child, which does not require insulin

None of these factors alone mean someone might have monogenic diabetes. Instead, they are considered together, along with blood test results.   
  
**Genetic Testing**: A health care provider can best determine whether genetic testing is needed. Testing of the genetic information in a blood sample can determine whether a person has a gene causing MODY or neonatal diabetes. Doctors also can check family members of the person with MODY or neonatal diabetes for the presence or risk of diabetes. These are commercially available.

**TREATMENT OPTIONS**

Treatment depends on the type of MODY. Some people do not need any treatment besides diet and exercise. Others need diabetes medicines. These include injected insulin or a sulfonylurea—a type of diabetes pill that helps the body make more insulin. In one type of MODY, patients also may need treatment for related conditions such as kidney cysts and gout.

Doctors choose treatment based on the cause. Some types of neonatal diabetes can be treated with a sulfonylurea, but others require insulin. Infants with transient neonatal diabetes may require insulin at first but the condition may disappear at about the age of 12 weeks. If the diabetes returns later in life, insulin might be needed.

If you or a family member has been diagnosed with type 1 or type 2 diabetes, but you suspect it might be monogenic diabetes, talk with your doctor. Only a specialist, such as an endocrinologist specializing in diabetes, can diagnosis monogenic diabetes.

## Monogenic Diabetes Management

Managing monogenic diabetes in children involves a multidisciplinary approach to address the unique needs of each patient. Here are some key strategies for effective management:

* Genetic Testing: Genetic testing is crucial for confirming the diagnosis of monogenic diabetes and identifying the specific gene mutation involved. This information helps guide treatment decisions and allows for personalized care.
* Dietary Modifications: A balanced diet plays a vital role in managing blood sugar levels in children with monogenic diabetes. Working with a dietitian to develop a customized meal plan can help regulate glucose levels and support overall health.
* Regular Monitoring: Monitoring blood sugar levels regularly is essential for tracking the effectiveness of treatment and making necessary adjustments. Continuous glucose monitoring systems can provide real-time data to help manage diabetes more effectively.

## Types of Monogenic Diabetes

Understanding the different types of monogenic diabetes is crucial for tailoring treatment approaches. Here are the main types of monogenic diabetes seen in children:

* MODY (Maturity Onset Diabetes of the Young): MODY is characterized by impaired insulin secretion and typically diagnosed before the age of 25. Genetic testing is necessary for accurate diagnosis and appropriate management.
* Neonatal Diabetes: Neonatal diabetes presents within the first six months of life and requires lifelong treatment with insulin. genetic mutations play a significant role in the development of this type of diabetes.

## Pediatric Diabetes Treatment Options

When it comes to treating monogenic diabetes in children, several options can help manage the condition effectively. Here are some common treatment approaches:

* Insulin Therapy: Children with monogenic diabetes may require insulin therapy to regulate blood sugar levels. Insulin doses are tailored to each child's needs based on factors like age, weight, and overall health.
* Oral Medications: In some cases, oral medications may be prescribed to help control blood sugar levels in children with monogenic diabetes. These medications work by increasing insulin sensitivity or reducing glucose production in the liver.

## Insulin Therapy for Children

Insulin therapy is a cornerstone of treatment for children with monogenic diabetes. Here are some essential points to consider:

* Insulin Administration: Children with monogenic diabetes may need multiple daily insulin injections or use an insulin pump for continuous insulin delivery. It's essential to follow a consistent insulin regimen to maintain stable blood sugar levels.
* Monitoring: Regularly monitoring blood sugar levels helps ensure that insulin therapy is effective and allows for timely adjustments to doses or timing. Continuous communication with healthcare providers is essential for optimizing insulin therapy.

## Genetic Testing for Diabetes

Genetic testing plays a crucial role in diagnosing and managing monogenic diabetes in children. Here's why genetic testing is essential:

* Accurate Diagnosis: Genetic testing helps confirm the presence of specific gene mutations associated with monogenic diabetes, enabling targeted treatment approaches.
* Personalized Treatment: Knowing the genetic cause of diabetes allows healthcare providers to tailor treatment plans to address the underlying genetic factors contributing to the condition.

## **Epidemiology of Monogenic Diabetes**

* Prevalence:  
  Monogenic diabetes, including maturity-onset diabetes of the young (MODY), accounts for approximately 1% to 5% of all diabetes cases, with most estimates clustering around 1% to 3% depending on the population studied. For example, MODY prevalence is estimated at about 100 cases per million people (0.01%) in the general population, and around 1.2% of pediatric diabetes cases in the United States.
* Prevalence in Diabetes Subgroups:  
  Among individuals diagnosed with diabetes before age 35, monogenic diabetes accounts for roughly 2% to 3% of cases. In some European cohorts, MODY prevalence ranges from 1 to 5 per 10,000 people (0.01% to 0.05%), representing 1% to 5% of all diabetes cases. In the UK, monogenic diabetes prevalence is estimated at 2.5% of all diabetes cases, with a minimum prevalence of 68 to 108 per million (0.0068% to 0.01%).
* Incidence:  
  The minimum incidence of monogenic diabetes in children and youth under 18 years is estimated at about 0.2 cases per 100,000 per year, with MODY incidence around 2.4% among children and adolescents newly diagnosed with diabetes.
* Geographic and Ethnic Variation:  
  Most prevalence data come from European populations with centralized genetic testing. Prevalence estimates vary by country:
  + Germany: ~24 per million
  + Netherlands: ~30 per million
  + UK: 68–108 per million
  + Australia: ~89 per million
  + United States: ~1.2% of pediatric diabetes cases  
    Data from Africa, Asia, South America, and the Middle East are limited but suggest variation in prevalence and mutation spectrum.
* Common Genetic Subtypes:  
  The most frequent MODY subtypes include *HNF1A*-MODY, *GCK*-MODY, *HNF4A*-MODY, and *HNF1B*-MODY, with regional variation in subtype distribution.
* Underdiagnosis:  
  Monogenic diabetes is often misdiagnosed as type 1 or type 2 diabetes due to overlapping clinical features and limited genetic testing, leading to underestimation of true prevalence.

**Differential Diagnosis of Monogenic Diabetes**  
Monogenic diabetes, including maturity-onset diabetes of the young (MODY) and neonatal diabetes, must be differentiated from the more common types of diabetes—type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM)—as well as other rare forms. Key points in differential diagnosis include clinical features, family history, biochemical markers, and genetic testing.  
1. Type 1 Diabetes Mellitus (T1DM)

* + Similarities: Early onset of diabetes, hyperglycemia, insulin dependence in many cases.
  + Differences:
    - T1DM is autoimmune, characterized by presence of pancreatic autoantibodies (e.g., GAD65, IA2).
    - Usually presents with rapid onset and ketoacidosis.
    - Monogenic diabetes typically lacks autoantibodies and ketoacidosis at diagnosis.
    - C-peptide levels are usually low or absent in T1DM, whereas monogenic diabetes patients often have preserved insulin secretion (detectable C-peptide).
    - Family history: T1DM has less consistent family history, while monogenic diabetes often shows autosomal dominant inheritance with multiple affected generations.
* 2. Type 2 Diabetes Mellitus (T2DM)
  + Similarities: Mild hyperglycemia, sometimes diagnosed in young adults, non-insulin-dependent initially.
  + Differences:
    - T2DM is strongly associated with obesity, insulin resistance, metabolic syndrome, and higher-risk ethnicities.
    - Monogenic diabetes patients are often non-obese with no features of insulin resistance.
    - Family history in T2DM is often less clear-cut and may lack the autosomal dominant pattern seen in monogenic diabetes.
    - Genetic testing can distinguish monogenic diabetes from T2DM.
* 3. Other Rare Forms of Diabetes
  + Neonatal Diabetes Mellitus (NDM)
    - Presents within the first 6 months of life, can be transient or permanent.
    - Genetic testing is crucial to differentiate from early-onset T1DM or other causes.
  + Secondary Diabetes
    - Due to pancreatitis, cystic fibrosis, medications, or endocrinopathies.
    - Usually lacks family history and genetic markers of monogenic diabetes.
* Diagnostic Tools to Aid Differential Diagnosis
  + Pancreatic Autoantibodies: Positive in 70–96% of T1DM at diagnosis; usually negative in monogenic diabetes.
  + Urinary C-Peptide Creatinine Ratio (UCPCR): Useful to assess endogenous insulin production; preserved in monogenic diabetes even years after diagnosis, low in T1DM.
  + Family History: Autosomal dominant inheritance pattern (diabetes in successive generations) strongly suggests monogenic diabetes.
  + Age of Onset: Diagnosis before age 25 with non-insulin dependence favors monogenic diabetes.

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**DIABETIC COMPLICATIONS**

ALTERNATIVE NAMES: Diabetic complications are referred to by several alternative names, including “**microvascular” and “macrovascular” complications**.

**DEFINITION / DESCRIPTION**

Diabetic complications refer to various health issues that can arise due to prolonged high blood sugar levels. These complications can affect multiple organs and systems in the body. Common complications include eye problems such as glaucoma, cataracts, and blindness, foot problems including nerve and blood vessel damage which can lead to sores, infections, and even amputation, and heart attacks due to damage to blood vessels. Additionally, diabetes can lead to kidney disease, neuropathy, and other chronic issues. There are also acute complications such as hypos and diabetic ketoacidosis (DKA). Over time, high blood sugar levels can damage nerves, leading to numbness, tingling, or shooting pains in the fingers, hands, toes, and feet. It is important to manage diabetes effectively to reduce the risk of these complications.

**TYPES OF DIABETIC COMPLICATIONS**

Diabetic complications can be categorized into acute and long-term (chronic) issues. Acute complications include hypoglycemia (low blood sugar) and diabetic ketoacidosis (DKA), which can be life-threatening and require immediate medical attention. Long-term complications arise from prolonged high blood sugar levels and can affect various organs and systems in the body. These include eye problems such as retinopathy, which can lead to blindness, foot problems due to nerve damage and reduced blood flow, which can result in ulcers and even amputation. Heart attacks and stroke are also common long-term complications due to damage to the blood vessels. Additionally, diabetes can cause nerve damage (neuropathy), leading to numbness, tingling, and pain, particularly in the extremities. Kidney disease (nephropathy) is another potential complication, which can progress to kidney failure. Diabetes can also lead to skin conditions, digestive problems, and sexual dysfunction. It is important to note that maintaining good blood glucose control, along with regular medical check-ups and a healthy lifestyle, can significantly reduce the risk of these complications.

Some diabetic complications include:

* Diabetic neuropathy
* Diabetic nephropathy
* Diabetic retinopathy
* Diabetic ophthalmopathy
* Peripheral vascular disease

**DIABETIC NEUROPATHY**

*ALTERNATIVE NAMES*: Diabetic neuropathy is also known by several alternative names, including “diabetic polyneuropathy”, “diabetic autonomic neuropathy”, “proximal neuropathy”, and “focal neuropathy”. Additionally, it is sometimes referred to as “peripheral neuropathy”, which is the most common type of neuropathy associated with diabetes. Other terms used include “diabetic amyotrophy”, “mononeuropathy”, and “mononeuropathy multiplex”.

**DEFINITION / DESCRIPTION**

Diabetes-related neuropathy is nerve damage that affects people with diabetes. The most common type is peripheral neuropathy, which often affects your feet. There’s no cure for diabetes-related neuropathy. But you can manage it with medication, therapies and tighter blood sugar management.

**What is diabetes-related neuropathy?**

Neuropathy is a complication of diabetes that can lead to problems throughout the body. Diabetes can affect nerves that control movement, sensation and other functions.

If you have diabetes, you can develop nerve problems at any time. Sometimes, neuropathy can be the first sign of diabetes. Significant nerve problems (clinical neuropathy) can develop within the first 10 years after a diabetes diagnosis. The risk of developing neuropathy increases the longer you have diabetes. About half of people with diabetes have some form of neuropathy.

Diabetes-related neuropathy happens when you experience nerve damage due to high blood sugar (hyperglycemia) that lasts a long time. It can affect people with long-term diabetes, like Type 1 diabetes and Type 2 diabetes. But not everyone with diabetes develops it.

Neuropathy can develop from other causes, too, like pinched nerves, inflammation, nutrient deficiencies and injuries affecting your nerves. Healthcare providers diagnose neuropathy as diabetes-related if you have diabetes and they can’t find another cause for it.

**Types of diabetes-related neuropathy**

Diabetes-related neuropathy can damage different nerves throughout your body. Types of diabetes-related neuropathy include:

* **Peripheral neuropathy**: This is the most common type of neuropathy. “Peripheral” refers to any of the nerves outside of your spinal cord. It often affects your feet and legs and sometimes your hands.
* **Autonomic neuropathy**: This type of neuropathy happens when you have damage to autonomic nerves, which control your involuntary body processes. They control things like your bladder, intestinal tract, blood pressure, heart and sex organs. Another name for autonomic neuropathy is dysautonomia.
* **Proximal neuropathy**: This is a rare type of neuropathy that affects nerves in your hip, thigh or buttock. It typically only affects one side of your body.

Some other types of diabetic neuropathy include:

**Focal Neuropathy (Diabetic Mononeuropathy)**

This type of diabetic neuropathy affects one nerve at a time, and the symptoms depend on which nerve is affected. For example, it can affect nerves in the chest (thoracic nerves) and cause numbness and pain in the chest wall that mimics angina, heart attack or appendicitis.

Other types of focal neuropathy can cause:

* Pain in the thighs.
* Severe pain in lower back or pelvis.
* Pain in the chest, stomach or flank.
* Aching behind the eyes.
* Inability to focus the eyes.
* Double vision.
* Paralysis on one side of the face.
* Hearing problems.

**Diabetic Polyneuropathy**

Diabetic polyneuropathy (DPN) affects multiple peripheral sensory and motor nerves that branch out from the spinal cord into the arms, hands, legs and feet. Typically, the longest nerves — those that extend from the spine to the feet — are affected the most.

DPN can cause:

* Unusual sensations (paresthesias) such as tingling, burning or prickling.
* Numbness and pain in the hands, legs and feet.
* Weakness of the muscles in the feet and hands.
* Sharp pains or cramps.
* Extreme sensitivity to touch.
* Insensitivity to pain or temperature changes.
* Loss of balance or coordination, and difficulty walking on uneven surfaces.

Because it inhibits the ability to sense problems, DPN can put a person at risk for injuries of the feet and toes, and lead to the development of ulcers, wounds and chronic infections in the feet.

Some mild cases of DPN may go unnoticed for years, but worsening nerve damage can cause severe pain and make the simplest of daily activities — such as sleeping or walking — extremely uncomfortable.

If left untreated, DPN can result in further nerve damage to other parts of the body, such as the eyes, digestive tract and sexual organs. It also is the primary cause of amputations, resulting in nearly one case every five-and-a-half minutes in the United States.

DPN has two distinct types: diabetic autonomic neuropathy and proximal neuropathy.

**Diabetic Autonomic Neuropathy**

Diabetic autonomic neuropathy primarily affects the autonomic nerves that serve internal organs, processes, and systems of the heart, digestive system, sexual organs, urinary tract and sweat glands.

This kind of diabetic polyneuropathy can cause symptoms such as:

* Persistent nausea and vomiting.
* Diarrhea, constipation.
* Sweating abnormalities.
* Sexual dysfunction.
* Digestive problems.
* Low blood pressure.
* Impaired perception of pain.
* Hypoglycemia.

**Proximal Neuropathy (Diabetic Amyotrophy)**

Proximal neuropathy is known by many names, and is a relatively rare type of diabetic neuropathy that occurs in about 1% of patients with type 2 diabetes. It tends to affect older adults, and can strike those with recently diagnosed or well-controlled diabetes.

The main symptom is nerve pain that starts in the upper thigh of one leg and can involve the hip and lower back. Weight loss is a symptom in about 35% of patients with proximal neuropathy, and about 18% experience weakness in the affected area in addition to the pain. Rarely, proximal neuropathy can occur in the arm.

As the condition progresses over months, the pain can spread to involve the upper and lower parts of both legs. After several months, symptoms tend to ease up, but patients can be left with lasting disability, including foot drop and recurrence of symptoms.

The symptoms of diabetic neuropathy may resemble other conditions or medical problems. Always consult your doctor for a diagnosis.

**CAUSES**

**What causes diabetes-related neuropathy?**

Perpetually high blood sugar levels can damage small blood vessels that provide oxygen and nutrients to your nerves. Without enough oxygen and nutrients, nerve cells can die, affecting the function of your nerve. This causes neuropathy.

Each person is different, so it’s almost impossible to predict how high blood sugar levels have to be — and for how long — to cause neuropathy. One study of people with Type 2 diabetes shows that having an A1C over 7% for at least three years increases your risk of diabetes-related neuropathy. An A1C of 7% means your blood sugar is 154 mg/dL on average.

What causes diabetic neuropathy?

Although the exact causes of diabetic neuropathy are unknown, several factors may contribute to the disorder, including:

* **High blood sugar (glucose)**. High blood glucose causes chemical changes in nerves and impairs the nerves’ ability to transmit signals. It can also damage blood vessels that carry oxygen and nutrients to the nerves.
* **Metabolic factors**. In addition to glucose levels, high triglyceride and cholesterol levels are also associated with increased risk of neuropathy. Patients who are overweight or obese are also at increased risk of developing neuropathy.
* **Inherited factors**. There are some genetic traits that may make some people more susceptible to nerve disease than others.

**RISK FACTORS**

**What are the risk factors for diabetes-related neuropathy?**

If you have diabetes, your chance of developing diabetes-related neuropathy increases the older you get and the longer you’ve had diabetes.

Studies show that peripheral neuropathy affects at least 20% of people with Type 1 diabetes who’ve had diabetes for at least 20 years. It affects 15% to 50% of people with Type 2 diabetes who’ve had diabetes for at least 10 years.

You’re also more likely to develop neuropathy if you have diabetes along with:

* High blood pressure (hypertension).
* High body mass index (BMI).
* High cholesterol.
* Kidney disease.
* Alcohol use disorder.
* Smoking.

Studies show that genetics may also increase your risk of diabetes-related neuropathy.

**SIGNS / SYMPTOMS**

Your symptoms will depend on which type of diabetes-related neuropathy you have.

**Symptoms of diabetes-related peripheral neuropathy**

Diabetes-related peripheral neuropathy commonly affects your feet. Symptoms include:

* Numbness, tingling and/or pins and needles sensations (paresthesia).
* Pain, which may be burning, stabbing or shooting.
* Unusual touch-based sensations (dysesthesia).
* Muscle weakness.
* Slow-healing leg or foot sores (ulcers).
* Total loss of sensation in your feet, like not feeling pain from foot injuries.

Nerve damage that causes peripheral neuropathy typically develops over many years. You may not notice symptoms of mild nerve damage for a long time.

**Symptoms of diabetes-related autonomic neuropathy**

Autonomic neuropathy can have many different symptoms because it can affect several body systems. Examples include:

* **Digestive system**: Indigestion, heartburn (Heartburn is a burning sensation that feels like it’s in your heart, but isn’t really. It’s in your esophagus, the swallowing tube that runs alongside your heart. The feeling is caused by acid refluxing up from your stomach. It’s treatable.), nausea and vomiting, gas, diarrhea and constipation. Gastroparesis is a type of digestive system neuropathy.
* **Urinary system**: Urinary incontinence, urinary retention and frequent UTIs (Urinary tract infection).
* **Sex organs**: Sexual dysfunction, erectile dysfunction, retrograde ejaculation, vaginal dryness and anorgasmia.
* **Cardiovascular system**: Low blood pressure, irregular heart rate, dizziness and fainting.
* **Sweat glands**: Excessive sweating or a lack of sweat.
* **Eyes**: Difficult for your pupils to adjust to changes in light.

Autonomic neuropathy can also cause hypoglycemia unawareness. This means you don’t experience the typical warning signs of low blood sugar, like shakiness, confusion and intense hunger.

**Symptoms of diabetes-related proximal neuropathy**

Symptoms of proximal neuropathy include:

* Sudden and severe pain in your hip, buttock or thigh.
* Weakness in your leg that makes it difficult to stand up.
* Loss of reflexes, like the knee-jerk reflex.
* Loss of muscle tissue (atrophy) in the affected area.
* Unexplained weight loss.

**DIAGNOSIS METHODS**

To start, a healthcare provider will ask detailed questions about your medical history and diabetes management. They’ll ask about your symptoms and do a physical exam. Tests that help confirm a diabetes-related neuropathy diagnosis include:

* **Diabetes foot exam**: Your provider will visually assess your feet for any injuries or issues. They’ll then touch your toes and feet with various tools to check if you have numbness. This exam helps diagnose peripheral neuropathy.
* **NCS (nerve conduction studies)**: This test checks how fast electrical signals move through your peripheral nerves in different parts of your body. It helps diagnose peripheral and proximal neuropathies.
* **EMG (electromyography)**: This test evaluates the health and function of your skeletal muscles and the nerves that control them. It helps diagnose peripheral and proximal neuropathies.

Tests to diagnose autonomic neuropathy vary depending on which body system is affected. For example, an ultrasound can show how well your bladder empties when you pee. Tests like gastric emptying scintigraphy (GES) can help diagnose digestive system issues.

It may take more time to get an autonomic neuropathy diagnosis, as many other conditions can cause the same symptoms.

**How is diabetic neuropathy diagnosed?**

Early diagnosis of diabetic neuropathy gives patients the best chance of effective treatment. But since not all foot or limb pain means diabetic neuropathy, accurate diagnosis is important to ensure appropriate treatment.

Diagnosis of diabetic neuropathies is based on history, clinical examination and supporting laboratory tests. Your doctor may:

* Check muscle strength and reflexes.
* Check muscle sensitivity to position, vibration, temperature and light touch.
* Request additional tests, such as:
  + Ultrasound to determine how parts of the urinary tract are functioning.
  + Electromyography to determine how muscles respond to electrical impulses.
  + Nerve conduction studies to check flow of electrical current through a nerve.
  + Skin biopsies to evaluate cutaneous nerve innervation.
  + Nerve and muscle biopsies for histopathological evaluation.

A comprehensive evaluation — including a review of blood pressure, cholesterol and blood glucose screenings — combined with more advanced screening, helps the doctor rule out other causes and identify the core problem.

**TREATMENT OPTIONS**

Diabetes-related neuropathy treatment involves carefully managing your blood sugar. This is the most important step to prevent nerve damage from getting worse. Your healthcare provider and other diabetes specialists — like a CDCES (Certified Diabetes Care and Education Specialist) — will work with you to achieve realistic blood sugar goals.

Treatment for the symptoms of neuropathy varies depending on the type you have. The following medications can help treat painful symptoms that disturb your sleep or daily activities:

* Pregabalin.
* Gabapentin.
* Capsaicin patches.
* Antidepressants.

Therapies are also helpful, including:

* **Physical therapy**: This therapy helps improve how you do physical movements. It’s essential if you have peripheral neuropathy, especially if you have muscle pain and weakness.
* **Occupational therapy**: This therapy helps improve your ability to perform daily tasks.
* **Speech therapy**: If you have nerve damage that affects your ability to swallow (dysphagia), speech therapy can help.
* **Acupuncture**: This therapy uses thin needles to stimulate specific points in your body
* **Nutrition consult**: This can help you learn how to plan, shop for and prepare healthy meals.

Treatments for autonomic neuropathy vary based on the specific issue. Your provider will work with you to find the best option for you.

**Can diabetes-related neuropathy be reversed?**

With improved blood sugar management, symptoms of diabetes-related neuropathy like numbness and other abnormal sensations may fade within one year. The more severe neuropathy is, the less likely it is that it’ll be reversible.

**What is the treatment for diabetic neuropathy?**

Treatment of diabetic neuropathies consists of two stages: using lifestyle changes and sometimes medications to achieve optimal diabetic control, and symptomatic control of pain and other complications.

**Controlling Blood Glucose Levels**

Getting blood glucose levels under control can’t reverse nerve damage but can prevent further damage from occurring. Your doctor will give you specific blood sugar goals. Managing these levels includes eating a healthy diet high in protein and low in carbs. When you eat carbs, try to choose food with a higher fiber content, avoiding chips and soda.

Regular exercise can help keep blood sugar levels manageable by increasing insulin sensitivity, meaning you’ll need to take less insulin each day. Getting enough sleep is also important, as we often crave high-carb foods when overtired.

**Improving Other Risk Factors**

Although getting blood glucose under control is important, it might not be enough. It is also important to control other risk factors such as high triglycerides or cholesterol, treat high blood pressure and quit smoking. Daily aerobic exercises are shown to protect the nerves and improve neuropathy outcomes. Losing weight is also important if a patient is obese or overweight.

**Managing Pain and Other Complications**

Diabetic neuropathy can cause chronic pain and complications such as gastrointestinal problems, dizziness and weakness, and urinary or sexual problems. There are a variety of treatments that can help, including:

* Pain medications.
* Anti-seizure medications.
* Antidepressants.
* Topical creams.
* Transcutaneous electronic nerve stimulation (TENS) therapy.
* Hypnosis.
* Relaxation training.
* Biofeedback training.
* Acupuncture.

Treatment will vary depending on your specific symptoms and the severity of your neuropathy.

It is also important to check your feet daily for problems such as ingrown toenails, blisters and sores, especially if you have peripheral neuropathy. Because of the numbness associated with neuropathy, you may not feel these conditions develop. Keeping your feet clean and covered can help protect them from injury and prevent further complications such as infections.

**PREVENTION TIPS**

You can decrease your risk of diabetes-related neuropathy by:

* Maintaining an A1C under 7%.
* Keeping your blood pressure below 140/90 mmHg or within the target your provider sets.
* Following a healthy meal and exercise plan.
* Maintaining a healthy weight.
* Avoiding or limiting alcohol.
* Avoiding or quitting smoking.
* Visiting your healthcare provider for a checkup and foot exam at least once per year.

It’s also important to do self-examinations of your feet every day to look for blisters, wounds or broken skin. This can help you catch signs of neuropathy — or complications from it — quickly.

**Living With**

Reversing nerve damage is difficult, so diabetes-related neuropathy may affect your day-to-day life. Besides working with your healthcare provider to carefully manage diabetes and getting treatment for neuropathy, you can make the following adjustments to take care of yourself:

* Use a cane or other mobility device to help you move more easily.
* Wear special shoes to protect your feet from injuries.
* Self-check and identify foot and leg wounds early. Get help from a wound clinic when you find them — don’t wait!
* Removing throw rugs and other tripping hazards in your home to prevent falls.
* Seek help from a psychologist or therapist if living with neuropathy is affecting your mental health.
* Educate loved ones about neuropathy and what they can do to help you.
* Join a support group to relate to others going through similar experiences.

**OUTLOOK / PROGNOSIS**

If you have diabetes-related neuropathy, your prognosis (outlook) depends on several factors, like:

* The type of neuropathy.
* The severity of neuropathy.
* Your age and overall health.

Your healthcare provider will be able to give you a better idea of what to expect.

Without proper treatment, peripheral neuropathy can affect your quality of life. This is why it’s essential to seek medical help as soon as you notice signs of it.

Autonomic neuropathy can be serious because it involves your body’s vital functions. When those don’t work correctly, it can have very severe — and sometimes, life-threatening — effects.

Poorly treated diabetics have higher morbidity and complication rates associated with DPN than well-controlled diabetics. DPN often leads to skin breakdown, infection, ulceration, and eventually to amputation. Further, the treatment of DPN is not satisfactory, and adverse cardiac events are common. Less than a third of patients achieve reasonable pain control. For most patients with DPN, the quality of life is poor.

**POSSIBLE COMPLICATIONS**

**What are the complications of diabetes-related neuropathy?**

Possible complications of peripheral neuropathy include:

* Skin breakdown.
* Infection.
* Ulceration.
* Charcot foot.
* Difficulty with mobility.
* Increased risk of falls and bone fractures.
* Amputation.

Complications of autonomic neuropathy vary depending on the affected body system(s).

Common complications of DPN include the following:

* Amputations of the toes, foot, or leg
* Infections of the foot
* Falls secondary to dizziness
* Diarrhea, failure to thrive, and dehydration
* Pain
* Cardiovascular neuropathy can cause death

**WHEN TO SEE A DOCTOR / RED FLAG**

You’ll need to see your healthcare provider regularly if you have diabetes-related neuropathy. This is so they can monitor your symptoms and see if they’re getting worse or better. You’ll also need to see your diabetes provider (like an endocrinologist) regularly to make adjustments to your diabetes management plan.

**DIFFERENTIAL DIAGNOSIS**

Establishing the diagnosis of diabetic neuropathy requires careful evaluation, because in 10-26% of diabetic patients with neuropathy, the neuropathy may have another cause

The differential diagnoses to consider vary with the presentation.

Cranial mononeuropathy includes the following:

* Intracranial aneurysms
* Bell palsy

Thoracoabdominal neuropathy includes the following:

* Herpes zoster
* Spinal tumors
* Myocardial infarction
* Acute cholecystitis
* Acute appendicitis
* Diverticulitis

Lumbosacral radiculoplexopathy includes the following:

* Anterior disk protrusion
* Spinal cord tumors
* Malignant nerve root infiltrations
* Inflammatory neuropathies

Peripheral neuropathy includes the following:

* Pernicious anemia
* Vitamin B-6 intoxication
* Alcoholism
* Uremia
* Chemical toxins
* Nerve entrapment and compression of benign etiology
* Hepatitis
* Idiopathic
* Congenital (various hereditary sensory motor neuropathies)
* Paraneoplastic syndrome
* Syphilis
* HIV/AIDS
* Medication (e.g., chemotherapy, isoniazid)
* Spine disease (e.g., radiculopathy, stenosis, arteriovenous [AV] fistula)

Cardiovascular autonomic neuropathy (in addition to some listed above) includes the following:

* Myocardial infarction
* Neuropathic arrhythmias (e.g., Wolff-Parkinson–White syndrome, sick sinus syndrome)
* Volume depletion
* Drugs

Gastrointestinal neuropathy includes the following:

* Gastrointestinal malignancy
* Peptic ulcer disease
* Postsurgical vagotomy
* Electrolyte imbalance

Bladder dysfunction includes the following:

* Bladder outlet obstruction
* Prostate cancer
* Spinal cauda equine syndrome

Mononeuropathy includes the following:

* Vasculitides / vasculitis
* Acromegaly
* Coagulopathies
* Hypothyroidism

**Differential Diagnoses**

* Alcohol (Ethanol) Related Neuropathy
* Amyloid polyneuropathy
* Chronic Inflammatory Demyelinating Polyradiculoneuropathy

**EPIDEMIOLOGY**

Overall, diabetes-related neuropathy is fairly common. Studies show that up to 50% of people with diabetes have peripheral neuropathy. More than 30% of people with diabetes have autonomic neuropathy.

At the time a patient is diagnosed with diabetes, the literature estimates that 10% to 20% of these patients are concomitantly diagnosed with DPN; however, studies analyzing patients with long-standing diabetes mellitus report that DPN has a higher prevalence in those patients. After 5 years, 26% have peripheral neuropathy, and 41% of patients with diabetes have neuropathy at 10 years. The literature reports that 50% to 66% of patients with diabetes mellitus will eventually develop DPN during their lifetime. DPN can occur in both type 1 and type 2 diabetes, but the prevalence is higher in individuals with type 2 diabetes due to the longer duration and higher rates of comorbidities. Diabetes mellitus is also the most common cause of Charcot neuroarthropathy, with an incidence of 0.1% to 0.4% and as high as 29% in patients with peripheral neuropathy.

About half of patients with DPN can clinically present with asymmetric sensory changes. Obesity and genetic factors increase the risk of developing diabetes. Peripheral and autonomic neuropathies are some of the leading causes of morbidity in diabetes mellitus. At 5 years, the risk of death for patients with a diabetic foot ulcer is 2.5 times as high as the risk of death for a patient with diabetes who does not have a foot ulcer. The rate of emergency department visits for diabetic foot ulcers and associated infection exceeds the rates for congestive heart failure, renal disease, depression, and most forms of cancer.

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**DIABETIC NEPHROPATHY**

*ALTERNATIVE NAMES:* Diabetic nephropathy is also known as “diabetic kidney disease”. Another name for diabetes-related nephropathy is “diabetes-related kidney disease (DKD)”.

**DEFINITION / DESCRIPTION**

Diabetic nephropathy, also known as diabetic kidney disease, is the **chronic loss of kidney function occurring in those with diabetes mellitus**. It is the leading cause of chronic kidney disease (CKD) and end-stage renal disease (ESRD) globally. The condition is characterized by damage to the small blood vessels in the kidneys, leading to proteinuria (albuminuria), rising blood pressure, and a progressive decline in kidney function. If left untreated, it can result in diminished kidney function and, eventually, renal failure.

Diabetic nephropathy is a serious complication of type 1 diabetes and type 2 diabetes. It's also called diabetic kidney disease. In the United States, about 1 in 3 people living with diabetes have diabetic nephropathy.

Diabetic nephropathy affects the kidneys' usual work of removing waste products and extra fluid from the body. The best way to prevent or delay diabetic nephropathy is by living a healthy lifestyle and keeping diabetes and high blood pressure managed.

Over years, diabetic nephropathy slowly damages the kidneys' filtering system. Early treatment may prevent this condition or slow it and lower the chance of complications.

Diabetic kidney disease can lead to kidney failure. This also is called end-stage kidney disease. Kidney failure is a life-threatening condition. Treatment options for kidney failure are dialysis or a kidney transplant.

**CAUSES**

Diabetic nephropathy happens when diabetes damages blood vessels and other cells in the kidneys.

**How the kidneys work**

**Healthy kidney vs. diseased kidney**

**Kidney cross section**

The kidneys have millions of tiny blood vessel clusters called glomeruli. Glomeruli filter waste from the blood. Damage to these blood vessels can lead to diabetic nephropathy. The damage can keep the kidneys from working as they should and lead to kidney failure.

**Diabetic nephropathy causes**

Diabetic nephropathy is a common complication of type 1 and type 2 diabetes.

Over time, diabetes that isn't well controlled can damage blood vessels in the kidneys that filter waste from the blood. This can lead to kidney damage and cause high blood pressure.

High blood pressure can cause more kidney damage by raising the pressure in the filtering system of the kidneys.

**RISK FACTORS**

If you have diabetes, the following can raise your risk of diabetic nephropathy:

* Uncontrolled high blood sugar, also called hyperglycemia.
* Uncontrolled high blood pressure, also called hypertension.
* Smoking.
* High blood cholesterol.
* Obesity.
* A family history of diabetes and kidney disease.

**SIGNS / SYMPTOMS**

In the early stages of diabetic nephropathy, there might not be symptoms. In later stages, symptoms may include:

* High blood pressure that gets harder to control.
* Swelling of feet, ankles, hands or eyes.
* Foamy urine.
* Confusion or difficulty thinking.
* Shortness of breath.
* Loss of appetite.
* Nausea and vomiting.
* Tiredness and weakness.
* Trouble sleeping or concentrating
* Poor appetite
* Itching (end-stage kidney disease) and extremely dry skin
* Drowsiness (end-stage kidney disease)
* Abnormalities in the hearts' regular rhythm, because of increased potassium in the blood
* Muscle twitching

As kidney damage progresses, your kidneys cannot remove the waste from your blood. The waste then builds up in your body and can reach poisonous levels, a condition known as uremia. People with uremia are often confused and occasionally become comatose.

**DIAGNOSIS METHODS**

**How Is Diabetic Nephropathy Diagnosed?**

Certain blood tests that look for specific blood chemistry can be used to diagnose kidney damage. It also can be detected early by finding protein in the urine. Treatments are available that can help slow progression to kidney failure. That's why you should have your urine tested every year if you have diabetes.

Diabetic nephropathy usually is diagnosed during the regular testing that's part of managing diabetes. Get tested every year if you have type 2 diabetes or have had type 1 diabetes for more than five years.

Routine screening tests may include:

* **Urinary albumin test.** This test can detect a blood protein called albumin in urine. Typically, the kidneys don't filter albumin out of the blood. Too much albumin in your urine can mean that the kidneys aren't working well.
* **Albumin/creatinine ratio.** Creatinine is a chemical waste product that healthy kidneys filter out of the blood. The albumin/creatinine ratio measures how much albumin compared to creatinine is in a urine sample. It shows how well the kidneys are working.
* **Glomerular filtration rate (GFR).** The measure of creatinine in a blood sample may be used to see how quickly the kidneys filter blood. This is called the glomerular filtration rate. A low rate means the kidneys aren't working well.

Other diagnostic tests may include:

* **Imaging tests.** X-rays and ultrasound can show the makeup and size of the kidneys. CT and MRI scans can show how well blood is moving within the kidneys. You may need other imaging tests, as well.
* **Kidney biopsy.** This is a procedure to take a sample of kidney tissue to be studied in a lab. It involves a numbing medicine called a local anesthetic. A thin needle is used to remove small pieces of kidney tissue.

**TREATMENT OPTIONS**

**How Is Diabetic Nephropathy Treated?**

Lowering blood pressure and maintaining blood sugar control are absolutely necessary to slow the progression of diabetic nephropathy. There are medications available which have been found to slow down the progression of kidney damage. They include:

* SGLT2 inhibitors including bexagliflozin (Brenzavvy), dapagliflozin (Farxiga), empagliflozin (Jardiance), and ertugliflozin (Steglatro), which help control high blood sugar.
* Angiotensin converting enzyme (ACE) inhibitors can help slow down the progression of kidney damage. Although ACE inhibitors -- including ramipril (Altace), quinapril (Accupril), and lisinopril (Prinivil, Zestril) -- are usually used to treat high blood pressure and other medical problems, they are often given to people with diabetes to prevent complications, even if their blood pressure is normal.
* Angiotensin receptor blockers (ARBs) can often be given instead if you have side effects from taking ACE inhibitors

If not treated, the kidneys will continue to fail and larger amounts of proteins can be detected in the urine. Advanced kidney failure requires treatment with dialysis or a kidney transplant.

The first step in treating diabetic nephropathy is to treat and control diabetes and high blood pressure. Treatment includes diet, lifestyle changes, exercise and prescription medicines. Controlling blood sugar and blood pressure might prevent or delay kidney issues and other complications.

**Medications**

In the early stages of diabetic nephropathy, your treatment might include medicines to manage the following:

* **Blood pressure.** Medicines called angiotensin-converting enzyme (ACE) inhibitors and angiotensin 2 receptor blockers (ARBs) are used to treat high blood pressure.
* **Blood sugar.** Medicines can help control high blood sugar in people with diabetic nephropathy. They include older diabetes medicines such as insulin. Newer drugs include Metformin (Fortamet, Glumetza, others), glucagon-like peptide 1 (GLP-1) receptor agonists and SGLT2 inhibitors.

Ask your health care professional if treatments such as SGLT2 inhibitors or GLP-1 receptor agonists might work for you. These treatments can protect the heart and kidneys from damage due to diabetes.

* **High cholesterol.** Cholesterol-lowering drugs called statins are used to treat high cholesterol and lower the amount of protein in urine.
* **Kidney scarring.** Finerenone (Kerendia) might help reduce tissue scarring in diabetic nephropathy. Research has shown that the medicine might lower the risk of kidney failure. It also may lower the risk of dying from heart disease, having heart attacks and needing to go to a hospital to treat heart failure in adults with chronic kidney disease linked to type 2 diabetes.

If you take these medicines, you'll need regular follow-up testing. The testing is done to see if your kidney disease is stable or getting worse.

**Treatment for advanced diabetic nephropathy**

For kidney failure, also called end-stage kidney disease, treatment focuses on either replacing the work of your kidneys or making you more comfortable. Options include:

* **Kidney dialysis.** This treatment removes waste products and extra fluid from the blood. Hemodialysis filters blood outside the body using a machine that does the work of the kidneys. For hemodialysis, you might need to visit a dialysis center about three times a week. Or you might have dialysis done at home by a trained caregiver. Each session takes 3 to 5 hours.

Peritoneal dialysis uses the inner lining of the abdomen, called the peritoneum, to filter waste. A cleansing fluid flows through a tube to the peritoneum. This treatment can be done at home or at work. But not everyone can use this method of dialysis.

* **Transplant.** Sometimes, a kidney transplant or a kidney-pancreas transplant is the best treatment choice for kidney failure. If you and your health care team decide on a transplant, you'll be assessed to find out if you can have the surgery.
* **Symptom management.** If you have kidney failure and you don't want dialysis or a kidney transplant, you'll likely live only a few months. Treatment may help keep you comfortable.

**Potential future treatments**

In the future, people with diabetic nephropathy may benefit from treatments being developed using techniques that help the body repair itself, called regenerative medicine. These techniques may help reverse or slow kidney damage.

For example, some researchers think that if a person's diabetes can be cured by a future treatment such as pancreas islet cell transplant or stem cell therapy, the kidneys might work better. These therapies, as well as new medicines, are still being studied.

**Lifestyle and home remedies**

Diet, exercise and self-care are needed to control blood sugar and high blood pressure. Your diabetes care team can help you with the following goals:

* **Monitor your blood sugar.** Your health care team will tell you how often to check your blood sugar level to make sure you stay in your target range. You may, for example, need to check it once a day and before or after exercise. If you take insulin, you may need to check your blood sugar level several times a day.
* **Be active most days of the week.** Aim for at least 30 minutes or more of moderate to vigorous aerobic exercise on most days. Go for a total of at least 150 minutes a week. Activities might include brisk walking, swimming, biking or running.
* **Eat a healthy diet.** Eat a high-fiber diet with lots of fruits, non starchy vegetables, whole grains and legumes. Limit saturated fats, processed meats, sweets and salt.
* **Quit smoking.** If you smoke, talk with your health care professional about ways to quit.
* **Stay at a healthy weight.** If you need to lose weight, talk with your health care professional about ways to do so. For some people, weight-loss surgery is an option.
* **Take a daily aspirin.** Talk with your health care professional about whether you should take a daily low-dose aspirin to lower the risk of heart disease.
* **Talk to your health care team.** Make sure all your health care professionals know that you have diabetic nephropathy. They can take steps to protect your kidneys from more damage by not doing medical tests that use contrast dye. These include angiograms and computerized tomography (CT) scans.

**Newer agents in diabetic patients with kidney disease**

*Dipeptidyl peptidase inhibitors*

The dipeptidyl peptidase (DPP)–4 inhibitors (ie, gliptins) are a newer class of antidiabetic agents that can be used in type 2 diabetes.

**Management of Hypertension**

In general, antihypertensive therapy, irrespective of the agent used, slows the development of diabetic glomerulopathy. Mogensen showed that antihypertensive treatment attenuates the rate of decline in renal function in patients who have type 1 DM, hypertension, and proteinuria.This is particularly significant when lowering of systemic blood pressure is accompanied with concomitant lessening of glomerular capillary pressure.

Careful blood pressure control is needed to prevent the progression of diabetic nephropathy and other complications; however, the optimal lower limit for systolic blood pressure is unclear. In the UKPDS, a 12% risk reduction in diabetic complications was found with each 10 mmHg drop in systolic pressure, the lowest risk being associated with a systolic pressure below 120 mm Hg.

**Angiotensin-converting enzyme inhibitors**

From a therapeutic standpoint, preventing the progression of kidney disease is better achieved with a non glycemic intervention, such as treatment with angiotensin-converting enzyme (ACE) inhibitors, which confer superior long-term protection even in comparison with triple therapy with reserpine, hydralazine, and hydrochlorothiazide or a calcium channel blocker (nifedipine).

Long-term treatment with ACE inhibitors, usually combined with diuretics, reduces blood pressure and albuminuria and protects kidney function in patients with hypertension, type 1 DM, and nephropathy. Beneficial effects on kidney function have also been reported in patients with normotension, type 1 DM, and nephropathy.

**Mineralocorticoid Receptor Antagonist Therapy**

In July 2021, the FDA approved finerenone (Kerendia) to lower the chances of sustained eGFR decline, end-stage kidney disease, cardiovascular death, nonfatal myocardial infarction, and hospitalization for heart failure in adults with chronic kidney disease (CKD) associated with type 2 DM. It is the first nonsteroidal mineralocorticoid receptor (MR) antagonist to be approved for this purpose. Approval was based on the FIDELIO-DKD trial, a placebo-controlled study that involved over 5700 patients with type 2 DM to whom the maximum-tolerated dose of renin-angiotensin system inhibitor (RASI) was already being administered. However, until more data on finerenone is gathered, RASIs and SGLT2 inhibitors will be the preferred agents for slowing chronic kidney disease in type 2 diabetes.

**Endothelin Antagonist Therapy**

Endothelin antagonists have demonstrated antifibrotic, anti-inflammatory, and antiproteinuric effects in experimental studies.

A randomized, placebo-controlled, double-blind, parallel-design, dosage-range study on the effect of the endothelin-A antagonist avosentan on urinary albumin excretion rate in 286 patients with diabetic nephropathy, macroalbuminuria, and a blood pressure of < 180/110 mm Hg found that all dosages of avosentan, administered in addition to standard treatment with an ACE inhibitor or an ARB, reduced the mean relative urinary albumin excretion rate (-16.3% to -29.9%, relative to baseline).

**Renal Replacement Therapy**

As for any other patient with ESRD, diabetic patients with ESRD can be offered renal replacement therapy. Carefully explain the therapeutic options and modalities of renal replacement therapy to patients, their partners, and their families in an early stage of renal failure. In chronically ill patients with diabetes, this tends to be much more important than in those renal patients who do not have diabetes.

In patients with diabetic nephropathy, starting at a creatinine clearance or estimated GFR of 10-15 mL/min is wise. In diabetic patients, starting earlier is useful when hypervolemia renders blood pressure uncontrollable, when the patient experiences anorexia and cachexia or other uremic symptoms, and when severe vomiting is the combined result of uremia and gastroparesis.

In principle, diabetic patients who require renal replacement therapy have the following 4 options:

* Refusal of further treatment for uremia, leading to a progressive decline in general health and ultimately leading to death
* Peritoneal dialysis (eg, machine-assisted intermittent peritoneal dialysis, continuous ambulatory peritoneal dialysis, continuous cyclic peritoneal dialysis)
* Hemodialysis (eg, facility hemodialysis, home hemodialysis)
* Renal transplantation (eg, cadaver donor kidney, living related-donor kidney, living unrelated-donor kidney [emotionally related donor], living unrelated-donor kidney [unrelated by family or emotionally; the so-called altruistic donor], pancreas plus kidney transplantation)

**Urate-Lowering Therapy**

A study by Ueno indicated that in patients with type 2 diabetes with hyperuricemia, kidney function significantly improves when serum urate levels are reduced below 6.0 mg/dL, possibly demonstrating a means of slowing nephropathy progression in these patients.

**Dietary Changes**

A meta-analysis examining the effects of dietary protein restriction (0.5-0.85 g/kg/d) in diabetic patients suggested a beneficial effect on the GFR, creatinine clearance, and albuminuria. However, a large, long-term prospective study is needed to establish the safety, efficacy, and compliance with protein restriction in diabetic patients with nephropathy. Limitations include ensuring compliance by patients.

The American Diabetic Association suggests diets of various energy intake (caloric values), depending on the patient. With advancing renal disease, protein restriction of as much as 0.8-1 g/kg/d may retard the progression of nephropathy.

When nephropathy is advanced, the diet should reflect the need for phosphorus and potassium restriction, with the use of phosphate binders.

A meta-analysis from the Cochrane Renal Group revealed that dietary salt reduction significantly reduced blood pressure (BP) in individuals with type 1 or type 2 diabetes.These findings, along with other evidence relating salt intake to BP and albuminuria in hypertensive and normotensive patients, make a strong case for a reduction in salt intake among patients with diabetes. The recommendation for the general population in public health guidelines is less than 5-6 g/d. Dietary salt reduction may help slow progression of kidney disease in both type 1 and type 2 diabetes.

**Restriction of Activity**

No restriction in activity is necessary for persons with diabetic nephropathy, unless warranted by other associated complications of diabetes, such as associated coronary disease or peripheral vascular disease.

**PREVENTION TIPS**

Measures for Prevention of Diabetic Nephropathy

Efforts should be made to modify and/or treat associated risk factors such as hyperlipidemia, smoking, and hypertension.

Specific goals for prevention include the following:

* Optimal blood glucose control (hemoglobin A1c [HbA1c] < 7%)
* Control of hypertension (BP < 120/70 Hg)
* Avoidance of potentially nephrotoxic substances such as nonsteroidal anti-inflammatory medications and aminoglycosides
* Early detection and optimal management of diabetes, especially in the setting of family history of diabetes

***To lower your risk of developing diabetic nephropathy:***

* **See your health care team regularly to manage diabetes.** Keep appointments to check on how well you are managing your diabetes and to check for diabetic nephropathy and other complications. Your appointments might be yearly or more often.
* **Treat your diabetes.** With good treatment of diabetes, you can keep your blood sugar levels in the target range as much as possible. This may prevent or slow diabetic nephropathy.
* **Manage high blood pressure or other medical conditions.** If you have high blood pressure or other conditions that raise your risk of kidney disease, work with your health care professional to control them.
* **Take medicines you get without a prescription only as directed.** Read the labels on the pain relievers you take. This might include aspirin and nonsteroidal anti-inflammatory drugs, such as naproxen sodium (Aleve) and ibuprofen (Advil, Motrin IB, others). For people with diabetic nephropathy, these types of pain relievers can lead to kidney damage.
* **Stay at a healthy weight.** If you're at a healthy weight, work to stay that way by being physically active most days of the week. If you need to lose weight, talk with a member of your health care team about the best way for you to lose weight.
* **Don't smoke.** Cigarette smoking can damage kidneys or make kidney damage worse. If you're a smoker, talk to a member of your health care team about ways to quit. Support groups, counseling and some medicines might help.

**POSSIBLE COMPLICATIONS**

Complications of diabetic nephropathy can come on slowly over months or years. They may include:

* Body fluid buildup. This could lead to swelling in the arms and legs, high blood pressure, or fluid in the lungs, called pulmonary edema.
* A rise in the levels of the mineral potassium in the blood, called hyperkalemia.
* Heart and blood vessel disease, also called cardiovascular disease. This could lead to a stroke.
* Fewer red blood cells to carry oxygen. This condition also is called anemia.
* Pregnancy complications that carry risks for the pregnant person and the growing fetus.
* Damage to the kidneys that can't be fixed. This is called end-stage kidney disease. Treatment is either dialysis or a kidney transplant.

**OUTLOOK / PROGNOSIS**

Diabetic nephropathy accounts for significant morbidity and mortality.

Proteinuria is a predictor of morbidity and mortality. (See Workup.) The overall prevalence of microalbuminuria and macroalbuminuria in both types of diabetes is approximately 30-35%. Microalbuminuria independently predicts cardiovascular morbidity, and microalbuminuria and macroalbuminuria increase mortality from any cause in diabetes mellitus. Microalbuminuria is also associated with increased risk of coronary and peripheral vascular disease and death from cardiovascular disease in the general nondiabetic population.

Patients in whom proteinuria has not developed have a low and stable relative mortality rate, whereas patients with proteinuria have a 40-fold higher relative mortality rate. Patients with type 1 DM and proteinuria have the characteristic bell-shaped relationship between diabetes duration/age and relative mortality, with maximal relative mortality in the age interval of 34-38 years (as reported in 110 females and 80 males).

ESRD is the major cause of death, accounting for 59-66% of deaths in patients with type 1 DM and nephropathy. In a prospective study in Germany, the 5-year survival rate was less than 10% in the elderly population with type 2 **support**

If you have diabetic nephropathy, these steps may help you cope:

* **Connect with other people who have diabetes and kidney disease.** Ask a member of your health care team about support groups in your area. Or contact groups such as the American Association of Kidney Patients or the National Kidney Foundation for groups in your area.
* **Stick to your usual routine, when possible.** Try to keep your usual routine, doing the activities you enjoy and working, if your condition allows. This may help you cope with feelings of sadness or loss that you may have after your diagnosis.
* **Talk with someone you trust.** Living with diabetic nephropathy can be stressful, and it may help to talk about your feelings. You may have a friend or family member who is a good listener. Or you may find it helpful to talk with a faith leader or someone else you trust. Ask a member of your health care team for the name of a social worker or counselor.

***Long-Term Monitoring***

Regular outpatient follow-up is key in managing diabetic nephropathy successfully. Regular annual urinalysis is recommended for screening for microalbuminuria (see the image below). Ensuring optimal glucose control, optimizing blood pressure, and screening for other associated complications of diabetes (e.g., retinopathy, diabetic foot, cardiovascular disease) are also crucial.

Screening for and prevention of the progression of microalbuminuria in diabetes mellitus. (ACE-I stands for angiotensin-converting enzyme inhibitor)

**WHEN TO SEE A DOCTOR / RED FLAG**

Make an appointment with your health care professional if you have symptoms of kidney disease. If you have diabetes, visit your health care professional yearly or as often as you're told for tests that measure how well your kidneys are working.

**DIFFERENTIAL DIAGNOSIS**

Several conditions can mimic diabetic nephropathy, but they are usually differentiated from diabetic nephropathy based on patient history and laboratory parameters. Some of these include:

* Multiple myeloma
* Amyloidosis
* Membranous nephropathy
* Renal artery stenosis
* Tubulointerstitial nephritis
* Hypertensive nephropathy
* Focal segmental glomerulosclerosis
* Infection-related glomerulonephritis

**RECENT GUIDELINES OR UPDATES**

*Guidelines Summary*

Recommendations regarding diabetic kidney disease:

* Optimize glucose control to reduce the risk or slow the progression of diabetic kidney disease
* Optimize blood pressure control to reduce the risk or slow the progression of diabetic kidney disease
* For people with non dialysis-dependent diabetic kidney disease, dietary protein intake should be approximately 0.8 g/kg body weight per day (the recommended daily allowance); for patients on dialysis, higher levels of dietary protein intake should be considered
* In nonpregnant patients with diabetes and hypertension, either an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin receptor blocker

**EPIDEMIOLOGY**

Since the 1950s, kidney disease has been clearly recognized as a common complication of diabetes mellitus (DM), with as many as 50% of patients with DM of more than 20 years’ duration having this complication.

***United States statistics***

Diabetic nephropathy rarely develops before 10 years’ duration of type 1 DM (previously known as insulin-dependent diabetes mellitus [IDDM]). Approximately 3% of newly diagnosed patients with type 2 DM (previously known as non–insulin-dependent diabetes mellitus [NIDDM]) have overt nephropathy. The peak incidence (3%/y) is usually found in persons who have had diabetes for 10-20 years, after which the rate progressively declines.

The risk for the development of diabetic nephropathy is low in a normoalbuminuria patient with diabetes’ duration of greater than 30 years. Patients who have no proteinuria after 20-25 years have a risk of developing overt renal disease of only approximately 1% per year.

In terms of diabetic kidney disease in the United States, the prevalence increased from 1988-2008 in proportion to the prevalence of diabetes.Among people with diabetes, the prevalence of diabetic kidney disease remained stable.

***International statistics***

Striking epidemiologic differences exist even among European countries. In some European countries, particularly Germany, the proportion of patients admitted for renal replacement therapy exceeds the figures reported from the United States.

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**DIABETIC RETINOPATHY**

ALTERNATIVE NAMES: Diabetic retinopathy is also known as “diabetic eye disease”, or “diabetes-related retinopathy”.

**DEFINITION / DESCRIPTION**

Diabetic retinopathy (die-uh-BET-ik ret-ih-NOP-uh-thee) is a diabetes complication that affects eyes. It's caused by damage to the blood vessels of the light-sensitive tissue at the back of the eye (retina).

At first, diabetic retinopathy might cause no symptoms or only mild vision problems. But it can lead to blindness.

The condition can develop in anyone who has type 1 or type 2 diabetes. The longer you have diabetes and the less controlled your blood sugar is, the more likely you are to develop this eye complication.

**The Two Stages of Diabetic Eye Disease**

There are two main stages of diabetic eye disease

This is the early stage of diabetic eye disease. Many people with diabetes have it.

With NPDR, tiny blood vessels leak, making the retina swell. When the macula swells, it is called macular edema. This is the most common reason why people with diabetes lose their vision.

Also, with NPDR, blood vessels in the retina can close off. This is called **macular ischemia**. When that happens, blood cannot reach the macula. Sometimes tiny particles called exudates can form in the retina. These can affect your vision too.

If you have NPDR, your vision will be blurry.

***PDR (proliferative diabetic retinopathy)***

PDR is the more advanced stage of diabetic eye disease. It happens when the retina starts growing new blood vessels. This is called neovascularization. These fragile new vessels often bleed into the vitreous. If they only bleed a little, you might see a few dark floaters. If they bleed a lot, it might block all vision.

These new blood vessels can form scar tissue. Scar tissue can cause problems with the macula or lead to a detached retina.

PDR is very serious, and can steal both your central and peripheral (side) vision.

**CAUSES**

Over time, too much sugar in your blood can lead to the blockage of the tiny blood vessels that nourish the retina, cutting off its blood supply. As a result, the eye attempts to grow new blood vessels. But these new blood vessels don't develop properly and can leak easily.

There are two types of diabetic retinopathy:

* **Early diabetic retinopathy.** In this more common form — called non-proliferative diabetic retinopathy (NPDR) — new blood vessels aren't growing (proliferating).

When you have NPDR, the walls of the blood vessels in your retina weaken. Tiny bulges protrude from the walls of the smaller vessels, sometimes leaking fluid and blood into the retina. Larger retinal vessels can begin to dilate and become irregular in diameter as well. NPDR can progress from mild to severe as more blood vessels become blocked.

Sometimes retinal blood vessel damage leads to a buildup of fluid (edema) in the center portion (macula) of the retina. If macular edema decreased vision, treatment is required to prevent permanent vision loss.

* **Advanced diabetic retinopathy.** Diabetic retinopathy can progress to this more severe type, known as proliferative diabetic retinopathy. In this type, damaged blood vessels close off, causing the growth of new, abnormal blood vessels in the retina. These new blood vessels are fragile and can leak into the clear, jellylike substance that fills the center of your eye (vitreous).

Eventually, scar tissue from the growth of new blood vessels can cause the retina to detach from the back of your eye. If the new blood vessels interfere with the normal flow of fluid out of the eye, pressure can build in the eyeball. This buildup can damage the nerve that carries images from your eye to your brain (optic nerve), resulting in glaucoma.

**Diabetic retinopathy**

In the early stages of diabetic retinopathy, the walls of the blood vessels in your retina weaken. Tiny bulges protrude from the vessel walls, sometimes leaking or oozing fluid and blood into the retina. Tissues in the retina may swell, producing white spots in the retina. As diabetic retinopathy progresses, new blood vessels may grow and threaten your vision.

***What causes diabetic retinopathy?***

Diabetic retinopathy is caused by high blood sugar due to diabetes. Over time, having too much sugar in your blood can damage your retina — the part of your eye that detects light and sends signals to your brain through a nerve in the back of your eye (optic nerve).

Diabetes damages blood vessels all over the body. The damage to your eyes starts when the sugar in your blood causes changes to the tiny blood vessels that go to your retina. These changes make it harder for the blood to flow, leading to blocked blood vessels that leak fluid or bleed. To make up for these blocked blood vessels, your eyes then grow new blood vessels that don’t work well. These new blood vessels can leak or bleed easily.

Diabetes-retinopathy can happen because of multiple types of diabetes. They include:

* Type 1 diabetes
* Type 2 diabetes
* Type 3c diabetes
* Gestational diabetes

Diabetes causes increased blood sugar levels and can damage the insides of blood vessels throughout your body over time. When you have diabetes-related retinopathy, damaged blood vessels in your retina are trying to repair and reroute to avoid an interruption in blood supply. As a result, fragile new blood vessels grow on the surface of your retina. These new blood vessels can cause retinal detachments and bleeding into the vitreous, a gel-like fluid in your eye. The damaged blood vessels can also leak fluid into your retina, causing macular edema. This can cause blurry vision.

**RISK FACTORS**

Anyone who has diabetes can develop diabetic retinopathy. The risk of developing the eye condition can increase as a result of:

* Having diabetes for a long time
* Poor control of your blood sugar level
* High blood pressure (hypertension)
* High cholesterol (hyperlipidemia)
* Pregnancy
* Tobacco use
* Being Black, Hispanic or Native American
* Heart-specific cardiovascular diseases, like heart disease and coronary artery disease
* Chronic kidney disease and kidney failure

## ***Am I at risk for diabetic retinopathy?***

Anyone with any kind of diabetes can get diabetic retinopathy — including people with type 1, type 2, and gestational diabetes (a type of diabetes that can develop during pregnancy).

Your risk increases the longer you have diabetes. Over time, more than half of people with diabetes will develop diabetic retinopathy. The good news is that you can lower your risk of developing diabetic retinopathy by controlling your diabetes.

Women with diabetes who become pregnant — or women who develop gestational diabetes — are at high risk for getting diabetic retinopathy. If you have diabetes and are pregnant, have a comprehensive dilated eye exam as soon as possible. Ask your doctor if you’ll need additional eye exams during your pregnancy.

**Duration of Diabetes**

Type 1 DM

1. 25% of patients will have DR after 5 years, 60% after 10 years and 80% after 15 years
2. 50% of patients under 30 years old will develop PDR if duration of DM is 20 years or more (WESDR)
3. 18% of patients after 15 years of diagnosis will develop PDR with no difference between type 1 and 2 (LALES-VER)

Type 2 DM

1. Patients >30 year 19 years, percentages are 84% and 53% respectively.
2. PDR will develop in 2% of patients if duration of DM is < 5 years and 25% if > 25 years

**Glycemic control**

1. Key modifiable risk factor
2. Recommendation: Hb A1c 7% or 6.5% in selected cases

**High Blood Pressure**

1. Slows progression of diabetic retinopathy

**Blood Lipids**

1. Slows progression of diabetic retinopathy

**Pregnancy**

1. Gestational diabetes does not require an eye examination during pregnancy and does not increase the risk of diabetic retinopathy.
2. Diabetic retinopathy can worsen during pregnancy; patients should have an eye examination before pregnancy and during the first trimester.
3. If a patient has no retinopathy or mild to moderate NPDR, examinations should be performed every 3 to 12 months.
4. If a pregnant patient has severe NPDR or worse, eye examinations should be performed every 1 to 3 months.
5. If neovascularization is detected during pregnancy, laser therapy should be performed.
6. Macular edema in pregnant patients can improve with delivery, no intravitreal anti-VEGF is recommended. Consider intravitreal steroids.
7. Diabetic retinopathy in a pregnant patient is not a contraindication for natural vaginal delivery.

**Renal Impairment**

**Age**

**Clotting factors +**

**Renal Disease +**

**Physical Inactivity +**

**Inflammatory Biomarkers +**

+ Encourage patients to be compliant with all medical aspects of their disease as these factors are associated with substantial cardiovascular morbidity and mortality.

**SIGNS / SYMPTOMS**

You might not have symptoms in the early stages of diabetic retinopathy. As the condition progresses, you might develop:

* Spots or dark strings floating in your vision (floaters)
* Blurred vision
* Fluctuating vision
* Dark or empty areas in your vision
* Vision loss

**What Happens When You Have Diabetic Retinopathy?**

You can have diabetic retinopathy and not know it. This is because it often has no symptoms in its early stages. As diabetic retinopathy gets worse, you will notice symptoms such as:

* seeing an increasing number of floaters
* having blurry vision
* having vision that changes sometimes from blurry to clear
* seeing blank or dark areas in your field of vision
* having poor night vision
* noticing colors appear faded or washed out
* losing vision

Diabetic retinopathy symptoms usually affect both eyes.

**DIAGNOSIS METHODS**

Diabetic retinopathy is best diagnosed with a comprehensive dilated eye exam. For this exam, drops placed in your eyes widen (dilate) your pupils to allow your doctor a better view inside your eyes. The drops can cause your close vision to blur until they wear off, several hours later.

During the exam, your eye doctor will look for abnormalities in the inside and outside parts of your eyes.

*Fluorescein angiography*

After your eyes are dilated, a dye is injected into a vein in your arm. Then pictures are taken as the dye circulates through your eyes' blood vessels. The images can pinpoint blood vessels that are closed, broken or leaking.

*Optical coherence tomography (OCT)*

With this test, pictures provide cross-sectional images of the retina that show the thickness of the retina. This will help determine how much fluid, if any, has leaked into retinal tissue. Later, OCT exams can be used to monitor how treatment is working.

Drops will be put in your eye to dilate (widen) your pupil. This allows your ophthalmologist to look through a special lens to see the inside of your eye.

Your doctor may do optical coherence tomography (OCT) to look closely at the retina. A machine scans the retina and provides detailed images of its thickness. This helps your doctor find and measure swelling of your macula.

Fluorescein angiography or OCT angiography helps your doctor see what is happening with the blood vessels in your retina. Fluorescein angiography uses a yellow dye called fluorescein, which is injected into a vein (usually in your arm). The dye travels through your blood vessels. A special camera takes photos of the retina as the dye travels throughout its blood vessels. This shows if any blood vessels are blocked or leaking fluid. It also shows if any abnormal blood vessels are growing. OCT angiography is a newer technique and does not need dye to look at the blood vessels.

**TREATMENT OPTIONS**

Treatment, which depends largely on the type of diabetic retinopathy you have and how severe it is, is geared to slowing or stopping the progression.

*Early diabetic retinopathy*

If you have mild or moderate nonproliferative diabetic retinopathy, you might not need treatment right away. However, your eye doctor will closely monitor your eyes to determine when you might need treatment.

Work with your diabetes doctor (endocrinologist) to determine if there are ways to improve your diabetes management. When diabetic retinopathy is mild or moderate, good blood sugar control can usually slow the progression.

*Advanced diabetic retinopathy*

If you have proliferative diabetic retinopathy or macular edema, you'll need prompt treatment. Depending on the specific problems with your retina, options might include:

* **Injecting medications into the eye.** These medications, called vascular endothelial growth factor inhibitors, are injected into the vitreous of the eye. They help stop growth of new blood vessels and decrease fluid buildup.

Three drugs are approved by the U.S. Food and Drug Administration (FDA) for treatment of diabetic macular edema — faricimab-svoa (Vabysmo), ranibizumab (Lucentis) and aflibercept (Eylea). A fourth drug, bevacizumab (Avastin), can be used off-label for the treatment of diabetic macular edema.

These drugs are injected using topical anesthesia. The injections can cause mild discomfort, such as burning, tearing or pain, for 24 hours after the injection. Possible side effects include a buildup of pressure in the eye and infection.

These injections will need to be repeated. In some cases, the medication is used with photocoagulation.

* **Photocoagulation.** This laser treatment, also known as focal laser treatment, can stop or slow the leakage of blood and fluid in the eye. During the procedure, leaks from abnormal blood vessels are treated with laser burns.

Focal laser treatment is usually done in your doctor's office or eye clinic in a single session. If you had blurred vision from macular edema before surgery, the treatment might not return your vision to normal, but it's likely to reduce the chance of the macular edema worsening.

* **Panretinal photocoagulation.** This laser treatment, also known as scatter laser treatment, can shrink the abnormal blood vessels. During the procedure, the areas of the retina away from the macula are treated with scattered laser burns. The burns cause the abnormal new blood vessels to shrink and scar.

It's usually done in your doctor's office or eye clinic in two or more sessions. Your vision will be blurry for about a day after the procedure. Some loss of peripheral vision or night vision after the procedure is possible.

* **Vitrectomy.** This procedure uses a tiny incision in your eye to remove blood from the middle of the eye (vitreous) as well as scar tissue that's tugging on the retina. It's done in a surgery center or hospital using local or general anesthesia.

While treatment can slow or stop the progression of diabetic retinopathy, it's not a cure. Because diabetes is a lifelong condition, future retinal damage and vision loss are still possible.

Even after treatment for diabetic retinopathy, you'll need regular eye exams. At some point, you might need additional treatment.

**Alternative medicine**

Several alternative therapies have suggested some benefits for people with diabetic retinopathy, but more research is needed to understand whether these treatments are effective and safe.

Let your doctor know if you take herbs or supplements. They can interact with other medications or cause complications in surgery, such as excessive bleeding.

It's vital not to delay standard treatments to try unproven therapies. Early treatment is the best way to prevent vision loss.

**Can Diabetic Retinopathy Go Away?**

Your treatment is based on what your ophthalmologist sees in your eyes. Treatment options may include:

***Medical control***

Controlling your blood sugar and blood pressure can stop vision loss. Carefully follow the diet your nutritionist has recommended. Take the medicine your diabetes doctor prescribed for you. **Sometimes, good sugar control can even bring some of your vision back.** Controlling your blood pressure keeps your eye’s blood vessels healthy.

***Medicine***

One type of medication is called anti-VEGF medication. These include Avastin, Eylea, and Lucentis. Anti-VEGF medication helps reduce swelling of the macula, slowing vision loss and perhaps improving vision. This drug is given by injections (shots) in the eye. Steroid medicine is another option to reduce macular swelling. This is also given as injections in the eye. Your doctor will recommend how many medication injections you will need over time.

***Laser surgery***

Laser surgery might be used to help seal off leaking blood vessels. This can reduce swelling of the retina. Laser surgery can also help shrink blood vessels and prevent them from growing again. Sometimes more than one treatment is needed.

***Vitrectomy***

If you have advanced PDR, your ophthalmologist may recommend surgery called vitrectomy. Your ophthalmologist removes vitreous gel and blood from leaking vessels in the back of your eye. This allows light rays to focus properly on the retina again. Scar tissue also might be removed from the retina.

**PREVENTION TIPS**

***What can I do to prevent diabetic retinopathy?***

Managing your diabetes is the best way to lower your risk of diabetic retinopathy. That means keeping your blood sugar levels in a healthy range. You can do this by getting regular physical activity, eating healthy, and carefully following your doctor’s instructions for your insulin or other diabetes medicines.

To make sure your diabetes treatment plan is working, you’ll need a special lab test called an A1C test. This test shows your average blood sugar level over the past 3 months. You can work with your doctor to set a personal A1C goal. Meeting your A1C goal can help prevent or manage diabetic retinopathy.

Having high blood pressure or high cholesterol along with diabetes increases your risk for diabetic retinopathy. So, controlling your blood pressure and cholesterol can also help lower your risk for vision loss.

You can't always prevent diabetic retinopathy. However, regular eye exams, good control of your blood sugar and blood pressure, and early intervention for vision problems can help prevent severe vision loss.

If you have diabetes, reduce your risk of getting diabetic retinopathy by doing the following:

* **Manage your diabetes.** Make healthy eating and physical activity part of your daily routine. Try to get at least 150 minutes of moderate aerobic activity, such as walking, each week. Take oral diabetes medications or insulin as directed.
* **Monitor your blood sugar level.** You might need to check and record your blood sugar level several times a day — or more frequently if you're ill or under stress. Ask your doctor how often you need to test your blood sugar.
* **Ask your doctor about a glycosylated hemoglobin test.** The glycosylated hemoglobin test, or hemoglobin A1C test, reflects your average blood sugar level for the two- to three-month period before the test. For most people with diabetes, the A1C goal is to be under 7%.
* **Keep your blood pressure and cholesterol under control.** Eating healthy foods, exercising regularly and losing excess weight can help. Sometimes medication is needed, too.
* **If you smoke or use other types of tobacco, ask your doctor to help you quit.** Smoking increases your risk of various diabetes complications, including diabetic retinopathy.
* **Pay attention to vision changes.** Contact your eye doctor right away if your vision suddenly changes or becomes blurry, spotty or hazy.

Remember, diabetes doesn't necessarily lead to vision loss. Taking an active role in diabetes management can go a long way toward preventing complications.

**5 Ways to Prevent Vision Loss from Diabetic Retinopathy**

* If you have diabetes, talk with your primary care doctor about controlling your blood sugar. High blood sugar damages retinal blood vessels. That causes vision loss.
* Do you have high blood pressure or kidney problems? Ask your doctor about ways to manage and treat these problems.
* See your ophthalmologist regularly for dilated eye exams. Diabetic retinopathy may be found before you even notice any vision problems.
* If you notice vision changes in one or both eyes, call your ophthalmologist right away.
* Get treatment for diabetic retinopathy as soon as possible. This is the best way to prevent vision loss.

Changes in blood sugar levels can affect your vision. Make sure your blood sugar is under control for at least a week before an eye exam. Eyeglasses prescribed when your blood sugar levels are stable work best!

**POSSIBLE COMPLICATIONS**

Diabetic retinopathy involves the growth of abnormal blood vessels in the retina. Complications can lead to serious vision problems:

* **Vitreous hemorrhage.** The new blood vessels may bleed into the clear, jellylike substance that fills the center of your eye. If the amount of bleeding is small, you might see only a few dark spots (floaters). In more-severe cases, blood can fill the vitreous cavity and completely block your vision.

Vitreous hemorrhage by itself usually doesn't cause permanent vision loss. The blood often clears from the eye within a few weeks or months. Unless your retina is damaged, your vision will likely return to its previous clarity.

* **Retinal detachment.** The abnormal blood vessels associated with diabetic retinopathy stimulate the growth of scar tissue, which can pull the retina away from the back of the eye. This can cause spots floating in your vision, flashes of light or severe vision loss.
* **Glaucoma.** New blood vessels can grow in the front part of your eye (iris) and interfere with the normal flow of fluid out of the eye, causing pressure in the eye to build. This pressure can damage the nerve that carries images from your eye to your brain (optic nerve).
* **Blindness.** Diabetic retinopathy, macular edema, glaucoma or a combination of these conditions can lead to complete vision loss, especially if the conditions are poorly managed.
* **Macular ischemia (loss of blood flow to the part of the retina responsible for color and sharp vision)**

**What other problems can diabetic retinopathy cause?**

Diabetic retinopathy can lead to other serious eye conditions:

* **Diabetic macular edema (DME).** Over time, about 1 in 15 people with diabetes will develop DME. DME happens when blood vessels in the retina leak fluid into the macula (a part of the retina needed for sharp, central vision). This causes blurry vision.
* **Neovascular glaucoma.** Diabetic retinopathy can cause abnormal blood vessels to grow out of the retina and block fluid from draining out of the eye. This causes a type of glaucoma (a group of eye diseases that can cause vision loss and blindness).
* **Retinal detachment.** Diabetic retinopathy can cause scars to form in the back of your eye. When the scars pull your retina away from the back of your eye, it’s called tractional retinal detachment.

Vision-threatening complications associated with poorly controlled diabetic retinopathy include diabetic macular edema, tractional retinal detachment, and vitreous hemorrhage as a late sequela of proliferative diabetic retinopathy.

Management of Diabetic retinopathy with anti-VEGF therapy, laser photocoagulation, or vitrectomy surgery is also not free of complications.

**Complications Related to Anti-VEGF Medications**

* IOP spike
* Cataract formation
* Iatrogenic retinal/posterior capsular tear
* Vitreous hemorrhage
* Rhegmatogenous Retinal detachment
* Worsening of traction over the macula if given in patients with tractional retinal detachment
* Endophthalmitis

**Complications Related to Laser Photocoagulation**

* Vitreous hemorrhage
* Exudative retinal detachment and choroidal detachment if too many laser shots are given in a single sitting
* Reduction of contrast sensitivity, peripheral vision, and night vision after pan-retinal photocoagulation
* Permanent scotomas in the visual field
* Worsening of preexisting macular edema or development of macular edema after laser/PRP
* Chances of worsening optic disc pallor

**Complications Related to Vitrectomy**

* Cataract formation
* IOP spike because of gas or oil tamponade
* Iatrogenic secondary tears leading to rhegmatogenous retinal detachment
* In chronic macular edema, the macular roof is very thin, so there are chances of deroofing at the macular region leading to a macular hole

**OUTLOOK / PROGNOSIS**

Laser photocoagulation is performed as an OPD (outpatient department) procedure. Maintaining proper glycemic control and taking care of other associated systemic illnesses are necessary. There are chances of worsening macular edema and moderate vision reduction after pan-retinal photocoagulation (PRP). If that happens, the patient should report to the retinal surgeon for documentation and for planning a further line of management.

It is common to have an acute spike of IOP after intravitreal injections for a few hours. It usually returns to normal within 3-6 hours. It may be prudent to routinely use a single tablet of acetazolamide 250 mg stat after intravitreal injection. After intravitreal injections, patients should be called for follow-up the next day; then, according to the stability of the ocular condition, follow-up at regular intervals should be planned. Sequential OCT and/or OCTA parameters are assessed in each follow-up visit, and depending on their findings, further management with repeat injections, observation, and/or switching to laser /vitrectomy surgery is planned.

***Post-operative Care***

After surgery, the eye is patched. After the patch is removed, the eye is cleaned, and topical administration of medications like antibiotics with steroid eye drops and cycloplegic eye drops are started. After injecting gases like sf6/c3f8 or silicone oil, there are chances of IOP rise post-operatively, which needs to be managed with appropriate antiglaucoma medications. Patients can then be called for regular, timely follow-ups to screen their post-operative outcomes. If silicone oil tamponade is done, the patient should be explained the need for a mandatory second surgery to remove oil.

**What can I expect if I have diabetes-related retinopathy?**

Diabetes-related retinopathy is a permanent, lifelong condition. There isn’t a cure, but you can take steps to manage it and limit loss of vision.

Diabetes-related retinopathy is likely to happen to people with diabetes, but having diabetes doesn’t guarantee you’ll develop it. Still, it’s important to do everything you can to avoid or delay it because it can so heavily impact your life.

With early diagnosis and timely treatment, you may be able to prevent vision loss and delay diabetes-related retinopathy progression. After diabetes-related retinopathy treatment, you’ll have the best chance of limiting or delaying the effects of this disease if you manage your diabetes and keep your blood sugar within ranges that your providers recommend.

Unfortunately, some people will still develop more severe complications. But there are ways to delay those complications as long as possible and manage diabetes-related vision changes. Anything you can do to limit the severity of any vision changes is preferable to developing more severe issues or changes early on.

**WHEN TO SEE A DOCTOR / RED FLAG**

Careful management of your diabetes is the best way to prevent vision loss. If you have diabetes, see your eye doctor for a yearly eye exam with dilation — even if your vision seems fine.

Developing diabetes when pregnant (gestational diabetes) or having diabetes before becoming pregnant can increase your risk of diabetic retinopathy. If you're pregnant, your eye doctor might recommend additional eye exams throughout your pregnancy.

Contact your eye doctor right away if your vision changes suddenly or becomes blurry, spotty or hazy.

If you have diabetes or diabetes-related retinopathy, it’s crucial that you see an eye care specialist regularly. They’ll recommend a schedule for regular follow-up visits, which can make a big difference when it comes to catching more serious changes before they're severe or permanent.

You should also call or see your provider if you notice any gradual vision changes like:

* Vision loss or trouble seeing as well as you used to
* Blurred or distorted vision
* Areas in your vision that look dim, faded or different from how you saw before

You should go to the nearest hospital or emergency room if you have SUDDEN vision changes like:

* Severe eye pain
* Complete loss of vision or severe loss of vision

**DIFFERENTIAL DIAGNOSIS**

**Diagnostic Considerations**

Patients with diabetes often develop ophthalmic complications, such as corneal abnormalities, glaucoma, iris neovascularization, cataracts, and neuropathies. The most common and potentially most blinding of these complications, however, is diabetic retinopathy. Microaneurysms are the earliest clinical sign of diabetic retinopathy.

*Differential Diagnoses*

* Branch Retinal Vein Occlusion (BRVO)
* Central Retinal Vein Occlusion (CRVO)
* Hemoglobinopathy Retinopathy
* Retinal Macroaneurysm
* Macular Edema in Diabetes
* Ocular Ischemic Syndrome
* Retinopathy, Diabetic, Nonproliferative
* Sickle Cell Disease
* Terson Syndrome
* Valsalva Retinopathy

The differential diagnosis of diabetic macular edema includes:

* Hypertensive retinopathy
* Central retinal vein occlusion
* Branch retinal vein occlusion
* Irvine Gass syndrome
* Post uveitic macular edema
* Ruptured microaneurysm
* Macular edema secondary to epiretinal membrane
* Choroidal neovascular membrane.

The diseases which can be mistaken as diabetic retinopathy based on the general fundus appearance include:

* Central retinal vein occlusion
* Hypertensive retinopathy
* Sickle cell retinopathy
* Terson syndrome
* Ocular ischemic syndrome
* Branch retinal vein occlusion
* Hemiretinal vein occlusion
* Valsalva retinopathy
* Post-traumatic retinal bleed
* Retinal macroaneurysm
* Retinopathy in thalassemia

**EPIDEMIOLOGY**

* Global Prevalence:  
  Among individuals with diabetes worldwide, the prevalence of diabetic retinopathy is approximately 22% to 25%. A large meta-analysis including 59 population-based studies estimated a global prevalence of 22.27% (95% CI, 19.73%-25.03%) for any DR and 25.2% in a recent 2024 study. This means roughly 1 in 4 people with diabetes have some degree of DR.
* Vision-Threatening DR (VTDR):  
  The prevalence of VTDR, which includes proliferative diabetic retinopathy and clinically significant macular edema, is about 6.2% to 10% among people with diabetes globally.
* Number of Affected Individuals:
  + In 2020, approximately 103 million adults worldwide had diabetic retinopathy, with 28.5 million having vision-threatening DR and 18.8 million with clinically significant macular edema.
  + These numbers are projected to rise to 160.5 million (DR), 44.8 million (VTDR), and 28.6 million (CSME) by 2045 due to increasing diabetes prevalence and aging populations.
* Regional Variations:
  + DR prevalence is highest in Africa (35.9%) and North America and the Caribbean (33.3%).
  + Lowest prevalence is reported in South and Central America (13.4%).
  + Hispanics and Middle Eastern populations with diabetes have higher odds of developing DR compared to Asians[1](https://pubmed.ncbi.nlm.nih.gov/33940045/).
  + Latin America and the Caribbean, and North Africa and the Middle East regions have the highest percentages of DR-related blindness and moderate/severe vision impairment.
* Prevalence by Diabetes Type:
  + DR is more common in type 1 diabetes, with approximately 75% developing retinopathy.
  + About 50% of people with type 2 diabetes develop retinopathy.
* Risk Factors:  
  Duration of diabetes, poor glycemic control (high HbA1c), hypertension, and dyslipidemia are strongly associated with increased risk and progression of DR. Genetic factors also contribute, especially in proliferative DR.
* Impact on Vision:  
  In 2020, about 1.07 million people were blind and 3.28 million had moderate to severe vision impairment due to diabetic retinopathy globally. Despite increasing diabetes prevalence, advances in treatment have helped reduce the proportion of vision impairment in some regions.

***Global Information***

* Worldwide, diabetic retinopathy is the leading cause of blindness among working-aged adults.
* The global burden of diabetic retinopathy includes:
  + 387 million people with diabetes mellitus (DM) in the world, estimated to increase to 592 million people in 2035.
  + 93 million people with diabetic retinopathy
  + Affects 1 out of 3 persons with diabetes mellitus
  + Proliferative diabetic retinopathy (PDR): 17 million people
  + Diabetic macular edema: 21 million people
  + Vision-threatening diabetic retinopathy: 28 million people
* Prevalence of diabetic retinopathy is worldwide with only slight ethnic differences.
* Worldwide prevalence of DR in patients with type 1 DM is 77.3% and with type 2 is 25.1%.
* Changes in diet and lifestyle are suspected in the increase in DR prevalence.
* Earlier detection of DR in patients with diabetes, owing to better health care systems, contributes to the prevalence figures.
* 5%-8% of people with DR will need laser treatment.
* 3%-10% will have diabetic macular edema and 30% of them will have visual impairment.
* 0.5% of diabetic patients will need a vitrectomy.

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**PERIPHERAL VASCULAR DISEASE**

ALTERNATIVE NAMES: Peripheral vascular disease (PVD) is also known as “peripheral artery disease (PAD)”, and “peripheral arterial disease”

**DEFINITION / DESCRIPTION**

Peripheral artery disease (PAD) is a common condition in which narrowed arteries reduce blood flow to the arms or legs.

This condition also may be called peripheral arterial disease.

In PAD, the legs or arms — usually the legs — don't get enough blood flow to keep up with demand. This may cause leg pain when walking, called claudication, and other symptoms.

Peripheral artery disease is usually a sign of a buildup of fatty deposits in the arteries, a condition called atherosclerosis.

Treatment for PAD includes exercising, eating healthy foods, and not smoking or using tobacco.

In healthy adults, blood flows freely through veins and arteries like a stream. However, when that stream gets gunked up, blood flow can be restricted. Peripheral vascular disease, or PVD, is a systemic disorder that involves the narrowing of peripheral blood vessels (vessels situated away from the heart or the brain). This happens as a result of arteriosclerosis, or a buildup of plaque, and can happen with veins or arteries.

When plaque accumulates, it may result in blood clots and dangerously limit the amount of oxygen that circulates to the arms and legs. The condition often causes pain and discomfort while walking. If peripheral vascular disease goes untreated, there is a chance that it may progress into critical limb ischemia, a severe stage of PVD that can result in the loss of an affected limb. But if caught in its early stages, peripheral vascular disease is a treatable and reversible disease.

**vascular disease**

Vascular disease includes any condition that affects your circulatory system, or system of blood vessels. This ranges from diseases of your arteries, veins and lymph vessels to blood disorders that affect circulation.

Blood vessels are elastic-like tubes that carry blood to every part of your body. Blood vessels include:

* Arteries that carry blood away from your heart.
* Veins that return blood back to your heart.
* Capillaries, your tiniest blood vessels, which link your small veins and arteries, deliver oxygen and nutrients to your tissues and take away their waste.

**Types of Vascular Disease**

Some vascular diseases affect your arteries, while others occur in your veins. They can also happen only in specific parts of your body.

***Peripheral artery disease***

Like the blood vessels of your heart (coronary arteries), your peripheral arteries (blood vessels outside your heart) also may develop atherosclerosis, the buildup of plaque (fat and cholesterol deposits), inside them. Over time, the buildup narrows the artery. Eventually, the narrowed artery causes less blood to flow, which may lead to ischemia, or inadequate blood flow to your body's tissue. Types of peripheral arterial disease include:

* **Peripheral artery disease**: A blockage in your legs. Total loss of circulation can lead to gangrene and loss of a limb.
* **Intestinal ischemic syndrome**: A blockage in the blood vessels leading to your gastrointestinal system.
* **Renal artery disease**: A blockage in your renal arteries can cause renal artery disease and kidney failure.
* **Popliteal Entrapment Syndrome**: A rare vascular disease that affects the legs of some young athletes. The muscle and tendons near the knee compress the popliteal artery, restricting blood flow to the lower leg and possibly damaging the artery.
* **Raynaud's Phenomenon**: Consists of spasms of the small arteries of your fingers, and sometimes toes, from exposure to cold or stress.
* **Buerger's Disease**: Most commonly affects the small and medium-sized arteries, veins and nerves. Although the cause is unknown, there is a strong association with tobacco use or exposure. The arteries of your arms and legs become narrowed or blocked, causing lack of blood supply (ischemia) to your fingers, hands, toes and feet. With severe blockages, the tissue may die (gangrene), making it necessary to amputate affected fingers and toes. Superficial vein inflammation and symptoms of Raynaud's can occur as well.

***Carotid artery issues***

These happen in the two main carotid arteries in your neck.

* **Carotid artery disease**: A blockage or narrowing in the arteries supplying your brain. This can lead to a transient ischemic attack (TIA) or stroke.
* **Carotid artery dissection**: Begins as a tear in one layer of your artery wall. Blood leaks through this tear and spreads between the wall layers.
* **Carotid body tumors**: Growths within the nervous tissue around your carotid artery.
* **Carotid artery aneurysm**: A bulge in your artery wall that weakens the wall and may cause a rupture.

***Venous disease***

Veins are flexible, hollow tubes with flaps inside, called valves. When your muscles contract, these one-way valves open, and blood moves through your veins. When your muscles relax, the valves close, keeping blood flowing in one direction through your veins.

If the valves inside your veins become damaged, the valves may not close completely. This allows blood to flow in both directions. When your muscles relax, the valves inside the damaged vein(s) will not be able to hold the blood. This can cause pooling of blood or swelling in your veins. The veins bulge and look like ropes under the skin. The blood begins to move more slowly through your veins and may stick to the sides of your vessel walls. Symptoms include heaviness, aching, swelling, throbbing or itching. Blood clots can form.

* **Varicose veins**: Bulging, swollen, purple, ropy veins, seen just under your skin. Damaged valves within the veins cause this.
* **Spider veins**: Small red or purple bursts on your knees, calves, or thighs. Swollen capillaries (small blood vessels) cause this.
* **Klippel-Trenaunay syndrome (KTS)**: A rare congenital (present at birth) vascular disorder.
* **May-Thurner syndrome (MTS)**: Your right iliac artery compresses your left iliac vein, which increases the risk of deep vein thrombosis (DVT) in your left extremity.
* **Thoracic outlet syndrome (TOS)**: A group of disorders that happen with compression, injury or irritation of the nerves and/or blood vessels (arteries and veins) in your lower neck, armpit and upper chest area.
* **Chronic venous insufficiency (CVI)**: A condition that happens when the venous wall and/or valves in your leg veins are not working effectively, making it difficult for blood to return to your heart from your legs.

***Blood clots***

A clot forms when clotting factors in your blood make it coagulate or become a solid, jelly-like mass. When a blood clot forms inside a blood vessel (a thrombus), it can come loose and travel through your bloodstream, causing a deep vein thrombosis, pulmonary embolism, heart attack or stroke.

Blood clots in your arteries can increase the risk for stroke, heart attack, severe leg pain, difficulty walking or even the loss of a limb.

* **Hypercoagulable states or blood clotting disorders**: Conditions that put people at increased risk for developing blood clots because they make blood more likely to form blood clots (hypercoagulable) in the arteries and veins. You can inherit these conditions (congenital, occurring at birth) or acquire them. These disorders include high levels of factors in your blood that cause blood to clot (fibrinogen, factor 8, prothrombin) or not enough natural anticoagulant (blood-thinning) proteins (antithrombin, protein C, protein S). The most aggressive disorders include circulating antiphospholipid antibodies, which can cause clots in both arteries and veins.
* **Deep vein thrombosis (DVT)**: A blood clot occurring in a deep vein.
* **Pulmonary embolism**: A blood clot that breaks loose from a vein and travels to your lungs.
* **Axillo-subclavian vein thrombosis, also called Paget-Schroetter Syndrome**: Most common vascular condition to affect young, competitive athletes. The condition develops when your collarbone (clavicle), first rib or the surrounding muscle compresses a vein in your armpit (axilla) or in front of your shoulder (the subclavian vein). This increases your risk of blood clots.
* **Superficial thrombophlebitis**: A blood clot in a vein just under your skin.

***Aortic aneurysm***

An aneurysm is an abnormal bulge in a blood vessel wall. Aneurysms can form in any blood vessel, but they occur most commonly in the aorta (aortic aneurysm) which is the main blood vessel leaving the heart:

* Thoracic aortic aneurysm.
* Abdominal aortic aneurysm.

***Fibromuscular dysplasia (FMD)***

Fibromuscular dysplasia (FMD): A rare medical condition in which people have abnormal cellular growth in the walls of their medium and large arteries. This can cause the arteries with abnormal growth to look beaded and become narrow. This can cause issues with the arteries, including aneurysms and dissection.

***Lymphedema***

The lymphatic system includes an extensive network of lymph vessels and lymph nodes that helps coordinate your immune system's function to protect your body from foreign substances. Lymphedema, an abnormal buildup of fluid, develops when lymph vessels or lymph nodes are missing, impaired, damaged or removed.

* **Primary lymphedema** (rare): Some people are born without certain lymph vessels or have abnormalities in them.
* **Secondary lymphedema**: Happens as a result of a blockage or interruption that alters the lymphatic system. Causes of this include: infection, malignancy, surgery, scar tissue formation, trauma, deep vein thrombosis (DVT), radiation or other cancer treatment.

***Vasculitis***

Your blood vessels can get inflamed because of a medicine, an infection or an unknown cause. This can make it hard for blood to travel through your blood vessels. This is sometimes associated with rheumatological conditions or connective tissue disease. Vasculitis can also cause an aneurysm.

**Who does vasculopathy affect?**

Some people are born with vascular diseases they inherit from their parents. In these cases, such as blood clotting disorders, they start dealing with this issue at a younger age. However, many vascular diseases develop over time because of an accumulation of plaque (fat and cholesterol) in the arteries, such as peripheral artery disease or carotid artery disease. Atherosclerosis, the hardening of the arteries, can start when you’re a teen and cause problems in middle age or later.

**CAUSES**

Peripheral artery disease (PAD) is often caused by a buildup of fats, cholesterol and other substances in and on the artery walls, a condition called atherosclerosis. The buildup is called plaque. Plaque can cause arteries to narrow, blocking blood flow. In PAD, plaque collects in the arteries of the arms or legs.

Less common causes of PAD include:

* Swelling and irritation of blood vessels.
* Injury to the arms or legs.
* Changes in the muscles or ligaments.
* Radiation exposure.

**What causes vascular disease?**

For some vascular problems, the cause isn’t known. Vascular disease causes include:

* High cholesterol.
* High blood pressure.
* Smoking or using tobacco products.
* Diabetes.
* Genes you get from your parents.
* Medicines.
* Injury.
* Infection.
* Blood clots.

**RISK FACTORS**

**What are the risk factors for peripheral vascular disease?**

Peripheral vascular disease is most commonly caused by smoking, high blood pressure, elevated cholesterol levels, and/or type 2 diabetes.

Men over the age of 50 and postmenopausal women are more likely to develop peripheral vascular disease. The likelihood increases if the patient is a smoker, overweight, sedentary, and/or has had any one or more of the following: diabetes, hypertension and/or kidney disease.

***Risk factors for peripheral artery disease (PAD) include:***

* A family history of peripheral artery disease, heart disease or stroke.
* Diabetes.
* High blood pressure.
* High cholesterol.
* Increasing age, especially after 65, or after 50 if you have risk factors for atherosclerosis.
* Obesity.
* Smoking.

**SIGNS / SYMPTOMS**

**What are the symptoms of peripheral vascular disease?**

Patients with peripheral vascular disease may experience no symptoms at first. And when symptoms begin to appear, they tend to be irregular and occur more often when a patient is active—especially when walking.

A patient may notice pain, cramping, and/or discomfort in his or her legs and feet. Other symptoms can include achiness, burning and fatigue.

If a patient’s peripheral vascular disease continues to progress, symptoms will probably occur with greater frequency and may manifest even when the patient is not walking or otherwise being active.

Other signs to watch for:

* Changes to the skin on the legs and feet, which can become thin and/or shiny
* A purplish tinge to arms and legs, or toes that become blue
* Wounds and ulcers appearing on the feet and legs
* Thinning of hair on the legs

Peripheral artery disease (PAD) may not cause symptoms, or symptoms may be mild. PAD symptoms include:

* Leg pain when walking.
* Muscle pain or cramping in the arms or legs, often in the calf.
* Muscle pain in the arms or legs that begins with exercise and ends with rest.
* Painful cramping in one or both of the hips, thighs or calves after walking or climbing stairs or other activities.
* Pain when using the arms, such as aching and cramping when knitting or writing.
* Coldness in the lower leg or foot, especially when compared with the other side.
* Leg numbness or weakness.
* No pulse or a weak pulse in the legs or feet.

The muscle pain in peripheral artery disease may:

* Be mild to extreme.
* Wake you up from sleep.
* Make it hard to walk or exercise.
* Occur during rest or when lying down if the condition is severe.

Other symptoms of PAD may include:

* Shiny skin on the legs.
* Skin color changes on the legs.
* Slow-growing toenails.
* Sores on the toes, feet or legs that won't heal.
* Hair loss or slower hair growth on the legs.
* Erectile dysfunction.

Symptoms vary depending on the type of vascular disease.

**Peripheral artery disease symptoms**

* **Peripheral artery disease:** Leg pain or cramps with activity but improve with rest; changes in skin color; sores or ulcers and tired legs.
* **Intestinal ischemic (or mesenteric ischemia) syndrome:** Severe stomach pain, nausea, throwing up, diarrhea, food fear and weight loss.
* **Renal artery disease:** Uncontrolled hypertension (high blood pressure), congestive heart failure and abnormal kidney function.
* **Popliteal entrapment syndrome:** Leg and foot cramps, numbness, tingling, discoloration.
* **Raynaud’s phenomenon:** Fingers and toes that look red, blue or white, throbbing, tingling, redness.
* **Buerger’s disease:** Pain in your arms, hands, legs and feet, even at rest. Blue or pale fingers or toes.

**Symptoms of carotid artery issues**

* **Carotid artery disease:** Usually no symptoms until having a stroke or transient ischemic attack (TIA or mini-stroke). Symptoms of these include trouble with vision or speech, confusion and difficulty with memory.
* **Carotid artery dissection:** Headache, neck pain and eye or facial pain.
* **Carotid body tumors:** Palpitations, high blood pressure, sweating and headaches.
* **Carotid artery aneurysm:** Stroke or transient ischemic attack (TIA or mini-stroke).

**Venous disease symptoms**

* **Varicose veins and spider veins:** Swelling, pain, blue or red veins visible on legs.
* **Klippel-Trenaunay syndrome (KTS):** Pain or heaviness in your leg or arm.
* **May-Thurner syndrome (MTS):** Swelling, tenderness, pain in your leg, red or discolored skin.
* **Thoracic outlet syndrome (TOS):** Neck, arm and shoulder pain, tingling and numbness in your arm or hand.
* **Chronic venous insufficiency (CVI):** Leg cramps, heavy or achy legs, swelling or pain in your legs.

**Blood clots**

* **Blood clotting disorders:** Deep vein thrombosis, pulmonary embolism.
* **Deep vein thrombosis (DVT):** Pain, swelling, warmth in your leg, red skin.
* **Pulmonary embolism:** Coughing up blood, chest pain, shortness of breath.
* **Axillo-subclavian vein thrombosis:** Swelling, heaviness or pain in your arm or hand, skin that looks blue.
* **Superficial thrombophlebitis:** Inflammation, pain, warmth around your vein, red skin.

**Aortic aneurysm symptoms**

* **Thoracic aortic aneurysm:** Chest pain, fast heart rate, trouble swallowing, swollen neck.
* **Abdominal aortic aneurysm:** Abdominal or back pain, dizziness, nausea and throwing up, fast heart rate (if the aneurysm ruptures).

**Fibromuscular Dysplasia (FMD) symptoms**

**Fibromuscular dysplasia (FMD):** Neck pain, vision changes, high blood pressure, dizziness, hearing a “whooshing sensation” or hearing your heartbeat in your ears.

**Lymphedema symptoms**

Swelling, most often in your arms or legs.

**Vasculitis symptoms**

Not feeling well, fever, swelling.

**DIAGNOSIS METHODS**

***How is vascular disease diagnosed?***

Your healthcare provider will want to do a physical exam and get your medical history, as well as a history of which diseases are in your family. It helps your healthcare provider look for vascular disease when you take your shoes and socks off before they examine you.

Depending on the type of vascular disease your provider suspects, they may do blood tests and imaging.

**What tests will be done to diagnose vasculopathy?**

Many vascular diseases involve clots or blockages in blood vessels. To diagnose these, your healthcare provider needs to be able to see inside your blood vessels using imaging methods that include:

* Vascular ultrasound.
* Catheter angiography.
* CT angiography.
* MR angiography.

To diagnose peripheral artery disease (PAD), a healthcare professional examines you. You are usually asked questions about your symptoms and medical history.

If you have peripheral artery disease, the pulse in the affected area may be weak or missing.

**Tests**

Tests to diagnose peripheral artery disease (PAD) or check for conditions that cause it may include:

* **Blood tests.** Blood tests are done to check for things that increase the risk of PAD, such as high cholesterol and high blood sugar.
* **Ankle-brachial index (ABI).** This is a common test used to diagnose PAD. It compares the blood pressure in the ankle with the blood pressure in the arm. You may be asked to walk on a treadmill. Blood pressure readings may be taken before and right after exercising to check the arteries during walking.
* **Ultrasound of the legs or feet.** Sound waves create pictures of how blood moves through the blood vessels of the legs or feet. Doppler ultrasound is a special type of ultrasound used to spot blocked or narrowed arteries.
* **Angiography.** This test uses imaging tests and a dye to look for blockages in the arteries. The dye is given through a blood vessel. It helps the arteries show up more clearly on the test images.

**TREATMENT OPTIONS**

**Management and Treatment**

**How is vascular disease treated?**

Eating healthier and exercising more can help with many vascular diseases. For others, you may need to take medicine or have a surgical procedure. Vascular disease treatments vary depending on the condition.

**Peripheral artery disease treatment**

* **Peripheral artery disease:**Diet, exercise, medicine, surgery.
* **Intestinal ischemic syndrome:** Pain medicine, clot-busting drugs, surgical removal of blood clot. Angioplasty, stenting or bypass surgery for chronic cases.
* **Renal artery disease:** Low-salt, heart-healthy diet. High blood pressure medicine, statins.
* **Popliteal entrapment syndrome:** Surgery to release the popliteal artery.
* **Raynaud’s phenomenon:** Keep hands and feet warm. Take medicine that helps blood vessels stay open (dilated).
* **Buerger’s disease:** Quit tobacco products. Warm up fingers and toes. Take medicine (vasodilators) to open blood vessels.

**Treatment of carotid artery issues**

* **Carotid artery disease:** Healthier diet. Blood thinners and cholesterol-lowering medicine. Plaque removal (carotid endarterectomy). Angioplasty and stenting to keep the artery open.
* **Carotid artery dissection:** Antiplatelets, anticoagulants, stenting.
* **Carotid body tumors:** Surgical removal of the tumor.
* **Carotid artery aneurysm:** Antihypertensives, cholesterol-lowering medicine, clot-busting medicine. Bypass or stent-graft surgery.

**Venous disease treatment**

* **Varicose veins and spider veins:** Removal using heat, saltwater or laser therapy.
* **Klippel-Trenaunay syndrome (KTS):** Same treatment as varicose veins.
* **May-Thurner syndrome (MTS):**Same as for deep vein thrombosis.
* **Thoracic outlet syndrome (TOS):** Physical therapy, medicine.
* **Chronic venous insufficiency (CVI):** Move legs frequently and wear compression stockings. Vein treatment with saltwater, laser or removal through an incision.

**Blood clot treatment**

* **Blood clotting disorders:** Same as for deep vein thrombosis and pulmonary embolism.
* **Deep vein thrombosis (DVT):** Elevate your legs. Take blood thinners and medicines for pain.
* **Pulmonary embolism:** Blood thinners and thrombolytics. Procedure to remove the clot.
* **Axillo-subclavian vein thrombosis:** Thrombolytics, blood thinners. Removal of the clot.
* **Superficial thrombophlebitis:** Raise your affected limb above your heart. Use a warm compress. Put on support stockings. Have the vein surgically removed.

**Aortic aneurysm treatment**

* **Thoracic aortic aneurysm:** Surgery to put in a fabric graft or a stent. This can be a major surgery depending on the location and surgical method.
* **Abdominal aortic aneurysm:** Surgery to put in a graft. An endovascular repair is less invasive.

**Fibromuscular Dysplasia (FMD)**

* Blood thinners, medicine for pain.
* Angioplasty. Surgery to prevent an artery rupture.

**Lymphedema**

* Let your arm rest above your heart level while you lie down for 45 minutes twice daily.
* Wear a compression sleeve.
* Use your affected limb for daily tasks.
* Visit a specialized lymphedema clinic if your healthcare provider recommends it.

**Vasculitis**

* Your provider may prescribe medications like steroids.

Therapy typically includes changes to diet and exercise, smoking cessation, and, if appropriate, medications including blood thinners to dissolve clots, statins to reduce cholesterol, and vasodilators, which widen the blood vessels.

surgical repair or unblocking of the blood vessels, also called angioplasty.

The goals of treatment for peripheral artery disease (PAD) are:

* Manage symptoms, such as leg pain, so exercise is comfortable.
* Improve artery health to reduce the risk of heart attack, stroke and other complications.

Treatment for peripheral artery disease may include:

* Lifestyle changes.
* Medicine.
* Surgery.

Lifestyle changes can help improve symptoms, especially if you have early peripheral artery disease. Such changes include:

* Don't smoke or use tobacco.
* Get regular exercise.
* Eat a healthy diet.

**Medications**

If you have symptoms or complications of peripheral artery disease (PAD), you may need medicines.

Medicine to treat peripheral artery disease may include:

* **Statins.** These are medicines to lower "bad" cholesterol. They help reduce plaque buildup in the arteries. The drugs also lower the risk of heart attacks and strokes.
* **Blood pressure medicines.** Uncontrolled high blood pressure can make arteries stiff and hard. This can slow the flow of blood. If you have high blood pressure, your healthcare professional may suggest medicines to control it. Ask your healthcare team what your blood pressure should be.
* **Diabetes medicine.** Diabetes makes you more likely to get PAD. Talk with your healthcare team about your blood sugar goals and how to reach them.
* **Medicines to prevent blood clots.** Reduced blood flow in PAD can cause blood clots. Aspirin or another medicine, such as clopidogrel (Plavix), may be used to prevent blood clotting.
* **Leg pain medicine.** A medicine called cilostazol can be used to treat leg pain in people with peripheral artery disease. The medicine increases blood flow to the area.

**Surgeries or other procedures**

**Graft bypass**

Sometimes, a surgery or procedure is needed to treat peripheral artery disease (PAD) or its symptoms.

* **Thrombolytic therapy.** If a blood clot is blocking an artery, medicine may be given directly into the affected artery to dissolve the clot.
* **Angioplasty and stent placement.** If a narrowed artery is causing PAD leg pain, this treatment may help. A tiny balloon on a tube, called a catheter, is placed in the artery. The balloon inflates, which makes the artery wider. This improves blood flow. A small wire mesh tube, called a stent, may be placed in the artery to keep the artery open.
* **Bypass surgery.** This surgery creates a new path for blood to flow around a blocked or partially blocked artery. A surgeon takes a healthy blood vessel from another part of the body. The vessel is connected below the blocked artery. The new pathway improves blood flow to the muscle.

**PREVENTION TIPS**

The best way to prevent leg pain due to peripheral artery disease (PAD) is to have a healthy lifestyle. That means:

* Don't smoke.
* Eat foods that are low in sugar, trans fats and saturated fats.
* Get regular exercise — but check with your care team about what type and how much is best for you.
* Keep a healthy weight.
* Manage blood pressure, cholesterol and diabetes.
* Get good sleep.
* Control stress.

**How can I reduce my risk of vascular disease?**

You can’t do anything about your age, family history or genetics, but you can:

* Manage your diabetes, high cholesterol and high blood pressure.
* Exercise regularly.
* Eat healthier foods.
* Move around once an hour if you have to sit or stand for hours.
* Stay at a healthy weight.
* Reduce your stress level.
* Avoid tobacco products.

**Living With**

**How do I take care of myself?**

In addition to the things mentioned above, you’ll also want to keep taking medicines your healthcare provider prescribes and keep going to your regular checkups.

**POSSIBLE COMPLICATIONS**

Complications of peripheral artery disease (PAD) caused by atherosclerosis include:

* **Critical limb ischemia.** In this condition, an injury or infection causes tissue to die. Symptoms include open sores on the limbs that don't heal. Treatment may include amputation of the affected limb.
* **Stroke and heart attack.** Plaque buildup in the arteries also can affect the blood vessels in the heart and brain.

**Complications/side effects of the treatment**

Any medicine can have side effects, but the benefits of medicines usually make them worth taking. Side effects often go away. If they don’t, you can ask your healthcare provider to switch you to a different drug.

When considering a procedure or surgery, talk to your provider about the risks and benefits. What’s right for your neighbor may not be the right treatment for you.

Peripheral vascular disease can affect several systems in the body leading to a number of complications as listed below:

* Acute coronary syndrome
* Stroke
* Nonhealing ulcer
* Gangrene
* Amputation
* Deep vein thrombosis
* Erectile dysfunction

**OUTLOOK / PROGNOSIS**

**What is the outlook for patients with peripheral vascular disease?**

Patients diagnosed early can typically expect a full recovery, provided that all treatments, including lifestyle changes such as quitting smoking, are adhered to over time.

Patients whose peripheral vascular disease has progressed to critical limb ischemia are seen at Yale Medicine’s multidisciplinary critical limb ischemia clinic.

*What can I expect if I have vasculopathy?*

Vascular disease can be a lifelong problem. Once your healthcare provider knows you have plaque accumulations in your blood vessels, they’ll want you to make some changes to how you live. These changes, such as exercising, not using tobacco products and choosing healthier foods, are things you’ll need to keep doing for years to come. You may also need to take medicines to decrease your risk of a heart attack or stroke.

***Outlook for this condition***

The outlook for many vascular conditions is good if your healthcare provider catches the problem early. Many vascular issues get harder to treat as they get worse. Some vascular conditions, such as carotid artery dissection, abdominal aortic aneurysm and pulmonary embolism, can be life-threatening.

The overall prognosis of patients with peripheral vascular disease must take into account patient risk factors, cardiovascular health, and disease severity. In terms of limb health at 5 years, nearly 80% of patients will have stable claudication symptoms. Only 1% to 2% of patients will progress to critical limb ischemia in 5 years. 20 to 30% of patients with PAD will die within 5 years, with 75% of those deaths attributed to cardiovascular causes.

**WHEN TO SEE A DOCTOR / RED FLAG**

Make an appointment for a health checkup if you have leg or arm pain or other symptoms of peripheral artery disease.

Contact your provider if anything changes with your vascular issue or if you have a problem with the medication they prescribed.

* Confusion or dizziness.
* Slurred speech.
* A droop on one side of your face.
* Severe chest pain.
* Severe abdominal pain.
* Loss of vision.
* Weakness in an arm or leg.

**What questions should I ask my doctor?**

* What’s the best treatment for my specific situation?
* Is there anything else I should be doing to take care of my vascular condition?
* Are there related conditions I should watch for with this vascular issue?

**DIFFERENTIAL DIAGNOSIS**

A provider has to take into account various differential diagnoses when a patient presents with the above-mentioned signs and symptoms. The following are some of the most important ones:

**Neurological**

* Nerve root compression
* Spinal stenosis
* Peripheral neuropathy
* Nerve entrapment

**Musculoskeletal**

* Medial tibial stress syndrome
* Osteoarthritis
* Muscle strain
* Baker cyst

**Vascular**

* Chronic venous insufficiency
* Thrombophlebitis
* Deep venous thrombosis
* Raynaud phenomenon
* Thromboangiitis obliterans

**EPIDEMIOLOGY**

* Global Prevalence and Trends:
  + The global prevalence of PAD increased by approximately 72% from about 65.8 million cases in 1990 to 113.4 million in 2019.
  + Age-standardized prevalence per 100,000 persons actually decreased by about 22%, reflecting population aging and growth as major drivers of absolute case increases.
  + In 2015, an estimated 236.6 million adults aged 25 years and older worldwide were living with PAD, with nearly 73% residing in low- and middle-income countries (LMICs).
  + Global prevalence rises sharply with age, reaching about 14.9% in people aged 80–84 years.
* Regional and Socioeconomic Differences:
  + PAD prevalence is higher in high-income countries (HICs) (~7.4%) compared to LMICs (~5.1%), but most cases occur in LMICs due to larger populations.
  + Disease burden (including disability-adjusted life years) increases with higher sociodemographic index (SDI).
  + Racial disparities exist, with Black individuals having higher PAD prevalence and lifetime risk (~30%) compared to non-Hispanic Whites (~20%). Hispanics and American Indians also show elevated prevalence.
* Sex Differences:
  + PAD prevalence and disability are generally higher among women, whereas mortality and years of life lost tend to be higher among men.
* United States Prevalence:
  + Estimated PAD prevalence is approximately 7% among US adults, affecting around 8.5 million people, based largely on older data from the 1990s and early 2000s.
  + Prevalence increases with age, but updated data for those aged 80+ are limited.
* Chronic Limb-Threatening Ischemia (CLTI):
  + Prevalence of CLTI, a severe PAD form, is about 1.3% among individuals aged 40 years and older in the US.
  + CLTI accounts for roughly 11% of overall PAD cases in some datasets.
  + Hospital admissions for CLTI have remained relatively stable from 2003 to 2011.
* Amputation Trends:
  + Nontraumatic lower extremity amputations related to PAD decreased from the 1990s to early 2000s but have increased by about 50% from 2009 to 2015 in people with diabetes in the US, mainly due to minor amputations below the ankle.
* Major Risk Factors:
  + Tobacco use, diabetes, and hypertension are the leading contributors to PAD burden globally, accounting for about 55% of disability-adjusted life years.
  + Other risk factors include hyperlipidemia, obesity, and aging.

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**CAUSES OF DIABETIC COMPLICATIONS**

Diabetic complications arise primarily from **prolonged high blood sugar levels**, which can damage blood vessels and nerves over time. This damage can lead to various health issues, including heart disease, kidney disease, nerve damage, and eye problems. Additionally, high blood sugar levels can cause damage to the blood vessels and nerves, which can result in complications such as foot problems, gum disease, and skin infections. Other factors that contribute to diabetic complications include being overweight, not getting enough exercise, and genetics. Smoking also increases the risk of complications, particularly heart disease. It is important to manage blood sugar levels, maintain a healthy lifestyle, and regularly monitor for any signs of complications to prevent or delay their onset.

**RISK FACTORS**

Common risk factors for the development of diabetes complications include **blood pressure, lipid parameters (i.e. total, HDL-, and LDL-cholesterol and triglycerides), heart rate, body weight, and uric acid**. Modifiable risk factors for complications of diabetes include overweight/obesity, poor diet, hypertension, smoking, and physical inactivity. Risk factors for diabetes, especially type 2 diabetes, include overweight and lack of physical exercise, smoking, a low-fiber, high-fat and sugary diet, medications that can affect the body’s metabolism of carbohydrates, and genetic factors which may cause some families to more likely develop diabetes.

**SIGNS / SYMPTOMS**

The signs of diabetic complications can vary depending on the specific complication, but they often include a range of symptoms and health issues. Here are some common signs:

* **Eye problems**: Symptoms may include blurred vision, difficulty seeing at night, and light sensitivity. If left untreated, these can lead to vision loss or blindness.
* **Foot problems**: Signs may include **sores, infections, or ulcers on the feet**. In severe cases, poor circulation and nerve damage can lead to amputation.
* **Heart problems**: Symptoms may include **chest pain, shortness of breath, and fatigue**. Diabetes increases the risk of heart disease and stroke.
* **Nerve damage (neuropathy)**: Symptoms may include **pain, burning, tingling, or loss of feeling, particularly in the hands and feet**. This can also affect other parts of the body, such as the digestive system and sexual function.
* **Kidney problems**: Symptoms may include swelling in the legs, fatigue, and changes in urination. Diabetes is a leading cause of kidney failure.
* **Skin conditions**: Symptoms may include **dry, itchy skin, infections, and slow-healing wounds**. Diabetes can also cause specific skin conditions such as acanthosis nigricans, which is characterized by darkened skin in certain areas.
* **Gum disease**: Symptoms may include swollen, tender, or bleeding gums. Diabetes increases the risk of gum disease and other oral health problems.
* **Hearing loss**: People with diabetes are twice as likely to experience hearing loss compared to those without diabetes.
* **Diabetic ketoacidosis (DKA)**: This is a serious complication that can occur when the body starts breaking down fat for energy, leading to the production of ketones. Symptoms include vomiting, stomach pain, fruity-smelling breath, and labored breathing.

It is important to note that many of these complications can be prevented or managed through proper diabetes management, including maintaining healthy blood sugar levels, regular check-ups, and lifestyle changes. If you experience any of these symptoms, it is crucial to consult a healthcare provider for proper diagnosis and treatment.

**DIAGNOSIS METHODS**

The diagnosis of diabetic complications involves various methods depending on the specific complication. For instance, retinopathy, a common complication affecting the eyes, can be diagnosed through comprehensive eye exams, including dilated eye exams and retinal imaging. Neuropathy, which affects the nerves, is often diagnosed using a combination of physical exams, nerve conduction studies, and electromyography.

For kidney complications, such as nephropathy, the diagnosis typically involves **urine tests to check for albumin (a protein that should not be present in large amounts in urine) and blood tests to measure creatinine levels**, which help estimate the glomerular filtration rate (GFR).

Foot complications, including ulcers and infections, are diagnosed through physical examination, assessment of foot pulses, and sometimes imaging studies like X-rays or MRI to check for bone involvement or abscesses.

Cardiovascular complications are assessed using electrocardiograms (ECGs), stress tests, and imaging techniques such as echocardiograms or coronary angiograms.

In addition, the diagnosis of diabetes itself, which is a prerequisite for many complications, can be made using fasting plasma glucose tests, A1C tests, random plasma glucose tests, or an oral glucose tolerance test. The A1C test measures the average blood glucose levels over the past two to three months and is particularly useful for monitoring long-term glucose control.

It is important to note that the diagnosis of diabetic complications often requires a multidisciplinary approach, involving various healthcare professionals to ensure comprehensive care and management.

**TREATMENT OPTIONS**

The treatment options for diabetic complications involve a combination of lifestyle changes, medications, and regular medical monitoring to manage and prevent further damage. Here are some key approaches:

* **Healthy Lifestyle Changes**: A healthy diet, regular physical activity, maintaining a normal body weight, and avoiding tobacco use are essential for preventing or delaying the onset of type 2 diabetes and its complications. These lifestyle measures can have a significant impact on diabetic control.
* **Medications**: Medications are often necessary to manage blood sugar levels. For type 2 diabetes, drug classes used include GLP-1 agonists, DPP-4 inhibitors, and SGLT-2 inhibitors, which can help reduce cardiovascular risk. Additionally, people with diabetes often need medications to lower their blood pressure and statins to reduce the risk of complications.
* **Regular Screening and Treatment**: Regular screening for complications is crucial. This includes checking for cardiovascular disease, kidney disease, eye problems, and nerve damage. Early detection and treatment can help prevent or delay the progression of these complications.
* **Managing Blood Sugar Levels**: Keeping blood glucose levels on target is the best line of defense against nerve damage and other complications. This involves monitoring blood sugar levels regularly and adjusting treatment as needed.
* **Specialist Care**: In some cases, specialist care may be required. For example, patients with severe complications may need to see an endocrinologist, a nephrologist for kidney issues, or an ophthalmologist for eye problems.
* **Emergency Care**: In cases of acute complications such as diabetic ketoacidosis (DKA) or hyperosmolar hyperglycemic state (HHS), immediate medical attention is necessary. These conditions can be life-threatening and require hospitalization.

By combining these approaches, individuals with diabetes can effectively manage their condition and reduce the risk of complications. It is important to work closely with healthcare providers to develop a personalized treatment plan

**PREVENTION TIPS**

To prevent diabetic complications, it is essential to maintain a healthy lifestyle and manage blood sugar levels effectively. Here are some key prevention tips:

* **Maintain a healthy diet**: Eating a balanced diet, such as the Mediterranean diet, can help reduce the risk of complications. Focus on whole foods, limit processed foods, and manage carbohydrate intake.
* **Engage in regular physical activity**: Aim for at least 30 minutes of physical activity most days of the week. Exercise helps improve blood sugar control, reduces cardiovascular risk, and maintains a healthy weight.
* **Monitor and control blood sugar levels**: Keeping blood glucose levels within a target range is crucial. Regular monitoring and logging of blood sugar levels can help prevent complications such as nerve damage, eye disease, and kidney problems.
* **Manage blood pressure and cholesterol**: High blood pressure and cholesterol increase the risk of heart disease and stroke. Work with your healthcare provider to keep these levels under control.
* **Quit smoking**: Smoking increases the risk of heart disease and other complications. Quitting smoking can significantly improve overall health.
* **Get regular checkups**: Regular visits to your healthcare provider are important for early detection and management of complications. These checkups can include tests for eye, kidney, and nerve damage. Schedule regular physical and eye exams.
* **Maintain a healthy weight**: Losing weight if needed can improve blood sugar control and reduce the risk of complications. Aim for a weight that is healthy for you.
* **Take medications as prescribed**: Follow your healthcare provider's instructions for medications to manage diabetes and related conditions.
* **Manage stress**: Chronic stress can affect blood sugar levels. Find healthy ways to manage stress, such as meditation, deep breathing, or engaging in hobbies. Take stress seriously.
* **Make a commitment to managing your diabetes**
* **Keep your blood pressure and cholesterol under control**
* Keep your vaccines up to date. Diabetes increases your risk of getting certain illnesses. Routine vaccines can help prevent them. Ask your health care provider about:
  + **Flu vaccine.** A yearly flu vaccine can help you stay healthy during flu season as well as prevent serious complications from the flu.
  + **Pneumonia vaccine.** Sometimes the pneumonia vaccine requires only one shot. If you have diabetes complications or you are age 65 or older, you may need a booster shot.
  + **Hepatitis B vaccine.** The hepatitis B vaccine is recommended for adults with diabetes who haven't previously received the vaccine and are younger than 60. If you're age 60 or older and have never received the hepatitis B vaccine, talk to your health care provider about whether it's right for you.
  + **Other vaccines.** Stay up to date with your tetanus shot (usually given every 10 years). Your doctor may recommend other vaccines as well.
* Take care of your teeth. Diabetes may leave you prone to gum infections. Brush your teeth at least twice a day with a fluoride toothpaste, floss your teeth once a day and schedule dental exams at least twice a year. Call your dentist if your gums bleed or look red or swollen.
* Pay attention to your feet. High blood sugar can reduce blood flow and damage the nerves in your feet. Left untreated, cuts and blisters can lead to serious infections. Diabetes can lead to pain, tingling or loss of sensation in your feet. To prevent foot problems:
  + Wash your feet daily in lukewarm water. Avoid soaking your feet, as this can lead to dry skin.
  + Dry your feet gently, especially between the toes.
  + Moisturize your feet and ankles with lotion or petroleum jelly. Do not put oils or creams between your toes — the extra moisture can lead to infection.
  + Check your feet daily for calluses, blisters, sores, redness or swelling.
  + Consult your doctor if you have a sore or other foot problem that doesn't start to heal within a few days. If you have a foot ulcer — an open sore — see your doctor right away.
  + Don't go barefoot, indoors or outdoors.
* Consider a daily aspirin. If you have diabetes and other cardiovascular risk factors, such as smoking or high blood pressure, your doctor may recommend taking a low dose of aspirin every day to help reduce your risk of heart attack and stroke. If you don't have additional cardiovascular risk factors, the risk of bleeding from aspirin use may outweigh any of its benefits. Ask your doctor whether daily aspirin therapy is appropriate for you, including which strength of aspirin would be best.

By following these prevention tips, individuals with diabetes can significantly reduce their risk of complications and improve their quality of life.

**POSSIBLE COMPLICATIONS**

Diabetes can lead to a variety of complications, which can be categorized into acute and chronic issues. Acute complications include **hypoglycemia (low blood sugar) and diabetic ketoacidosis (DKA),** which can be life-threatening and require immediate medical attention. Chronic complications, on the other hand, develop over time due to prolonged high blood sugar levels and can affect multiple organs and systems in the body.

Chronic complications of diabetes include:

* **Eye problems**: High blood sugar levels can damage the blood vessels in the retina, leading to diabetic retinopathy, which can cause vision loss or blindness. Other eye conditions such as glaucoma and cataracts are also more common in people with diabetes.
* **Foot problems**: Nerve damage (neuropathy) and reduced blood flow can lead to numbness, tingling, and pain in the feet. This can result in ulcers, infections, and in severe cases, amputations.
* **Heart attacks and stroke**: Diabetes increases the risk of cardiovascular diseases, including coronary artery disease, heart attack, and stroke. High blood sugar levels can damage blood vessels and contribute to the development of atherosclerosis.
* **Nerve damage (neuropathy)**: Prolonged high blood sugar levels can damage nerves, leading to symptoms such as numbness, tingling, and pain, particularly in the hands and feet. Neuropathy can also affect other parts of the body, including the digestive system, heart, and sexual function.
* **Kidney disease (nephropathy)**: High blood sugar levels can damage the kidneys, leading to chronic kidney disease (CKD). If left untreated, CKD can progress to kidney failure, requiring dialysis or a kidney transplant.
* **Skin and mouth infections**: High blood sugar levels can increase the risk of infections, including skin infections, gum disease, and oral health problems. These infections can be more severe and harder to treat in people with diabetes.
* **Hearing loss**: Studies suggest that diabetes may increase the risk of hearing loss, although the exact mechanisms are not fully understood.
* **Depression and mental health issues**: People with diabetes are at a higher risk of developing depression and other mental health issues. The risk increases with the development of diabetes-related health problems.

It is important to note that many of these complications can be prevented or delayed through proper management of diabetes, including maintaining good blood sugar control, adopting a healthy lifestyle, and regular medical check-ups. Early detection and treatment of complications can significantly improve outcomes and quality of life for people with diabetes.

**OUTLOOK / PROGNOSIS**

Diabetic complications can significantly impact a person's health and life expectancy, but effective management strategies can help reduce their effects. Chronic high blood sugar can lead to severe complications, which are usually irreversible, and can shorten lifespan and worsen quality of life. These complications include eye disease, foot problems, gum disease, and other issues due to damage to blood vessels and nerves.

The risk of complications is higher for individuals diagnosed with type 2 diabetes at a younger age, but adopting effective management strategies can help a person with type 2 diabetes live as long as someone without the condition. Lifestyle changes, such as maintaining a healthy diet, regular physical activity, and avoiding smoking, along with proper medical care, can help prevent or delay complications.

Strict metabolic control, including managing blood sugar levels, blood pressure, and blood lipid levels, can prevent or delay the onset of diabetes-related complications. Additionally, maintaining a healthy lifestyle and regular medical check-ups are crucial for managing diabetes and reducing the risk of complications.

In summary, while diabetic complications can be severe, proactive management and lifestyle changes can significantly improve the prognosis and quality of life for individuals with diabetes.

**WHEN TO SEE A DOCTOR / RED FLAG**

If you are experiencing any signs of diabetic complications, it is important to see a doctor immediately. These complications can affect various parts of the body, including the eyes, kidneys, nerves, and feet. For example, diabetes can damage the nerves in your feet and reduce blood supply, leading to sores, infections, and in severe cases, amputations. It is also important to have your feet checked every year by a healthcare professional.

**If you have developed complications such as problems with your eyes, kidneys, or nerves**, you should definitely see a specialist. Additionally, if you are having frequent low blood sugars (hypoglycemia) or have ever had severe low blood sugar or diabetic ketoacidosis, it is recommended to see a specialist.

In general, if your blood glucose levels are not well managed, or if you notice new health problems, you should make an appointment to see your endocrinologist as soon as possible. Each time you visit your doctor, your blood pressure, weight, and the condition of your feet should be checked to make sure complications aren't developing.

**DIFFERENTIAL DIAGNOSIS**

The differential diagnosis for diabetic complications involves identifying conditions that may mimic or coexist with diabetes, as well as understanding the various types of diabetes and their associated complications. Diabetic complications can be broadly categorized into microvascular and macrovascular complications. Microvascular complications include retinopathy, nephropathy, and neuropathy, while macrovascular complications involve cardiovascular diseases such as coronary artery disease, heart attack, and atherosclerosis.

In addition to these, there are other conditions that can present with symptoms similar to diabetes, such as secondary diabetes caused by other medical conditions like organ injury, hormonal disturbances, tumors, and medication side effects. The differential diagnosis also includes other forms of diabetes, such as Type 1 diabetes, Type 2 diabetes, gestational diabetes, and monogenic forms of diabetes like Maturity-onset diabetes of the young (MODY) and neonatal diabetes.

For the differential diagnosis of diabetes, several laboratory tests are used, including **fasting blood sugar, oral glucose tolerance test, and random plasma glucose testing**. The hemoglobin A1C test is also used to assess average blood glucose levels over the past 2 to 3 months.

In the context of diabetes complications, it is crucial to differentiate between various types of diabetes and their underlying causes to ensure appropriate treatment. For example, Type 1 diabetes is an autoimmune condition, while Type 2 diabetes is characterized by insulin resistance. Gestational diabetes occurs during pregnancy and can increase the risk of developing Type 2 diabetes later in life.

The management of diabetes and its complications involves a multifaceted approach, including blood sugar monitoring, lifestyle modifications, medication, and regular medical check-ups. Patients with diabetes are also at higher risk for other health issues, such as cardiovascular diseases, nerve damage, kidney failure, and vision loss.

In summary, the differential diagnosis for diabetic complications requires a comprehensive evaluation of the patient's symptoms, medical history, and laboratory results to identify the specific type of diabetes and its associated complications. This approach ensures that patients receive the most effective and personalized treatment plan.

Notable updates to the *Standards of Care in Diabetes—2025* include*:*

* Consideration of continuous glucose monitor (CGM) use for adults with type 2 diabetes on glucose-lowering agents other than insulin.
* Guidance on actions to take during circumstances of medication unavailability, such as medication shortages.
* Additional guidance on the use of GLP-1 receptor agonists beyond weight loss for heart and kidney health benefits.
* Guidance on continuation of weight management pharmacotherapy beyond reaching weight loss goals.
* Guidance for treatment of metabolic dysfunction-associated steatotic liver disease (MASLD) with moderate or advanced liver fibrosis using a thyroid hormone receptor-beta agonist.
* Emphasis on the use of antibody-based screening for presymptomatic type 1 diabetes in those who have a family history or known genetic risk.
* Guidance on the use of recreational cannabis for type 1 diabetes and those with other forms of diabetes at risk for diabetic ketoacidosis (DKA).
* Key updates highlighting potentially harmful medications in pregnancy and guidance for appropriately modifying the care plan.
* Expanded nutrition guidance to encourage evidence-based eating patterns, including those incorporating plant-based proteins and fiber, that keep nutrient quality, total calories, and metabolic goals in mind.

The ADA annually updates its *Standards of Care* through the efforts of its Professional Practice Committee (PPC). Comprising global experts from diverse professional backgrounds, the PPC includes physicians, nurse practitioners, certified diabetes care and education specialists, registered dietitian nutritionists, pharmacists, and methodologists. Its members hold expertise in a range of related fields. The 2025 *Standards of Care* has garnered endorsements from the American College of Cardiology (Section 10), the American Geriatrics Society , the American Society of Bone and Mineral Research (Bone Health, Section 4), and the Obesity Society .

Other noteworthy changes include:

* Emphasis on water intake over nutritive and nonnutritive sweetened beverages; and the use of nonnutritive sweeteners over sugar-sweetened products in moderation and for the short term to reduce overall calorie and carbohydrate intake.
* Importance of meeting resistance training guidelines for those treated with weight management pharmacotherapy or metabolic surgery.
* Guidance for DKA and hyperglycemic hyperosmolar state (HHS) in the outpatient and inpatient settings.
* Screening updates for fear of hypoglycemia, diabetes distress, and anxiety.
* Improved approach for diabetes care delivery for older adults.
* Guidance on the use of GLP-1 receptor agonists and dual GIP and GLP-1 receptor agonists in the perioperative care setting.

**EPIDEMIOLOGY**

Diabetic complications have a significant impact on global health, with epidemiological data showing a rise in prevalence and associated morbidity and mortality. According to the World Health Organization (WHO), diabetes is a chronic disease that occurs when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin it produces. Hyperglycaemia, or raised blood glucose, can lead to serious damage to many of the body's systems, especially the nerves and blood vessels.4 **In 2022, 14% of adults aged 18 years and older were living with diabetes**, an increase from 7% in 1990.

The epidemiology of diabetes-related complications includes **cardiovascular disease, kidney disease, neuropathy, blindness, and lower-extremity amputation**. These complications are a significant cause of increased morbidity and mortality among people with diabetes, and they result in a heavy economic burden on the healthcare system.4 In the United States, for example, the National Diabetes Statistics Report indicates that more than 38.4 million people have diabetes, with 11.6% of the U.S. population affected. Additionally, 97.6 million people aged 18 years or older have prediabetes, highlighting the widespread nature of the condition.

Diabetic complications are also influenced by various risk factors, including age, ethnicity, family history of diabetes, smoking, obesity, and physical inactivity.4 The prevalence of these complications is particularly high among elderly people and in minority racial or ethnic groups. For instance, in the United States, 39.2% of adults with diagnosed diabetes have chronic kidney disease (CKD, stages 1–4), with higher rates observed among non-Hispanic Black adults compared to other groups.

Globally, the burden of diabetes and its complications is substantial. The WHO reports that diabetes accounts for approximately 4.2 million deaths every year, with an estimated 1.5 million caused by either untreated or poorly treated diabetes. The major types of diabetes are type 1 and type 2, with type 2 diabetes accounting for 85–90% of all cases worldwide. Lifestyle changes, such as maintaining a healthy diet, regular physical activity, and avoiding tobacco use, are effective in preventing or delaying the onset of type 2 diabetes.

In China, the epidemiology of diabetes and its complications is also a growing concern. The country has witnessed one of the most dramatic rises in diabetes prevalence, with approximately 11% of the population affected. Risk factors for diabetes in the Chinese population are similar to those in other populations, though gestational diabetes and young-onset diabetes are becoming increasingly common. Cardiovascular and renal complications are significant contributors to morbidity and mortality among individuals with diabetes in China.

The global trends in diabetes complications indicate that while the incidence of some complications, such as end-stage renal disease (ESRD), has declined in certain populations, others remain a significant challenge. For example, in the United States, the incidence of ESRD in people with diabetes declined by 28% between 1990 and 2010, but the incidence of treated ESRD remained relatively stable in Asian individuals with diabetes. Additionally, the incidence of diabetic retinopathy has decreased over time, likely due to earlier identification and treatment of both diabetes and diabetic retinopathy, as well as reductions in smoking rates.

In summary, the epidemiology of diabetic complications is complex and multifaceted, involving a range of risk factors and health outcomes. The global burden of these complications underscores the need for continued research, prevention strategies, and effective management of diabetes to reduce its impact on individuals and healthcare systems.

**How common is vascular disease?**

Vascular diseases are very common in America, partly because so many people weigh too much and have diabetes. The most common vascular diseases include peripheral artery disease (PAD) and carotid artery disease.

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**THYROID DISORDERS**

Thyroid disorders are also prevalent and include **hypothyroidism (underactive thyroid) and hyperthyroidism (overactive thyroid).** Hypothyroidism occurs when the thyroid gland does not produce enough thyroid hormone, while hyperthyroidism is when it produces too much.8

Adrenal gland disorders, such as Addison's disease, occur when the adrenal glands do not produce enough cortisol and aldosterone.2

Other endocrine diseases include acromegaly, which causes parts of the body to grow larger, and polycystic ovary syndrome (PCOS), a hormonal condition that affects many females in their reproductive years.28

Endocrinologists specialize in diagnosing and treating these conditions by rebalancing hormones and treating symptoms.

Endocrinology deals with diseases and disorders related to hormones and the glands that produce them. Common endocrine disorders include **diabetes and thyroid diseases**.

**Thyroid Diseases**: These involve the thyroid gland, which produces hormones that regulate metabolism. Common thyroid diseases include:

* **Hypothyroidism**: The thyroid gland does not produce enough thyroid hormone, leading to symptoms like fatigue, constipation, dry skin, and depression.
* **Hyperthyroidism**: The thyroid gland produces too much thyroid hormone, causing symptoms such as weight loss, fast heart rate, sweating, and nervousness. The most common cause of hyperthyroidism is an autoimmune disorder called Grave's disease.
* **Thyroid Nodules**: These are lumps in the thyroid gland that can be benign or cancerous. They may cause swelling in the neck or affect thyroid hormone levels.

If you have symptoms of these conditions or need specialized care for hormone-related issues, you may need to see an endocrinologist, a doctor who specializes in diagnosing and treating hormone disorders.

**HYPOTHYROIDISM**

*ALTERNATIVE NAMES:* Hypothyroidism is also known as “underactive thyroid”, “low thyroid”, or “hypothyreosis”.

**DEFINITION / DESCRIPTION**

Hypothyroidism happens when the thyroid gland doesn't make enough thyroid hormone. This condition also is called underactive thyroid. Hypothyroidism may not cause noticeable symptoms in its early stages. Over time, hypothyroidism that isn't treated can lead to other health problems, such as high cholesterol and heart problems.

Blood tests are used to diagnose hypothyroidism. Treatment with thyroid hormone medicine usually is simple, safe and effective once you and your health care provider find the right dosage for you.

**CAUSES**

The thyroid is a small, butterfly-shaped gland located at the base of the neck, just below the Adam's apple. The thyroid gland makes two main hormones: thyroxine (T-4) and triiodothyronine (T-3). These hormones affect every cell in the body. They support the rate at which the body uses fats and carbohydrates. They help control body temperature. They have an effect on heart rate. And they help control how much protein the body makes.

Hypothyroidism happens when the thyroid gland doesn't make enough hormones. Conditions or problems that can lead to hypothyroidism include:

* **Autoimmune disease.** The most common cause of hypothyroidism is an autoimmune disease called Hashimoto's disease. Autoimmune diseases happen when the immune system makes antibodies that attack healthy tissues. Sometimes that process involves the thyroid gland and affects its ability to make hormones.
* **Thyroid surgery.** Surgery to remove all or part of the thyroid gland can lower the gland's ability to make thyroid hormones or stop it completely.
* **Radiation therapy.** Radiation used to treat cancers of the head and neck can affect the thyroid gland and lead to hypothyroidism.
* **Thyroiditis.** Thyroiditis happens when the thyroid gland becomes inflamed. This may be due to an infection. Or it can result from an autoimmune disorder or another medical condition affecting the thyroid. Thyroiditis can trigger the thyroid to release all of its stored thyroid hormone at once. That causes a spike in thyroid activity, a condition called hyperthyroidism. Afterward, the thyroid become underactive.
* **Medicine.** A number of medicines may lead to hypothyroidism. One such medicine is lithium, which is used to treat some psychiatric disorders. If you're taking medicine, ask your healthcare provider about its effect on the thyroid gland.

Less often, hypothyroidism may be caused by:

* **Problems present at birth.** Some babies are born with a thyroid gland that doesn't work correctly. Others are born with no thyroid gland. In most cases, the reason the thyroid gland didn't develop properly is not clear. But some children have an inherited form of a thyroid disorder. Often, infants born with hypothyroidism don't have noticeable symptoms at first. That's one reason why most states require newborn thyroid screening.
* **Pituitary disorder.** A relatively rare cause of hypothyroidism is the failure of the pituitary gland to make enough thyroid-stimulating hormone (TSH). This is usually because of a noncancerous tumor of the pituitary gland.
* **Pregnancy.** Some people develop hypothyroidism during or after pregnancy. If hypothyroidism happens during pregnancy and isn't treated, it raises the risk of pregnancy loss, premature delivery and preeclampsia. Preeclampsia causes a significant rise in blood pressure during the last three months of pregnancy. Hypothyroidism also can seriously affect the developing fetus.
* **Not enough iodine.** The thyroid gland needs the mineral iodine to make thyroid hormones. Iodine is found mainly in seafood, seaweed, plants grown in iodine-rich soil and iodized salt. Too little iodine can lead to hypothyroidism. Too much iodine can make hypothyroidism worse in people who already have the condition. In some parts of the world, it's common for people not to get enough iodine in their diets. The addition of iodine to table salt has almost eliminated this problem in the United States.

**What causes hypothyroidism?**

Hypothyroidism has several causes, including

* Hashimoto’s disease
* thyroiditis, or inflammation of the thyroid
* congenital hypothyroidism, or hypothyroidism that is present at birth
* surgical removal of part or all of the thyroid
* radiation treatment of the thyroid
* some medicines

Less often, hypothyroidism is caused by too much or too little iodine in the diet or by disorders of the pituitary gland or hypothalamus. Iodine deficiency, however, is extremely rare in the United States.

**Hashimoto’s disease**

Hashimoto’s disease, an autoimmune disorder, is the most common cause of hypothyroidism. With this disease, your immune system attacks the thyroid. The thyroid becomes inflamed and can’t make enough thyroid hormones.

**Thyroiditis**

Thyroiditis, an inflammation of your thyroid, causes stored thyroid hormone to leak out of your thyroid gland. At first, the leakage increases your blood’s hormone levels, leading to thyrotoxicosis, a condition in which thyroid hormone levels are too high. The thyrotoxicosis may last for many months. After that, your thyroid may become underactive and, over time, the condition may become permanent, requiring thyroid hormone replacement.

Three types of thyroiditis can cause thyrotoxicosis followed by hypothyroidism.2

* Subacute thyroiditis involves a painfully inflamed and enlarged thyroid.
* Postpartum thyroiditis develops after a woman gives birth.
* Silent thyroiditis is painless, even though your thyroid may be enlarged. Experts think it is probably an autoimmune condition.

**Congenital hypothyroidism**

Some babies are born with a thyroid that is not fully developed or does not work properly. If untreated, congenital hypothyroidism can lead to intellectual disability and growth failure—when a baby doesn’t grow as expected. Early treatment can prevent these problems. That’s why most newborns in the United States are tested for hypothyroidism.

**RISK FACTORS**

Although anyone can develop hypothyroidism, you're at an increased risk if you:

* Are a woman.
* Have a family history of thyroid disease.
* Have an autoimmune disease, such as type 1 diabetes or celiac disease.
* Have received treatment for hyperthyroidism.
* Received radiation to your neck or upper chest.
* Have had thyroid surgery.

**SIGNS / SYMPTOMS**

The symptoms of hypothyroidism depend on the severity of the condition. Problems tend to develop slowly, often over several years.

At first, you may barely notice the symptoms of hypothyroidism, such as fatigue and weight gain. Or you may think they are just part of getting older. But as your metabolism continues to slow, you may develop more-obvious problems.

Hypothyroidism symptoms may include:

* Tiredness.
* More sensitivity to cold.
* Constipation.
* Dry skin.
* Weight gain.
* Puffy face.
* Hoarse voice.
* Coarse hair and skin.
* Muscle weakness.
* Muscle aches, tenderness and stiffness.
* Menstrual cycles that are heavier than usual or irregular.
* Thinning hair.
* Slowed heart rate, also called bradycardia.
* Depression.
* Memory problems.

### **Hypothyroidism in infants**

Anyone can get hypothyroidism, including infants. Most babies born without a thyroid gland or with a gland that doesn't work correctly don't have symptoms right away. But if hypothyroidism isn't diagnosed and treated, symptoms start to appear. They may include:

* Feeding problems.
* Poor growth.
* Poor weight gain.
* Yellowing of the skin and the whites of the eyes, a condition called jaundice.
* Constipation.
* Poor muscle tone.
* Dry skin.
* Hoarse crying.
* Enlarged tongue.
* A soft swelling or bulge near the belly button, a condition called umbilical hernia.

When hypothyroidism in infants isn't treated, even mild cases can lead to severe physical and mental development problems.

### **Hypothyroidism in children and teens**

In general, children and teens with hypothyroidism have symptoms similar to those in adults. But they also may have:

* Poor growth that leads to short stature.
* Delayed development of permanent teeth.
* Delayed puberty.
* Poor mental development.

**Symptoms of hypothyroidism**

Hypothyroidism has many symptoms that can vary from person to person. Some common symptoms of hypothyroidism include

* fatigue
* weight gain
* trouble tolerating cold
* joint and muscle pain
* dry skin or dry, thinning hair
* heavy or irregular menstrual periods or fertility problems
* slowed heart rate
* depression

Dry, thinning hair is one of many symptoms that might indicate hypothyroidism.

Because hypothyroidism develops slowly, you may not notice symptoms of the disease for months or even years.

Many of these symptoms, especially fatigue and weight gain, are common and do not necessarily mean you have a thyroid problem.

### **DIAGNOSIS METHODS**

### The symptoms of hypothyroidism can be different from person to person. And they often look like symptoms of other health problems. Because of that, a diagnosis of hypothyroidism doesn't rely on symptoms alone. It's usually based on the results of blood tests.

### The first blood test typically done to diagnose hypothyroidism measures the level of thyroid-stimulating hormone (TSH) in the blood. If it's high, the test is done again, along with a blood test for the thyroid hormone T-4. If the results show that TSH is high and T-4 is low, then the diagnosis is hypothyroidism. In some cases, the thyroid hormone T-3 may be measured as well.

### If the second test shows high TSH but T-4 and T-3 are in the standard range, then the diagnosis is a condition called subclinical hypothyroidism. It usually doesn't cause any noticeable symptoms.

### TSH tests also play an important role in managing hypothyroidism over time. They help your health care provider find and maintain the right dosage of medication for you.

### The results of these blood tests can be affected by some medicines or supplements. This includes biotin, a vitamin taken as a stand-alone supplement or as part of a multivitamin. Before you have blood tests done, tell your healthcare provider about any medicines or supplements you take.

**How do doctors diagnose hypothyroidism?**

A blood test might confirm a diagnosis of hypothyroidism.

Your doctor will take your medical history and perform a physical exam. A hypothyroidism diagnosis can’t be based on symptoms alone because many of its symptoms are the same as those of other diseases.1 That’s why your doctor may use several thyroid blood tests and imaging tests to confirm the diagnosis and find its cause.

Because hypothyroidism can cause fertility problems, women who have trouble getting pregnant often get tested for thyroid problems.

### **TREATMENT OPTIONS**

### Treatment for hypothyroidism usually includes taking the thyroid hormone medicine levothyroxine (Levo-T, Synthroid, others) every day. This medicine is taken by mouth. It returns hormone levels to a healthy range, eliminating symptoms of hypothyroidism.

### You'll likely start to feel better one or two weeks after you begin treatment. Treatment with levothyroxine likely will be lifelong. Because the dosage you need may change, your health care provider may check your TSH level every year.

### **Finding the right dosage**

### To find the right dosage of levothyroxine for you, your health care provider checks your level of TSH about 6 to 8 weeks after you start taking the medicine. You may need another blood test to check TSH again six months later. Too much levothyroxine can cause side effects, such as:

### Tiredness.

### Increased appetite.

### Sleep problems.

### Shakiness.

### Pounding of the heart, sometimes called heart palpitations.

### Levothyroxine typically causes no side effects when used in the correct dose. If you change brands of the medicine, tell your health care provider, as the dosage may need to change.

### If you have coronary artery disease or severe hypothyroidism, your health care provider may start treatment with a smaller amount of medicine and then slowly increase the dosage. This allows your heart to adjust to the rise in your body's metabolism.

### *Taking levothyroxine correctly*

### Levothyroxine is best taken on an empty stomach at the same time every day. Ideally, you take the hormone in the morning, and then wait 30 to 60 minutes before you eat or take other medicine. If you take the medicine at bedtime, wait to take it until at least four hours after your last meal or snack.

### Don't skip doses or stop taking the medicine because you feel better. If you do, it's likely that the symptoms of hypothyroidism will slowly return. If you miss a dose of levothyroxine, take two pills the next day.

### Some medicines, supplements and even some foods may affect your body's ability to absorb levothyroxine. Talk to your health care provider if you eat large amounts of soy products, or if you typically eat a high-fiber diet. Also, tell your provider if you take other medicines, especially:

### Iron supplements or multivitamins that contain iron.

### Aluminum hydroxide, which is found in some antacids.

### Calcium supplements.

### **Subclinical hypothyroidism**

### If you are diagnosed with subclinical hypothyroidism, talk about treatment with your healthcare provider. For a mild rise in TSH, thyroid hormone medicine may not be useful. If your TSH level is higher, but still in the subclinical range, thyroid hormones may improve some symptoms.

### **Alternative medicine**

### Most health care providers recommend taking the medicine levothyroxine to treat hypothyroidism. But an extract containing thyroid hormone derived from the thyroid glands of pigs is available. It is sometimes called desiccated thyroid extract. However, this treatment is not recommended because the amount of T-4 and T-3 in it may not be consistent from batch to batch. It is not safe for pregnant people to take desiccated thyroid extract because it can harm a fetus's development.

### **POSSIBLE COMPLICATION**

### Hypothyroidism that isn't treated can lead to other health problems, including:

### Goiter. Hypothyroidism may cause the thyroid gland to become larger. This condition is called a goiter. A large goiter may cause problems with swallowing or breathing.

### Heart problems. Hypothyroidism can lead to a higher risk of heart disease and heart failure. That's mainly because people with an underactive thyroid tend to develop high levels of low-density lipoprotein (LDL) cholesterol — the "bad" cholesterol.

### Peripheral neuropathy. Hypothyroidism that goes without treatment for a long time can damage the peripheral nerves. These are the nerves that carry information from the brain and spinal cord to the rest of the body. Peripheral neuropathy may cause pain, numbness and tingling in the arms and legs.

### Infertility. Low levels of thyroid hormone can interfere with ovulation, which can limit fertility. Some of the causes of hypothyroidism, such as autoimmune disorders, also can harm fertility.

### Birth defects. Babies born to people with untreated thyroid disease may have a higher risk of birth defects compared with babies born to mothers who do not have thyroid disease. Infants with hypothyroidism present at birth that goes untreated are at risk of serious physical and mental development problems. But if the condition is diagnosed within the first few months of life, the chances of typical development are excellent.

### Myxedema coma. This rare, life-threatening condition can happen when hypothyroidism goes without treatment for a long time. A myxedema coma may be triggered by sedatives, infection or other stress on the body. Its symptoms include intense cold intolerance and drowsiness, followed by an extreme lack of energy and then unconsciousness. Myxedema coma requires emergency medical treatment.

## **Is hypothyroidism during pregnancy a problem?**

Left untreated, hypothyroidism during pregnancy can affect both mother and baby. However, thyroid medicines can help prevent problems and are safe to take during pregnancy. Many women who are taking thyroid hormone medicine need a higher dose during pregnancy, so contact your doctor right away if you find out you’re pregnant.

## **What are the complications of hypothyroidism?**

Hypothyroidism can contribute to high cholesterol. If you have high cholesterol, you should get tested for hypothyroidism. Rarely, severe untreated hypothyroidism may lead to myxedema coma, an extreme form of hypothyroidism in which the body’s functions slow to a life-threatening point. Myxedema coma requires immediate medical treatment.

## **PREVENTION TIPS**

### **Can hypothyroidism be prevented?**

### You can’t prevent hypothyroidism. If you develop symptoms like the ones mentioned above, let your healthcare provider know right away. Early diagnosis and treatment are the best ways to reduce your risk of complications and live a healthy life.

## **OUTLOOK / PROGNOSIS**

### **Can hypothyroidism be cured?**

### Currently, there’s no cure for hypothyroidism. But you can successfully manage the condition with hormone replacement therapy.

#### **How long hypothyroidism lasts**

### Hypothyroidism is a lifelong condition. If you receive a diagnosis, you’ll need to take medication every day to keep your thyroid hormone levels in check.

### **Outlook for hypothyroidism**

### People with hypothyroidism have a great outlook if they receive treatment. Left untreated, an underactive thyroid can cause life-threatening complications like myxedema.

### **WHEN TO SEE A DOCTOR / RED FLAG**

See your health care provider if you're feeling tired for no reason or if you have other symptoms of hypothyroidism.

If you're taking thyroid hormone medicine for hypothyroidism, follow your health care provider's advice on how often you need medical appointments. At first, you may need regular appointments to make sure you're receiving the right dose of medicine. Over time, you may need checkups so that your healthcare provider can monitor your condition and medicine.

### If you develop hypothyroidism symptoms like weight gain, dry skin or fatigue, let your healthcare provider know. They may want to run tests to rule out other conditions.

### If you already take medication for hypothyroidism, let your provider know if your symptoms come back or persist. They may need to adjust your dosage.

**DIFFERENTIAL DIAGNOSIS**

Owing to the subtle signs and symptoms of hypothyroidism, the list of differential diagnoses is extensive. Differential diagnosis is based on signs and symptoms; for instance, fatigue can point to iron deficiency anemia, sleep apnea, depression, and rheumatological diseases. The following disorders may have to be considered in the differential process.

* Euthyroid sick syndrome
* Goiter
* Myxedema coma
* Anemia
* Riedel thyroiditis
* Subacute thyroiditis
* Thyroid lymphoma
* Iodine deficiency
* Addison disease
* Chronic fatigue syndrome
* Depression
* Dysmenorrhea
* Erectile dysfunction
* Familial hypercholesterolemia
* Infertility

Euthyroid Sick Syndrome (ESS): A condition seen in patients with acute or chronic nonthyroidal illnesses where thyroid hormone levels (especially low T3 and sometimes low T4) are abnormal despite a normally functioning thyroid gland. It commonly occurs in critical illnesses such as sepsis, trauma, myocardial infarction, kidney or liver failure, and starvation. TSH is usually normal or low, and reverse T3 is elevated. Symptoms may mimic hypothyroidism but treatment targets the underlying illness rather than thyroid hormone replacement

* Goiter: Enlargement of the thyroid gland due to iodine deficiency, autoimmune disease, or nodular thyroid disease.
* Myxedema Coma: A severe, life-threatening form of hypothyroidism characterized by altered mental status, hypothermia, and multi-organ dysfunction.
* Anemia: A condition marked by reduced red blood cell count or hemoglobin, often associated with chronic disease or nutritional deficiencies.
* Riedel Thyroiditis: A rare fibrosing inflammatory disease causing a hard, fixed thyroid mass mimicking malignancy.
* Subacute Thyroiditis: A painful, self-limited thyroid inflammation often following viral infection, causing transient thyrotoxicosis.
* Thyroid Lymphoma: A rare malignancy of lymphoid tissue in the thyroid, usually arising in the setting of chronic lymphocytic thyroiditis.
* Iodine Deficiency: Lack of sufficient iodine leading to goiter and hypothyroidism.
* Addison Disease: Primary adrenal insufficiency causing cortisol deficiency, often with autoimmune etiology.
* Chronic Fatigue Syndrome: A complex disorder characterized by persistent fatigue not relieved by rest, sometimes associated with altered thyroid function tests.
* Depression: A mood disorder that can be associated with altered thyroid hormone metabolism and may overlap with euthyroid sick syndrome features.
* Dysmenorrhea: Painful menstruation, often unrelated to thyroid but common in endocrine disorders.
* Erectile Dysfunction: The inability to achieve or maintain an erection, which can be influenced by endocrine disorders including hypothyroidism.
* Familial Hypercholesterolemia: A genetic disorder causing high cholesterol and increased cardiovascular risk.
* Infertility: The inability to conceive, which may be related to thyroid dysfunction or other endocrine abnormalities.

**EPIDEMIOLOGY**

The National Health and Nutrition Examination Survey (NHANES III) study found the prevalence of overt hypothyroidism among individuals aged 12 years and older in the US to be 0.3% and subclinical hypothyroidism 4.3%. Female gender and increasing age are associated with a higher risk for thyroid-stimulating hormone (TSH) and an increased prevalence of antithyroid antibodies. Hypothyroidism is more prevalent in women with small stature at birth and low body mass index in childhood.

**How common is hypothyroidism?**

Nearly 5 out of 100 Americans ages 12 years and older have hypothyroidism, although most cases are mild or have few obvious symptoms.

**Who is more likely to develop hypothyroidism?**

Women are much more likely than men to develop hypothyroidism. The disease is also more common among people older than age 60.

You are more likely to have hypothyroidism if you

* had a thyroid problem before, such as a goiter
* had surgery or radioactive iodine to correct a thyroid problem
* received radiation treatment to the thyroid, neck, or chest
* have a family history of thyroid disease
* were pregnant in the past 6 months
* have Turner syndrome , a genetic disorder that affects women

Your thyroid is also more likely to be underactive if you have other health problems, including

* Celiac disease
* Sjögren’s syndrome , a disease that causes dry eyes and mouth
* pernicious anemia , a condition caused by a vitamin B12 deficiency
* type 1 or type 2 diabetes
* rheumatoid arthritis , an autoimmune disease that affects the joints
* lupus , a chronic autoimmune inflammatory condition

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**HASHIMOTO DISEASE**

ALTERNATIVE NAMES: Hashimoto disease is also known as “chronic lymphocytic thyroiditis”, “autoimmune thyroiditis”, “struma lymphomatosa”, and “Hashimoto’s thyroid”. It is also referred to as “chronic autoimmune thyroiditis” and “lymphocytic thyroiditis”. Additionally, it is sometimes called “Hashimoto's disease” or “chronic thyroiditis”.

**DEFINITION / DESCRIPTION**

**Hashimoto's disease is a type of thyroiditis**. Specifically, it is an autoimmune form of thyroiditis known as Hashimoto's thyroiditis, chronic autoimmune thyroiditis, or chronic lymphocytic thyroiditis. It occurs when the immune system attacks the thyroid gland, leading to inflammation and eventually hypothyroidism.4 Hashimoto's thyroiditis is the most common type of thyroiditis

Hashimoto's disease is an autoimmune disorder affecting the thyroid gland. The thyroid is a butterfly-shaped gland located at the base of the neck just below Adam's apple. The thyroid produces hormones that help regulate many functions in the body.

An autoimmune disorder is an illness caused by the immune system attacking healthy tissues. In Hashimoto's disease, immune-system cells lead to the death of the thyroid's hormone-producing cells. The disease usually results in a decline in hormone production (hypothyroidism).

Although anyone can develop Hashimoto's disease, it's most common among middle-aged women. The primary treatment is thyroid hormone replacement.

Hashimoto's disease is also known as Hashimoto's thyroiditis, chronic lymphocytic thyroiditis and chronic autoimmune thyroiditis.

**CAUSES**

Hashimoto's disease is an autoimmune disorder. The immune system creates antibodies that attack thyroid cells as if they were bacteria, viruses or some other foreign body. The immune system wrongly enlists disease-fighting agents that damage cells and lead to cell death.

What causes the immune system to attack thyroid cells is not clear. The onset of disease may be related to:

* Genetic factors
* Environmental triggers, such as infection, stress or radiation exposure
* Interactions between environmental and genetic factors

**RISK FACTOR**

The following factors are associated with an increased risk of Hashimoto's disease:

* **Sex.** Women are much more likely to get Hashimoto's disease.
* **Age.** Hashimoto's disease can occur at any age but more commonly occurs during middle age.
* **Other autoimmune diseases.** Having another autoimmune disease — such as rheumatoid arthritis, type 1 diabetes or lupus — increases your risk of developing Hashimoto's disease.
* **Genetics and family history.** You're at higher risk for Hashimoto's disease if others in your family have thyroid disorders or other autoimmune diseases.
* **Pregnancy.** Typical changes in immune function during pregnancy may be a factor in Hashimoto's disease that begins after pregnancy.
* **Excessive iodine intake.** Too much iodine in the diet may function as a trigger among people already at risk for Hashimoto's disease.
* **Radiation exposure.** People exposed to excessive levels of environmental radiation are more prone to Hashimoto's disease.

**SIGNS / SYMPTOMS**

Hashimoto's disease progresses slowly over the years. You may not notice signs or symptoms of the disease. Eventually, the decline in thyroid hormone production can result in any of the following:

* Fatigue and sluggishness
* Increased sensitivity to cold
* Increased sleepiness
* Dry skin
* Constipation
* Muscle weakness
* Muscle aches, tenderness and stiffness
* Joint pain and stiffness
* Irregular or excessive menstrual bleeding
* Depression
* Problems with memory or concentration
* Swelling of the thyroid (goiter)
* A puffy face
* Brittle nails
* Hair loss
* Enlargement of the tongue

**DIAGNOSIS METHODS**

A number of conditions may lead to the signs and symptoms of Hashimoto's disease. If you're experiencing any of these symptoms, your health care provider will conduct a thorough physical exam, review your medical history and ask questions about your symptoms.

### **Testing thyroid function**

To determine if hypothyroidism is the cause of your symptoms, your provider will order blood tests that may include the following:

* **TSH test.** Thyroid stimulating hormone (TSH) is produced by the pituitary gland. When the pituitary detects low thyroid hormones in the blood, it sends TSH to the thyroid to prompt an increase in thyroid hormone production. High TSH levels in the blood indicates hypothyroidism.
* **T-4 tests.** The main thyroid hormone is thyroxine (T-4). A low blood level of T-4 confirms the findings of a TSH test and indicates the problem is within the thyroid itself.

### **Antibody tests**

More than one disease process can lead to hypothyroidism. To determine if Hashimoto's disease is the cause of hypothyroidism, your health care provider will order an antibody test.

The intended purpose of an antibody is to flag disease-causing foreign agents that need to be destroyed by other actors in the immune system. In an autoimmune disorder, the immune system produces rogue antibodies that target healthy cells or proteins in the body.

Usually in Hashimoto's disease, the immune system produces an antibody to thyroid peroxidase (TPO), a protein that plays an important part in thyroid hormone production. Most people with Hashimoto's disease will have TPO antibodies in their blood. Lab tests for other antibodies associated with Hashimoto's disease may need to be done.

**TREATMENT OPTIONS**

Most people with Hashimoto's disease take medication to treat hypothyroidism. If you have mild hypothyroidism, you may have no treatment but get regular thyroid stimulating hormone (TSH) tests to monitor thyroid hormone levels.

### **T-4 hormone replacement therapy**

Hypothyroidism associated with Hashimoto's disease is treated with a synthetic hormone called levothyroxine (Levoxyl, Synthroid, others). The synthetic hormone works like the thyroxine (T-4) hormone naturally produced by the thyroid.

The treatment goal is to restore and maintain adequate T-4 hormone levels and improve symptoms of hypothyroidism. You will need this treatment for the rest of your life.

### **Monitoring the dosage**

Your healthcare provider will determine a dosage of levothyroxine that's appropriate for your age, weight, current thyroid production, other medical conditions and other factors. Your provider will retest your TSH levels about 6 to 10 weeks later and adjust the dosage as necessary.

Once the best dosage is determined, you will continue to take the medication once a day. You'll need follow-up tests once a year to monitor TSH levels or any time after your provider changes your dosage.

A levothyroxine pill is usually taken in the morning before you eat. Talk to your doctor if you have any questions about when or how to take the pill. Also, ask what to do if you accidentally skip a dose. If your health insurance requires you to switch to a generic drug or a different brand, talk to your doctor.

### **Precautions**

Because levothyroxine acts like natural T-4 in the body, there are generally no side effects as long as the treatment is resulting in "natural" levels of T-4 for your body.

Too much thyroid hormone can worsen bone loss that causes weak, brittle bones (osteoporosis) or cause irregular heartbeats (arrhythmias).

### **Effects of other substances**

Certain medications, supplements and foods may affect your ability to absorb levothyroxine. It may be necessary to take levothyroxine at least four hours before these substances. Talk to your doctor about any of the following:

* Soy products
* High-fiber foods
* Iron supplements, including multivitamins that contain iron
* Cholestyramine (Prevalite), a medication used to lower blood cholesterol levels
* Aluminum hydroxide, which is found in some antacids
* Sucralfate, an ulcer medication
* Calcium supplements

### **T-3 hormone replacement therapy**

Naturally produced T-4 is converted into another thyroid hormone called triiodothyronine (T-3). The T-4 replacement hormone is also converted into T-3, and for most people the T-4 replacement therapy results in an adequate supply of (T-3) for the body.

For people who need better symptom control, a doctor also may prescribe a synthetic T-3 hormone (Cytomel) or a synthetic T-4 and T-3 combination. Side effects of T-3 hormone replacement include rapid heartbeat, insomnia and anxiety. These treatments may be tested with a trial period of 3 to 6 months.

**ALTERNATIVE MEDICINE**

Products with triiodothyronine (T-3) and thyroxine (T-4) hormones derived from pigs or other animals are available as prescriptions or as dietary supplements, such as Armour Thyroid, in the United States. Concerns about these products include the following:

* The balance of T-4 and T-3 in animals isn't the same as in humans.
* The exact amount of T-4 and T-3 in each batch of a natural extract product can vary, leading to unpredictable levels of these hormones in your blood.

**POSSIBLE COMPLICATION**

Thyroid hormones are essential for the healthy function of many body systems. Therefore, when Hashimoto's disease and hypothyroidism are left untreated, many complications can occur. These include:

* **Goiter.** A goiter is enlargement of the thyroid. As thyroid hormone production declines due to Hashimoto's disease, the thyroid receives signals from the pituitary gland to make more. This cycle may result in a goiter. It's generally not uncomfortable, but a large goiter can affect your appearance and may interfere with swallowing or breathing.
* **Heart problems.** Hypothyroidism can result in poor heart function, an enlarged heart and irregular heartbeats. It can also result in high levels of low-density lipoprotein (LDL) cholesterol — the "bad" cholesterol — that is a risk factor for cardiovascular disease and heart failure.
* **Mental health issues.** Depression or other mental health disorders may occur early in Hashimoto's disease and may become more severe over time.
* **Sexual and reproductive dysfunction.** In women, hypothyroidism can result in a reduced sexual desire (libido), an inability to ovulate, and irregular and excessive menstrual bleeding. Men with hypothyroidism may have a reduced libido, erectile dysfunction and a lowered sperm count.
* **Poor pregnancy outcomes.** Hypothyroidism during pregnancy may increase the risk of a miscarriage or preterm birth. Babies born to women with untreated hypothyroidism are at risk for decreased intellectual abilities, autism, speech delays and other developmental disorders.
* **Myxedema (miks-uh-DEE-muh).** This rare, life-threatening condition can develop due to long-term, severe, untreated hypothyroidism. Its signs and symptoms include drowsiness followed by profound lethargy and unconsciousness. A myxedema coma may be triggered by exposure to cold, sedatives, infection or other stress on your body. Myxedema requires immediate emergency medical treatment.

## **PREVENTION TIPS**

### **Can I prevent Hashimoto’s disease?**

Unfortunately, there’s nothing you can do to prevent Hashimoto’s disease. The risk factors for it — like your genetics and age — aren’t modifiable.

## **OUTLOOK / PROGNOSIS**

### **What is the prognosis for Hashimoto’s disease?**

With lifelong monitoring and treatment, the prognosis (outlook) for people with Hashimoto’s disease is excellent.

If you have hypothyroidism from Hashimoto’s disease that’s untreated, it can lead to certain health problems, including:

* High cholesterol.
* Heart disease and heart failure.
* High blood pressure.
* Depression.
* Myxedema coma. This is a rare complication of severe hypothyroidism. Your body’s functions slow down so much that it can be deadly.

Without treatment, hypothyroidism can also cause problems during pregnancy.

#### **Hashimoto’s disease during pregnancy**

Untreated hypothyroidism during pregnancy can increase the risk of:

* Miscarriage.
* Premature birth.
* Stillbirth.

Or it may cause a dangerous rise in your blood pressure in late pregnancy called preeclampsia. Untreated hypothyroidism can also affect the fetus’s growth and brain development. Your providers will work with you to make sure your hypothyroidism is well-managed during pregnancy.

Hypothyroidism during pregnancy isn’t common. But it can be easy to miss its symptoms that are also common during pregnancy, like fatigue and weight gain. Let your providers know right away if you notice any hypothyroidism symptoms or feel like you’re developing a goiter.

**WHEN TO SEE A DOCTOR / RED FLAG**

If you have Hashimoto’s disease, you’ll need to see your healthcare provider regularly. They’ll perform routine thyroid hormone blood tests to make sure your levels are in range and that the dose of medication you’re taking is right for you.

Otherwise, see your healthcare provider if you develop new or worsening symptoms or notice a change in your thyroid.

If you have symptoms of myxedema coma, call 911 or get to the emergency room as soon as possible. This complication of severe hypothyroidism is life-threatening.

Symptoms include:

* A body temperature below 95 degrees Fahrenheit or 35 degrees Celsius (hypothermia).
* Swelling (edema) in your body, especially your face, tongue and lower legs.
* A slow heart rate and faint pulse.
* Slowed breathing (bradypnea) and difficulty breathing (dyspnea).
* Confusion or loss of consciousness.

## **EPIDEMIOLOGY**

### *Occurrence in the United States*

Hashimoto thyroiditis is the most common cause of hypothyroidism in the United States after age 6 years, with the incidence estimated to be 1.3% in a series of 5000 children aged 11-18 years. In adults, the incidence is estimated to be 3.5 per 1000 per year in women and 0.8 per 1000 per year in men. The incidence may be as high as 6% in the Appalachian region.

In the Colorado Thyroid Disease Prevalence Study, involving 25,862 adults, the prevalence of elevated TSH in symptomatic and asymptomatic adults was 9.5%, with a greater percentage of those involved being women. The prevalence of hypothyroidism and of thyroid disease in general increases with age.

### *International occurrence*

Worldwide, the most common cause of hypothyroidism is iodine deficiency. However, Hashimoto thyroiditis remains the most common cause of spontaneous hypothyroidism in areas of adequate iodine intake. The annual incidence of Hashimoto thyroiditis worldwide is estimated to be 0.3-1.5 cases per 1000 persons.

Climate conditions have been thought to play a role in pathogenesis of Hashimoto thyroiditis, as Siberian women have higher TPO titers than does the general population.

### *Sex- and age-related demographics*

The incidence of Hashimoto thyroiditis is estimated to be 10-15 times higher in females.

## **DIFFERENTIAL DIAGNOSIS**

* Diffuse Toxic Goiter (Graves Disease)
* Euthyroid Sick Syndrome
* Goiter
* Hypopituitarism (Panhypopituitarism)
* Lithium-Induced Goiter
* Nontoxic Goiter
* Thyroid Lymphoma
* Toxic Nodular Goiter
* Type I Polyglandular Autoimmune Syndrome
* Type II Polyglandular Autoimmune Syndrome

## ***Diagnostic Considerations***

The following autoimmune phenomena may occur or be found in association with Hashimoto thyroiditis:

* Addison disease
* Alopecia areata, totalis, and universalis
* Autoimmune gastritis (pernicious anemia)
* Chronic active hepatitis
* Idiopathic hypoparathyroidism
* Polymyalgia rheumatica and giant cell arteritis
* Primary biliary cirrhosis
* Primary ovarian or testicular failure
* Rheumatoid arthritis
* Sjögren syndrome
* Systemic lupus erythematosus (SLE)
* Systemic sclerosis (scleroderma)
* Type 1 diabetes mellitus
* Vitiligo

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**HYPOTHYROID MYOPATHY**

*ALTERNATIVE NAMES:* Hypothyroid myopathy is also known as “Hoffman’s syndrome”, “Hoffmann’s syndrome”, “Hoffmann’s disease”, “Acro paresthesia”, or “palmar reflex myoclonus”. Additionally, it is known as “hypothyroid myopathy with muscle pseudohypertrophy”, particularly in cases where there is an enlargement of muscles alongside weakness.

**DEFINITION / DESCRIPTION**

Hypothyroid myopathy, observed in 30% to 80% of individuals with hypothyroidism, manifests in both congenital and acquired cases, presenting with generalized myalgias, muscle weakness, and muscle pain or stiffness. Thyroid hormone is pivotal for metabolism, growth, and organ function, thus influencing the musculoskeletal system. Severe or untreated hypothyroidism can lead to substantial muscle disease, resulting in severe functional limitations.

The symptoms of hypothyroid myopathy can be gradual in onset and nonspecific, necessitating a high index of suspicion from clinicians to differentiate this condition from fatigue and other muscle disorders with similar presentations. All patients diagnosed with hypothyroidism should be questioned about musculoskeletal symptoms. Proximal muscles, such as those in the thighs, hips, shoulders, and neck, are particularly affected, impacting activities such as stair climbing, rising from a seated position, and lifting objects. Rarely, severe hypothyroid myopathy can result in muscle necrosis, acute compartment syndrome, or respiratory failure

**CAUSES**

Hypothyroid myopathy is a condition that occurs when the thyroid gland does not produce enough thyroid hormones. These hormones play a crucial role in the body's metabolism, including the metabolism of muscles. Consequently, low levels of thyroid hormones can result in muscle weakness, fatigue, and other symptoms. Some common causes of hypothyroidism are listed below.

* Autoimmune disorders: Hashimoto thyroiditis is an autoimmune disorder in which the body's immune system attacks the thyroid gland, leading to hypothyroidism. This disorder stands as the most common cause of hypothyroidism in the developed world.
* Iodine deficiency: Iodine is an essential nutrient that is required for the production of thyroid hormones. Insufficient iodine in the diet can lead to hypothyroidism and hypothyroid myopathy, making it the most prevalent cause worldwide.
* Thyroid surgery or radiation therapy: Surgery or radiation therapy to the thyroid gland can damage the gland or reduce its function, resulting in hypothyroidism and hypothyroid myopathy.
* Medications: Certain medications, such as lithium, can interfere with the production of thyroid hormones.
* Congenital hypothyroidism: An underactive thyroid gland at birth can cause significant developmental delays and physical deficiencies.
* Aging: The natural aging process may cause a decline in thyroid function.

Overall, hypothyroid myopathy is caused by a lack of thyroid hormones in the body, which can be due to a variety of factors such as autoimmune disorders, iodine deficiency, thyroid surgery, medications, congenital hypothyroidism, and aging.

**What is Hoffman’s syndrome?**

Hoffmann’s syndrome is a form of hypothyroid myopathy and a relatively rare neurological condition affecting the body’s muscles and nerves, particularly in the hands and arms. It’s named after the French neurologist Johann Hoffman, who first identified and described the syndrome. Hoffman’s syndrome is also known by several other names, including Hoffman’s disease, acroparesthesia, and palmar reflex myoclonus. It’s also known as Hypothyroid myopathy.

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**CAUSES OF HOFFMAN’S SYNDROME**

Hoffman’s syndrome is caused by a dysfunction in the mitochondria, which are the powerhouses of the cells that produce energy. This dysfunction leads to a lack of energy production, resulting in muscle weakness and fatigue.

One possible cause of Hoffman’s syndrome is genetics. Studies have shown that there may be a genetic predisposition to this condition, meaning it can be passed down from parents to their children. This finding suggests that specific genetic mutations or variations may increase the risk of developing Hoffman’s syndrome. However, in some cases, it can occur spontaneously without any familial history. Hoffman’s syndrome is also believed to be related to autoimmune hypothyroidism, which also has a genetic component.

Another potential cause of Hoffman’s syndrome is neurological damage or injury. Trauma to the spinal cord or brain can disrupt the nervous system’s normal functioning, leading to abnormal muscle spasms and twitches. This damage could result from accidents, injuries, or medical conditions such as tumors or infections.

Additionally, some medications and drugs have been linked to the development of muscle spasms similar to those seen in Hoffman’s syndrome. Certain medications used to treat psychiatric disorders, such as antipsychotics or antidepressants, have been associated with the onset of this condition. Drugs such as cocaine or amphetamines can also affect the nervous system and potentially trigger muscle spasms.

Several medical conditions have also been linked to the development of Hoffman’s syndrome. Neurological disorders such as multiple sclerosis or brain tumors can disrupt the normal communication between the nerves and muscles, leading to abnormal muscle movements. Conditions such as hypocalcemia, which affects the hormonal or electrolyte balance in the body, can also contribute to the development of muscle spasms.

Deficiency of thyroid hormone leads to a state called hypothyroidism. Common causes of hypothyroidism include the following:

* Treatment with radioactive iodine (I131) for Graves’ disease
* Hashimoto disease - An autoimmune process in which lymphocytic infiltration and fibrous tissue accumulation cause replacement of normal thyroid tissue
* Drug-induced hypothyroidism - Known to occur with amiodarone and iodine (i.e., Wolff-Chaikoff effect)
* Hereditary disorders of the iodothyronine synthesis pathway (thyroxine [T4] and triiodothyronine [T3])
* Pituitary tumors and related surgical resections

Hypothyroidism can cause several symptoms, ranging from mild (e.g., fatigue, weight gain, cold intolerance, mental slowing, muscle cramping) to severe (e.g., heart enlargement, myxedema coma [rare]).

Without regard to the cause of hypothyroidism, neuromuscular and musculoskeletal manifestations can be observed in many patients with the condition.These manifestations can occur at any time in the hypothyroidism disease process. Usually mild, they include weakness, pain, aching, and stiffness.

**RISK FACTORS**

Hypothyroid myopathy is associated with several risk factors, including **untreated hypothyroidism**, which is a significant contributor to the condition. Other risk factors include autoimmune disorders, iodine deficiency, thyroid surgery, medications, congenital hypothyroidism, and aging. Additionally, hypothyroidism is more common in women compared to men and typically manifests between the ages of 40 and 70. The prevalence of hypothyroidism increases with age, making older adults more susceptible to hypothyroid myopathy. Furthermore, factors such as severe exercise, trauma, alcohol intake, and electrolyte imbalance can precipitate complications like rhabdomyolysis in individuals with hypothyroid myopathy.

**SIGNS / SYMPTOMS OF HOFFMAN’S SYNDROME**

Hypothyroid myopathy typically manifests as polymyositis-like myopathy with proximal muscle weakness and an increased creatine kinase level.[[4](about:blank),[5](about:blank)]However, it sometimes manifests as muscle enlargement (pseudohypertrophy) and stiffness; in adults, this condition is called Hoffman syndrome.[[6](about:blank),[7](about:blank),[8](about:blank)]In children with hypothyroid disease (cretinism), a pattern of proximal weakness and diffuse muscle enlargement is known as Kocher-Debré-Sémélaigne syndrome.

The symptoms of Hoffman’s syndrome typically appear in early adulthood, although they can sometimes show up later in life. In Hoffman’s syndrome, muscle weakness is predominantly seen in the proximal muscles – the muscles nearest to the trunk of the body. This weakness can affect the ability to perform basic daily activities such as climbing stairs, getting up from a seated position, or even lifting objects.

One of the primary symptoms of Hoffman’s syndrome is muscle weakness. This weakness can affect various body parts, including the arms, legs, and sometimes even the facial muscles. Individuals with Hoffman’s syndrome often struggle with tasks that require strength, such as lifting heavy objects or participating in sports activities. The weakness can gradually progress over time, affecting daily activities and mobility.

In addition to muscle weakness, individuals with Hoffman’s syndrome may also experience muscle stiffness or spasticity. This stiffness can occur in different muscle groups, leading to movement, coordination, and balance difficulties. They may have a decreased range of motion, making it challenging to perform specific tasks or even simple activities like walking or getting out of a chair.

Another common symptom of Hoffman’s syndrome is muscle twitching, also known as fasciculations. These involuntary muscle twitches can occur randomly or be triggered by specific actions or movements. Although muscle twitching is not usually painful, it can be uncomfortable and may interfere with everyday activities.

Individuals with this condition may also experience sensory changes. They might have decreased sensation or numbness in certain areas of their body. It can affect different senses, such as touch, temperature, or even proprioception (the sense of body position). These sensory changes can further impact their daily functioning and coordination.

In some cases, individuals with Hoffman’s syndrome may have associated symptoms like fatigue, tingling, numbness, pain in hands and feet, muscle cramps, or tremors. Fatigue can be debilitating, causing a significant decrease in energy levels and overall physical endurance. Muscle cramps and pain can also interfere with daily activities and cause discomfort.

It’s important to note that the severity and specific symptoms of Hoffman’s syndrome can vary from person to person. Some individuals may have milder symptoms that only slightly impact their daily lives, while others may experience more significant challenges.

**THE LINK BETWEEN HOFFMAN’S SYNDROME AND HYPOTHYROIDISM**

Thyroid hormones are responsible for the normal growth and development of muscle tissue, as well as maintaining their strength and coordination. When thyroid hormone levels are low, it can lead to hypothyroid myopathy – muscle weakness and fatigue – and, in more severe cases, Hoffman’s syndrome.

How hypothyroidism leads to Hoffman’s syndrome is not fully understood. However, research has shown, specifically, that treatment of hypothyroidism can improve or even resolve Hoffman’s syndrome. One study reported that Hoffmann’s syndrome is one of the rare forms of myopathy that completely reverses with timely treatment and, therefore, has a good outcome. Another study reported on a patient with Hoffman’s syndrome whose muscle weakness fully resolved after thyroid hormone replacement treatment.

**DIAGNOSIS METHODS**

**How is Hoffman’s syndrome diagnosed?**

Several approaches and clinical guidelines are used to diagnose Hoffman’s syndrome.

Medical history and physical exam: A healthcare provider will begin by taking a detailed medical history, including any symptoms you are experiencing, their severity, and when they first appeared. They will also perform a physical examination to assess your reflexes, muscle strength, and coordination.

Thyroid panel: In patients who have not yet been diagnosed with hypothyroidism, a complete thyroid blood test panel will usually be done to assess thyroid function. For patients already being treated, a thyroid panel can help determine if the condition is being optimally treated.

Other blood tests: Blood tests may be ordered to rule out other conditions that could be causing similar symptoms. These tests may include a complete blood count (CBC), metabolic panel, and tests to check for specific markers of inflammation or autoimmune disorders.

Hoffman’s reflex test: This test involves applying brief, firm downward pressure to the middle finger or thumb, causing the hand and fingers to twitch or jerk involuntarily. This reflex is known as the Hoffman reflex and is a characteristic feature of Hoffman’s syndrome. A positive Hoffman’s reflex indicates the presence of the condition.

Babinski test: This test is sometimes used in addition to the Hoffman’s reflex test. The Babinski test involves gently stroking the sole of the foot, from the heel to the big toe. In individuals with Hoffman’s syndrome, there may be an abnormal response known as an upward plantar reflex, where the big toe extends upward rather than curling downward. This abnormal response is a sign of neurological dysfunction and can support the diagnosis of Hoffman’s syndrome.

Nerve conduction studies (NCS): NCS involves using small electrodes placed on the skin to measure the speed at which electrical impulses travel along the nerves. This test helps determine if there is nerve damage or dysfunction, which could indicate Hoffman’s syndrome.

Electromyography (EMG): EMG measures the electrical activity of muscles at rest and during contraction. It involves the insertion of a fine needle electrode into the muscle tissue to assess its function. EMG can help identify muscle abnormalities and determine if the symptoms are related to muscle dysfunction.

Genetic testing: Hoffman’s syndrome has been associated with specific genetic mutations. In some cases, genetic testing may be performed to identify these mutations and confirm the diagnosis.

It is important to note that diagnosing Hoffman’s syndrome can be challenging due to its rarity and similarity to other neurological conditions. Therefore, consulting with a healthcare professional specializing in neurology or movement disorders is crucial. They will have the expertise to differentiate Hoffman’s syndrome from other conditions and implement the appropriate tests and guidelines for an accurate diagnosis.

**TREATMENT OPTIONS FOR HOFFMAN’S SYNDROME**

The good news is that Hoffman’s syndrome is considered reversible! Here are the various treatment options available for individuals with Hoffman’s syndrome and hypothyroidism.

**Thyroid hormone replacement medication**

In Hoffman’s syndrome, the body’s tissues do not respond to thyroid hormone effectively. Therefore, treatment aims to provide the body with an increased supply of thyroid hormones to compensate for the resistance. Thyroid hormone replacement therapy replaces the inadequate production by the thyroid gland. Thyroid medication works by supplementing the body with an artificial source of thyroid hormone, bypassing the body’s resistance and helping to alleviate symptoms, including muscle weakness.

When starting thyroid hormone replacement medication for Hoffman’s syndrome, working closely with a healthcare professional specializing in hypothyroidism is essential. They will be able to determine the appropriate medication dosage based on your individual needs and monitor treatment progress over time.

Regular monitoring of thyroid hormone levels through blood tests is essential to ensure that the medication dosage is adequate. These tests measure levels of thyroid-stimulating hormone (TSH), free thyroxine (T4), and free triiodothyronine (T3) in the blood, which can provide valuable insight into your thyroid function.

It is important to note that thyroid hormone replacement medication is not a cure for Hoffman’s syndrome. Thyroid treatment helps manage the symptoms associated with the condition and improve overall well-being. The thyroid medication dosage may need to be adjusted periodically based on symptoms and blood test results.

**Physical therapy and exercise**

Physical therapy is also an important part of the treatment plan for muscle weakness due to Hoffman’s syndrome and hypothyroid myopathy. A physical therapist can develop a customized exercise program to help improve mobility, strength, and coordination in the affected hand and fingers. These exercises may include stretching, strengthening, and range of motion exercises, as well as techniques to improve fine motor skills. Physical therapy can also help individuals learn adaptive techniques and strategies to manage their symptoms in daily activities.

**Botulinum toxin injections**

One of the most common treatment approaches for Hoffman’s syndrome is the use of botulinum toxin injections. Botulinum toxin, commonly known as Botox, is a medication that can temporarily paralyze the muscles and reduce muscle contractions. Injecting Botox into the affected hand and fingers can help alleviate involuntary movements and provide relief for individuals with Hoffman’s syndrome. The effects of Botox injections typically last for a few months, so that regular follow-up treatments may be necessary.

**Oral medications**

In some cases, oral medications may be prescribed to help manage the symptoms of Hoffman’s syndrome. Prescription muscle relaxants or anti-seizure medications can be used to reduce muscle contractions and relieve pain or discomfort. However, it is important to note that medication effectiveness may vary from person to person, and there may be potential side effects to consider.

**Surgery**

In severe cases of Hoffman’s syndrome where conservative treatments have not been effective, surgery may be considered as a treatment option. Surgical procedures, such as selective denervation, aim to selectively weaken or remove some of the overactive muscles to reduce involuntary movements. However, surgery is generally considered a last resort and is only recommended when other treatment options have been exhausted.

**Healthy diet**

It is also essential for individuals with Hoffman’s syndrome and hypothyroidism to adopt a healthy, well-balanced diet rich in essential nutrients and vitamins. Eating a well-balanced diet is crucial for thyroid function. Include foods high in iodine, such as seaweed, seafood, and dairy products. Selenium-rich foods like Brazil nuts, mushrooms, and sunflower seeds can also support healthy thyroid function. Avoid or limit processed foods, refined sugars, and excessive caffeine, as they can negatively affect thyroid function and increase inflammation.

**Physical activity**

Regular physical activity can help relieve thyroid symptoms, improve well-being, and increase flexibility, balance, and muscle stiffness. Both yoga and Tai Chi are gentle forms of exercise that incorporate slow movements, stretching, and breathing techniques. These practices are especially recommended for patients with Hoffman’s syndrome. Additionally, they promote relaxation, reduce stress levels, and enhance overall physical and mental well-being.

**Sleep and stress management**

Lack of sleep and chronic stress can contribute to thyroid dysfunction and symptoms in Hoffman’s syndrome. Aim for 7 to 9 hours of quality sleep per night. And incorporate stress-management techniques into your daily routine, such as meditation, deep breathing exercises, or yoga. Engaging in activities you enjoy and spending time with loved ones can also help reduce stress levels.

**Supplements**

Certain dietary supplements, such as omega-3 fatty acids, vitamin D, and selenium, may benefit people with Hoffman’s syndrome and hypothyroid myopathy. These supplements can help support muscle function, reduce inflammation, and improve overall health. However, consulting with a healthcare professional before starting any supplementation regimen is important.

**Acupuncture**

Acupuncture sessions can help reduce Hoffman’s syndrome and hypothyroid myopathy symptoms. Acupuncture, an ancient Chinese practice, involves the insertion of thin needles into specific points on the body to stimulate energy flow and promote healing. It has shown promising results in managing muscle pain and fatigue and improving overall well-being. Some studies also suggest that acupuncture may improve thyroid function and hormone levels in individuals with hypothyroidism.

**Massage therapy**

Massage therapy can be beneficial in managing muscle stiffness, pain, and tension associated with Hoffman’s syndrome and hypothyroidism. Massage techniques, such as deep tissue and Swedish massage, help increase blood circulation, reduce muscle tightness, and promote relaxation. Regular sessions can provide relief and improve overall muscle function.

**PREVENTION TIPS**

Hypothyroid myopathy is a muscle disease caused by a deficiency in thyroid hormone production, and while there are no specific prevention tips for the condition itself, managing hypothyroidism effectively can help prevent or reduce its symptoms. Early diagnosis and treatment of hypothyroidism are crucial in preventing the development of myopathy. Regular monitoring of thyroid function and adherence to prescribed thyroid hormone replacement therapy, such as levothyroxine, can help maintain normal thyroid hormone levels and minimize the risk of muscle-related complications.

In addition, individuals with hypothyroidism should be cautious about medications that may exacerbate myopathy, such as statins, and should consult their healthcare provider about potential interactions. Maintaining a healthy lifestyle, including regular physical activity and a balanced diet, can also support overall muscle health and function.

It is important to note that hypothyroid myopathy is not inherited, but there may be a genetic predisposition to autoimmune diseases that can lead to hypothyroidism. Therefore, individuals with a family history of thyroid disorders should be vigilant about monitoring their thyroid health. If symptoms of muscle weakness, stiffness, or cramping persist despite treatment for hypothyroidism, further evaluation by a healthcare provider is recommended to rule out other potential causes.

**POSSIBLE COMPLICATIONS**

Hypothyroid myopathy can lead to several complications, including **falls and fractures due to muscle weakness and impaired bone health, as well as respiratory compromise from weakness of respiratory muscles**. In severe cases, the prognosis may be poor, particularly when diagnosis is delayed. Rhabdomyolysis, a condition where muscle breaks down rapidly, is a rare complication of hypothyroidism that can be triggered by strenuous exercise or the use of statin medications. This condition can lead to complications such as acute compartment syndrome and kidney failure. Additionally, “my oedema”, characterized by a small bump on the muscle surface after light pressure, can occur due to sustained muscle contraction and slow calcium return to muscle cells. Acute compartment syndrome, a rare complication of hypothyroidism, can impair blood supply to muscles and is caused by heavy exercise, statin or alcohol use.

**OUTLOOK / PROGNOSIS**

The prognosis for hypothyroid myopathy is generally good with prompt and appropriate treatment, such as thyroid hormone replacement therapy. Most patients experience improvement in muscle strength and function, although the recovery process may take time and ongoing treatment may be necessary.

However, the prognosis may be poor in severe cases, particularly when diagnosis is delayed or when the patient has other underlying medical issues. In such cases, patients may experience permanent muscle damage, leading to loss of muscle strength and function.

The prognosis can also vary depending on the severity of the condition and the timeliness of diagnosis and treatment.8 In some cases, hypothyroid myopathy can progress and lead to symptoms and complications such as long-term disability, increased risk of falls, respiratory complications, cardiovascular complications, and psychological impact.

With treatment, hypothyroidism has a good prognosis. An early diagnosis and the prompt introduction of thyroid supplemental treatment are needed. Complete resolution of weakness and other symptoms of hypothyroid myopathy may take several months to years of treatment.

In a study of patients with endocrine disorder myopathies, Sharma et al found that out of 10 hypothyroid patients with apparent muscle dysfunction, 7 patients (70%) achieved resolution of muscle complaints after being treated for low T4 levels for an average period of 6.4 months.

**WHEN TO SEE A DOCTOR / RED FLAG**

**If you experience symptoms of hypothyroid myopathy, such as muscle weakness, pain, or stiffness**, it is important to see a doctor for proper diagnosis and treatment. Symptoms like weakness in the shoulders, hips, or thighs, along with slowed reflexes, may indicate hypothyroid myopathy. Additionally, if you have and notice unexplained muscle pain or weakness, it is advisable to consult a healthcare provider. Early diagnosis and treatment can help alleviate symptoms and prevent complications. If you experience severe symptoms, such as difficulty breathing or swallowing, seek immediate medical attention.

**EPIDEMIOLOGY**

Hypothyroidism is one of the most commonly diagnosed medical conditions, affecting up to 12% of Americans during their lifetime. Women are affected more often compared to men, and it can manifest at any age, although it is commonly observed between the ages of 40 and 70. No specific racial predilection has been identified in studies regarding this condition. The prevalence of hypothyroidism also increases with age, with older adults being more affected compared to younger individuals.

**Frequency**

*United States*

In North America, acquired impairment of thyroid function affects about 2% of adult women and about 0.1-0.2% of adult men.

Neonatal hypothyroidism occurs with a frequency of 0.02% in the white population. In the black population, the frequency falls to 0.003%.

Of individuals with hypothyroidism, 30-80% manifest neuromuscular symptoms, depending on the severity of hypothyroidism. Weakness is observed in one third of patients with hypothyroidism. Carpal tunnel syndrome, although not part of the myopathy, is a peripheral nerve dysfunction found in 15-30% of patients with hypothyroidism.

*International*

In a prospective cohort study done in The Netherlands, in newly diagnosed patients with hypothyroidism, 79% had neuromuscular complaints, 38% had clinical weakness (manual muscle strength testing) in one or more muscle groups, 42% had signs of sensorimotor axonal neuropathy, and 29% had carpal tunnel syndrome.

Neonatal screening programs for congenital hypothyroidism in many areas of the world show that hypothyroidism is present in 1 out of every 4000 newborns. In iodine-deficient areas of the world, the incidence of hypothyroidism is 10- to 20-fold higher.

**Mortality/Morbidity**

Mortality has not been shown to be increased in patients with hypothyroid myopathy. Morbidity is significantly increased, reflected in the performance of activities of daily living (ADL) and in patients' quality of life.

**DIFFERENTIAL DIAGNOSIS**

The differential diagnosis of hypothyroid myopathy includes:

* Acid maltase deficiency
* Acute poliomyelitis
* Amyotrophic lateral sclerosis
* Becker muscular dystrophy
* Inclusion body myositis
* Polymyositis
* Post-polio syndrome
* Peripheral neuropathy

*Diagnostic Considerations*

**Myasthenia gravis**

Myasthenia gravis has been associated with Graves’ disease and hypothyroidism.Patients present with proximal muscle weakness that may be fatigable. Eventually, they can have dysphagia and respiratory distress.

**Other metabolic, mitochondrial, and inflammatory myopathies**

Glycogen metabolism deficiencies: These conditions are divided into dynamic and static deficiencies.

Dynamic myopathies: Manifestations of these disorders include exercise intolerance, pain, muscle cramps, and myoglobinuria.

* Type V - Phosphorylase (McArdle disease)
* Type VII - Phosphofructokinase (Tarui disease)
* Type VIII - Phosphorylase B kinase
* Type IX - Phosphoglycerate kinase
* Type X - Phosphoglycerate mutase
* Type XI - Lactate dehydrogenas

Static deficiencies: These disorders are associated with fixed weakness, but not with exercise intolerance or myoglobinuria.

* Type II - Alpha-1,4 glucosidase (acid maltase)
* Type III - Debranching
* Type IV - Branching

Lipid metabolism deficiencies: These disorders can be accompanied by the following dynamic or static manifestations:

* Carnitine palmitoyl transferase
* Primary systemic/muscle carnitine deficiency
* Secondary carnitine deficiency (eg, beta-oxidation defects, medications [such as valproic acid])
* Purine metabolism deficiencies (eg, myoadenylate deaminase deficiency)

**Mitochondrial myopathies**

* Pyruvate dehydrogenase complex deficiencies (eg, Leigh syndrome)
* Progressive external ophthalmoplegia
* Kearns-Sayre syndrome
* Mitochondrial encephalopathy with lactic acidosis and strokelike episodes
* Myoclonic epilepsy and ragged red fibers
* Mitochondrial neurogastrointestinal encephalomyopathy
* Mitochondrial depletion syndrome

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**THYROIDITIS**

*ALTERNATIVE NAMES:* Alternative names for thyroiditis include “de Quervain’s thyroiditis”, “granulomatous giant cell thyroiditis”, and “subacute thyroiditis”. Other terms used to describe specific types of thyroiditis are “Hashimoto's thyroiditis”, “silent thyroiditis”, “postpartum thyroiditis”, “drug-induced thyroiditis”, “radiation-induced thyroiditis”, and “acute thyroiditis”.

**DEFINITION / DESCRIPTION**

Thyroiditis is inflammation of your thyroid gland. Your thyroid is a small, butterfly-shaped gland located at the front of your neck under your skin. It’s a part of your endocrine system and controls many of your body’s important functions by producing and releasing certain hormones.

Thyroiditis includes a group of individual conditions that cause thyroid inflammation but have different causes and symptoms. Thyroiditis can lead to over- or under-production of thyroid hormone.

In most types of thyroiditis, there are three phases, including:

1. Thyrotoxic phase: During this phase, your thyroid is inflamed and releases too many hormones, causing temporary thyrotoxicosis.
2. Hypothyroid phase: Following the excessive release of thyroid hormones for a few weeks or months, your thyroid won’t have enough thyroid hormones to release. This leads to a lack of thyroid hormones or hypothyroidism. Hashimoto’s thyroiditis and radiation-induced thyroiditis usually permanently stay in the hypothyroid phase.
3. Euthyroid phase: During the euthyroid phase, your thyroid hormone levels are normal. This phase may come temporarily after the thyrotoxic phase before going to the hypothyroid phase, or it may come at the end after your thyroid gland has recovered from the inflammation and can maintain a normal hormone level.

### **Types of thyroiditis**

Types of thyroiditis include:

* Hashimoto’s thyroiditis: This autoimmune condition, also called chronic lymphocytic thyroiditis, is caused by antithyroid antibodies. It’s the most common form of thyroiditis and the most common cause of hypothyroidism.
* Silent or painless thyroiditis: This is an autoimmune condition caused by antithyroid antibodies.
* Postpartum thyroiditis: This is an autoimmune condition caused by antithyroid antibodies that can occur within one year after giving birth. It’s relatively rare.
* Radiation-induced thyroiditis: This is a condition caused by radiation therapy used as a medical treatment for certain cancers or by radioactive iodine used to treat hyperthyroidism.
* Subacute thyroiditis or de Quervain’s thyroiditis: This is an often-painful condition thought to be caused by a virus. It’s usually preceded by upper respiratory infections.
* Acute infectious thyroiditis: This is a rare condition caused by an infectious organism or bacterium.
* Drug-induced thyroiditis: This is a condition caused by the use of medications such as amiodarone, interferons, lithium and cytokines. It only occurs in a small fraction of people using these drugs.
* Riedel thyroiditis: This is a rare disease caused by chronic inflammation and fibrosis of your thyroid gland. Fibrosis is the thickening or scarring of tissue.

**What is Hashimoto thyroiditis?**

Thyroiditis is when your thyroid gland becomes irritated or inflamed. Hashimoto thyroiditis is the most common type of this health problem. It may also be called chronic autoimmune thyroiditis. This thyroiditis is an autoimmune disease. It occurs when your body makes antibodies that attack the cells in your thyroid. The thyroid gland becomes overrun with white blood cells and becomes scarred. This makes the gland feel firm and rubbery. The thyroid then can’t make enough of the thyroid hormone.

Many people with this problem have an underactive thyroid gland or hypothyroidism. They have to take medicine to keep their thyroid hormone levels normal.

**What causes Hashimoto thyroiditis?**

Hashimoto thyroiditis is an autoimmune disorder. Normally, your immune system protects your body by attacking bacteria and viruses. But with this disease, your immune system attacks your thyroid gland by mistake. Your thyroid then can’t make enough thyroid hormone, so your body can’t work as well.

**Risk for Hashimoto thyroiditis**

Things that may make it more likely for to get Hashimoto thyroiditis are:

* **Being a woman.** Women are more likely to have the disease. Hashimoto thyroiditis sometimes begins during pregnancy. The condition may get better in some women during pregnancy. But then it may return after delivery.
* **Being middle aged.** Most cases happen between ages 30 and 60. But it has been seen in younger people.
* **Having a family member with the disease (heredity).** The disease tends to run in families. But no gene has been found that carries it.
* **Having other autoimmune diseases.** These health problems raise a person’s risk. Some examples are rheumatoid arthritis, Addison disease, and type 1 diabetes. Having Hashimoto thyroiditis also increases your risk for other autoimmune illnesses.

**Symptoms of Hashimoto thyroiditis**

Each person’s symptoms may vary. Symptoms may include:

**Underactive thyroid**

When your thyroid doesn’t make enough thyroid hormone, it can cause these symptoms:

* Tiredness
* Muscle weakness and joint pain
* Constipation
* Weight gain
* Not being able to handle cold
* Depression
* Hair and skin changes

**Overactive thyroid**

When the thyroid is attacked by antibodies, it may at first release more thyroid hormone. This is called thyrotoxicosis. It does not happen to everyone. But it can cause these symptoms:

* Not being able to handle heat
* Fast heart rate
* Sweating
* Weight loss
* Tremors
* Anxiety

These symptoms may look like other health problems. Always see your healthcare provider for a diagnosis.

**DIAGNOSIS AND TEST**

Your healthcare provider will ask about your health history and give you a physical exam. You will also have blood tests. These can measure your thyroid hormone levels and check for certain antibodies that form against proteins in the thyroid.

**How is Hashimoto thyroiditis treated?**

Treatment will depend on your symptoms, age, and general health. It will also depend on how severe the condition is.

You will not need treatment if your thyroid hormone levels are normal. But Hashimoto thyroiditis can cause an underactive thyroid gland. If so, it can be treated with medicine. The medicine replaces lost thyroid hormone. That should stop your symptoms. Some people with Hashimoto's develop an enlarged thyroid gland called a goiter. Others develop an atrophic, or shrunken, thyroid gland. If the goiter grows quickly or is large, surgical removal of the goiter may be recommended to avoid problems with swallowing, speaking, or even breathing.

**CHRONIC LYMPHOCYTIC THYROIDITIS**

Chronic lymphocytic thyroiditis (Hashimoto's thyroiditis) is the most common inflammatory condition of the thyroid gland and the most common cause of goiter in the United States. It is an autoimmune condition characterized by high titers of circulating antibodies to thyroid peroxidase and thyroglobulin.

Hashimoto's disease is an autoimmune disorder affecting the thyroid gland. The thyroid is a butterfly-shaped gland located at the base of the neck just below Adam's apple. The thyroid produces hormones that help regulate many functions in the body.

An autoimmune disorder is an illness caused by the immune system attacking healthy tissues. In Hashimoto's disease, immune-system cells lead to the death of the thyroid's hormone-producing cells. The disease usually results in a decline in hormone production (hypothyroidism).

Although anyone can develop Hashimoto's disease, it's most common among middle-aged women. The primary treatment is thyroid hormone replacement.

Hashimoto's disease is also known as Hashimoto's thyroiditis, chronic lymphocytic thyroiditis and chronic autoimmune thyroiditis.

## 

## **Causes of CHRONIC LYMPHOCYTIC THYROIDITIS**

Hashimoto's disease is an autoimmune disorder. The immune system creates antibodies that attack thyroid cells as if they were bacteria, viruses or some other foreign body. The immune system wrongly enlists disease-fighting agents that damage cells and lead to cell death.

What causes the immune system to attack thyroid cells is not clear. The onset of disease may be related to:

* Genetic factors
* Environmental triggers, such as infection, stress or radiation exposure
* Interactions between environmental and genetic factors

**Risk factors of CHRONIC LYMPHOCYTIC THYROIDITIS**

The following factors are associated with an increased risk of Hashimoto's disease:

* **Sex.** Women are much more likely to get Hashimoto's disease.
* **Age.** Hashimoto's disease can occur at any age but more commonly occurs during middle age.
* **Other autoimmune disease.** Having another autoimmune disease — such as rheumatoid arthritis, type 1 diabetes or lupus — increases your risk of developing Hashimoto's disease.
* **Genetics and family history.** You're at higher risk for Hashimoto's disease if others in your family have thyroid disorders or other autoimmune diseases.
* **Pregnancy.** Typical changes in immune function during pregnancy may be a factor in Hashimoto's disease that begins after pregnancy.
* **Excessive iodine intake.** Too much iodine in the diet may function as a trigger among people already at risk for Hashimoto's disease.
* **Radiation exposure.** People exposed to excessive levels of environmental radiation are more prone to Hashimoto's disease.

## **Symptoms of CHRONIC LYMPHOCYTIC THYROIDITIS**

Hashimoto's disease progresses slowly over the years. You may not notice signs or symptoms of the disease. Eventually, the decline in thyroid hormone production can result in any of the following:

* Fatigue and sluggishness
* Increased sensitivity to cold
* Increased sleepiness
* Dry skin
* Constipation
* Muscle weakness
* Muscle aches, tenderness and stiffness
* Joint pain and stiffness
* Irregular or excessive menstrual bleeding
* Depression
* Problems with memory or concentration
* Swelling of the thyroid (goiter)
* A puffy face
* Brittle nails
* Hair loss
* Enlargement of the tongue

## 

## **Diagnosis of CHRONIC LYMPHOCYTIC THYROIDITIS**

A number of conditions may lead to the signs and symptoms of Hashimoto's disease. If you're experiencing any of these symptoms, your health care provider will conduct a thorough physical exam, review your medical history and ask questions about your symptoms.

### Testing thyroid function

To determine if hypothyroidism is the cause of your symptoms, your provider will order blood tests that may include the following:

* TSH test. Thyroid stimulating hormone (TSH) is produced by the pituitary gland. When the pituitary detects low thyroid hormones in the blood, it sends TSH to the thyroid to prompt an increase in thyroid hormone production. High TSH levels in the blood indicates hypothyroidism.
* T-4 tests. The main thyroid hormone is thyroxine (T-4). A low blood level of T-4 confirms the findings of a TSH test and indicates the problem is within the thyroid itself.

### Antibody tests

More than one disease process can lead to hypothyroidism. To determine if Hashimoto's disease is the cause of hypothyroidism, your health care provider will order an antibody test.

The intended purpose of an antibody is to flag disease-causing foreign agents that need to be destroyed by other actors in the immune system. In an autoimmune disorder, the immune system produces rogue antibodies that target healthy cells or proteins in the body.

Usually in Hashimoto's disease, the immune system produces an antibody to thyroid peroxidase (TPO), a protein that plays an important part in thyroid hormone production. Most people with Hashimoto's disease will have TPO antibodies in their blood. Lab tests for other antibodies associated with Hashimoto's disease may need to be done.

## **Treatment of CHRONIC LYMPHOCYTIC THYROIDITIS**

Most people with Hashimoto's disease take medication to treat hypothyroidism. If you have mild hypothyroidism, you may have no treatment but get regular thyroid stimulating hormone (TSH) tests to monitor thyroid hormone levels.

### **T-4 hormone replacement therapy**

Hypothyroidism associated with Hashimoto's disease is treated with a synthetic hormone called levothyroxine (Levoxyl, Synthroid, others). The synthetic hormone works like the thyroxine (T-4) hormone naturally produced by the thyroid.

The treatment goal is to restore and maintain adequate T-4 hormone levels and improve symptoms of hypothyroidism. You will need this treatment for the rest of your life.

### **Monitoring the dosage**

Your healthcare provider will determine a dosage of levothyroxine that's appropriate for your age, weight, current thyroid production, other medical conditions and other factors. Your provider will retest your TSH levels about 6 to 10 weeks later and adjust the dosage as necessary.

Once the best dosage is determined, you will continue to take the medication once a day. You'll need follow-up tests once a year to monitor TSH levels or any time after your provider changes your dosage.

A levothyroxine pill is usually taken in the morning before you eat. Talk to your doctor if you have any questions about when or how to take the pill. Also, ask what to do if you accidentally skip a dose. If your health insurance requires you to switch to a generic drug or a different brand, talk to your doctor.

### **Precautions**

Because levothyroxine acts like natural T-4 in the body, there are generally no side effects as long as the treatment is resulting in "natural" levels of T-4 for your body.

Too much thyroid hormone can worsen bone loss that causes weak, brittle bones (osteoporosis) or cause irregular heartbeats (arrhythmias).

### **Effects of other substances**

Certain medications, supplements and foods may affect your ability to absorb levothyroxine. It may be necessary to take levothyroxine at least four hours before these substances. Talk to your doctor about any of the following:

* Soy products
* High-fiber foods
* Iron supplements, including multivitamins that contain iron
* Cholestyramine (Prevalite), a medication used to lower blood cholesterol levels
* Aluminum hydroxide, which is found in some antacids
* Sucralfate, an ulcer medication
* Calcium supplements

### **T-3 hormone replacement therapy**

Naturally produced T-4 is converted into another thyroid hormone called triiodothyronine (T-3). The T-4 replacement hormone is also converted into T-3, and for most people the T-4 replacement therapy results in an adequate supply of (T-3) for the body.

For people who need better symptom control, a doctor also may prescribe a synthetic T-3 hormone (Cytomel) or a synthetic T-4 and T-3 combination. Side effects of T-3 hormone replacement include rapid heartbeat, insomnia and anxiety. These treatments may be tested with a trial period of 3 to 6 months.

**Complications of CHRONIC LYMPHOCYTIC THYROIDITIS**

Thyroid hormones are essential for the healthy function of many body systems. Therefore, when Hashimoto's disease and hypothyroidism are left untreated, many complications can occur. These include:

* **Goiter.** A goiter is enlargement of the thyroid. As thyroid hormone production declines due to Hashimoto's disease, the thyroid receives signals from the pituitary gland to make more. This cycle may result in a goiter. It's generally not uncomfortable, but a large goiter can affect your appearance and may interfere with swallowing or breathing.
* **Heart problems.** Hypothyroidism can result in poor heart function, an enlarged heart and irregular heartbeats. It can also result in high levels of low-density lipoprotein (LDL) cholesterol — the "bad" cholesterol — that is a risk factor for cardiovascular disease and heart failure.
* **Mental health issues.** Depression or other mental health disorders may occur early in Hashimoto's disease and may become more severe over time.
* **Sexual and reproductive dysfunction.** In women, hypothyroidism can result in a reduced sexual desire (libido), an inability to ovulate, and irregular and excessive menstrual bleeding. Men with hypothyroidism may have a reduced libido, erectile dysfunction and a lowered sperm count.
* **Poor pregnancy outcomes.** Hypothyroidism during pregnancy may increase the risk of a miscarriage or preterm birth. Babies born to women with untreated hypothyroidism are at risk for decreased intellectual abilities, autism, speech delays and other developmental disorders.
* **Myxedema (miks-uh-DEE-muh).** This rare, life-threatening condition can develop due to long-term, severe, untreated hypothyroidism. Its signs and symptoms include drowsiness followed by profound lethargy and unconsciousness. A myxedema coma may be triggered by exposure to cold, sedatives, infection or other stress on your body. Myxedema requires immediate emergency medical treatment.

## **Alternative medicine**

Products with triiodothyronine (T-3) and thyroxine (T-4) hormones derived from pigs or other animals are available as prescriptions or as dietary supplements, such as Armour Thyroid, in the United States. Concerns about these products include the following:

* The balance of T-4 and T-3 in animals isn't the same as in humans.
* The exact amount of T-4 and T-3 in each batch of a natural extract product can vary, leading to unpredictable levels of these hormones in your blood.

The following autoimmune phenomena may occur or be found in association with Hashimoto thyroiditis:

* Addison disease
* Alopecia areata, totalis, and universalis
* Autoimmune gastritis (pernicious anemia)
* Chronic active hepatitis
* Idiopathic hypoparathyroidism
* Polymyalgia rheumatica and giant cell arteritis
* Primary biliary cirrhosis
* Primary ovarian or testicular failure
* Rheumatoid arthritis
* Sjögren syndrome
* Systemic lupus erythematosus (SLE)
* Systemic sclerosis (scleroderma)
* Type 1 diabetes mellitus
* Vitiligo

## Differential Diagnoses of **CHRONIC LYMPHOCYTIC THYROIDITIS**

* Diffuse Toxic Goiter (Graves Disease)
* Euthyroid Sick Syndrome
* Goiter
* Hypopituitarism (Panhypopituitarism)
* Lithium-Induced Goiter
* Nontoxic Goiter
* Thyroid Lymphoma
* Toxic Nodular Goiter
* Type I Polyglandular Autoimmune Syndrome
* Type II Polyglandular Autoimmune Syndrome

**EPIDEMIOLOGY**

Chronic lymphocytic thyroiditis is the most common cause of hypothyroidism in the United States, and euthyroid persons with Hashimoto's disease develop hypothyroidism at a rate of approximately 5 percent per year. Up to 95 percent of cases of chronic lymphocytic thyroiditis occur in women, usually between 30 and 50 years of age. Chronic lymphocytic thyroiditis is also the most common cause of sporadic goiter in children. The incidence of Hashimoto's disease has risen exponentially over the past 50 years, and this increase may be related to an increased iodine content in the North American diet.

A genetic predisposition to thyroid auto-immunity exists; it is inherited as a dominant trait. Hashimoto's disease has been linked to other autoimmune diseases, including systemic lupus erythematosus, rheumatoid arthritis, pernicious anemia, diabetes mellitus and Sjögren's syndrome. A rare but serious complication of chronic autoimmune thyroiditis is thyroid lymphoma. These lymphomas, generally the B-cell, non-Hodgkin's type, tend to occur in women 50 to 80 years of age and are usually limited to the thyroid gland.

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**SUBACUTE LYMPHOCYTIC THYROIDITIS**

Subacute lymphocytic thyroiditis occurs most often in the postpartum period but may also occur sporadically. Therefore, it is subdivided into two groups, postpartum thyroiditis and sporadic painless thyroiditis. Antimicrosomal antibodies are present in 50 to 80 percent of patients, while antithyroid peroxidase antibodies are present in nearly all patients. Subacute lymphocytic thyroiditis starts with an initial hyperthyroid phase, followed by subsequent hypothyroidism and, finally, a return to the euthyroid state. In the postpartum patient, thyrotoxicosis usually develops in the first three months following delivery and lasts for one or two months. Then the patient returns to a euthyroid state or hyperthyroidism ensues for several months. Patients with an initial episode of postpartum subacute lymphocytic thyroiditis have a notably high risk of recurrence in subsequent pregnancies. Serum TSH testing is indicated in symptomatic patients.

## **Risk Factors for Subacute Lymphocytic Thyroiditis**

## Risk factors associated with Subacute Lymphocytic Thyroiditis include:

* Female gender, especially postpartum women; between 5-10% of all postpartum women are known to develop the condition
* Women with a history of postpartum Subacute Lymphocytic Thyroiditis have a higher risk for recurrence of the condition following the next pregnancy
* Positive family history of the condition (or other forms of thyroiditis)
* Presence of autoimmune disorders or a family history of the same
* Radiation therapy
* Viral infections

It is important to note that having a risk factor does not mean that one will get the condition. A risk factor increases one’s chances of getting a condition compared to an individual without the risk factors. Some risk factors are more important than others.

Also, not having a risk factor does not mean that an individual will not get the condition. It is always important to discuss the effect of risk factors with your healthcare provider.

## **Causes of Subacute Lymphocytic Thyroiditis**

The exact cause of Subacute Lymphocytic Thyroiditis is not well-established.

* It is believed to develop due to an immune attack by the body against the thyroid gland (autoimmune disorder) that may be triggered by various factors
* It is reported that almost all individuals present antithyroid peroxidase antibodies (indicating some form of autoimmune thyroid disease), and between 50% to 80% of them present antimicrosomal antibodies (antibodies generated when the thyroid gland is damaged)

## **Signs and Symptoms of Subacute Lymphocytic Thyroiditis**

Subacute Lymphocytic Thyroiditis typically begins with hyperthyroidism that may last for a short period. This is generally followed by hypothyroidism, resulting in associated symptoms, and is followed by a return to normal state (euthyroidism). However, the course of the condition may be variable; it may alternate between hyperthyroidism and hypothyroidism too.

The associated signs and symptoms of hyperthyroidism may include:

* Sleeping difficulties including insomnia
* Excess sweating and intolerance to heat
* Increased to excessive hunger
* Irritation, restlessness, and nervousness
* Protrusion of the eyes
* Menstrual abnormalities in women; menstruation may be irregular or short
* Abnormal heartbeat rate including rapid heart rate
* Sudden weight loss

The signs and symptoms associated with hypothyroidism may include:

* Enlarged or swollen thyroid gland; small or shrunken thyroid gland (late in the disease)
* Difficulty concentrating or thinking
* Fatigue and tiredness
* Dry skin
* Hair loss, which may be in excess while showering
* Constipation or difficult bowel movements
* Weight gain that may be slow and gradual
* Heavy and irregular periods (in women)
* Abnormal sensitivity to cold; the affected individuals may not tolerate cold very well

## **How is Subacute Lymphocytic Thyroiditis Diagnosed?**

The diagnosis of Subacute Lymphocytic Thyroiditis may involve the following tests and procedures:

* Complete evaluation of medical history and a thorough physical examination
* Assessment of the signs and symptoms
* Blood tests to evaluate the levels of:
  + T3 and T4; thyroid hormones produced in the thyroid gland
  + Serum TSH
  + Antithyroid peroxidase antibody (anti-TPO); antibodies against thyroid peroxidase, an enzyme in the thyroid gland
  + Antithyroglobulin antibody; antibodies interacting with thyroglobulin, a protein found on the thyroid cells
* Ultrasound scans of the thyroid gland
* Fine needle aspiration (FNA) biopsy or core biopsy of the thyroid gland, if needed
* Tests and procedures to rule out any underlying condition, if necessary

Many clinical conditions may have similar signs and symptoms. Your healthcare provider may perform additional tests to rule out other clinical conditions to arrive at a definitive diagnosis.

## **possible Complications of Subacute Lymphocytic Thyroiditis**

Subacute Lymphocytic Thyroiditis is a generally self-limiting condition. However, sometimes, the thyroid function does not completely come back to normal levels.

Some potential complications associated with hyperthyroidism include:

* Thyrotoxicosis, or the presence of excess thyroid hormones in the body tissues
* Mental health issues such as depression
* Increased risk for heart diseases

Some potential complications associated with hypothyroidism include:

* Infertility
* Heart diseases
* Increased risk of infection

## **How is Subacute Lymphocytic Thyroiditis Treated?**

In many cases, Subacute Lymphocytic Thyroiditis is a self-limiting condition that resolves on its own. If treatment is provided, then it is based upon the presenting symptoms:

* During the hyperthyroid stage, antithyroid drugs are usually not necessary
* Sometimes, thyroid hormone replacement is needed if symptoms of hypothyroidism persist and/or are severe
* Beta-blockers are known to relieve an elevated heart rate and excessive sweating, which may be prescribed if necessary
* Follow-up care with screening and check-ups are important at regular intervals

## **How can Subacute Lymphocytic Thyroiditis be Prevented?**

The exact cause of Subacute Lymphocytic Thyroiditis is not known, and hence currently, there is no known preventive method reported for the condition. However, considering certain factors may help lower one’s risk for the same:

* Knowledge about one’s family history is helpful in assessing future risks for the condition
* Early detection and prompt treatment of autoimmune disorders may lower one’s risk

## **Prognosis of Subacute Lymphocytic Thyroiditis**

## In a vast majority of cases, Subacute Lymphocytic Thyroiditis resolves on its own over a few months to a year. As the condition resolves on its own, the thyroid gland function comes back to normalcy (euthyroid state)

* Women with postpartum thyroiditis are at a higher risk for recurrence of the condition (observed in 1-6% of the cases). In rare cases, the condition may become chronic and result in chronic hypothyroidism

A close follow-up is necessary at periodic intervals; during the follow-up visits, thyroid hormone levels in blood need to be checked.

**EPIDEMIOLOGY**

Subacute lymphocytic thyroiditis comprises 29 to 50 percent of all cases of thyroiditis and occurs most often in women between 30 and 50 years of age. There is a higher incidence of antimicrosomal antibodies in the postpartum form (80 percent) of the disease than in the sporadic form (50 percent). A family history of autoimmune thyroid disease is found in 50 percent of patients with the postpartum form of thyroiditis. The severity of the hypothyroid phase correlates directly with the antimicrosomal antibody titer. A titer of 1:1,600 or greater early in pregnancy is associated with a high risk of postpartum hypothyroidism. Approximately 6 percent of patients who have the postpartum form develop chronic hypothyroidism.

**SUBACUTE GRANULOMATOUS THYROIDITIS**

### De Quervain’s Thyroiditis

De Quervain’s thyroiditis, also referred to as subacute granulomatous thyroiditis, giant cell thyroiditis or painful subacute thyroiditis, can affect people of all ages and genders but is most common in females aged between 20 and 50. It is part of the resolving thyroiditis family and is named after Fritz De Quervain but should not be confused with De Quervain’s syndrome which he also identified.

De Quervain’s thyroiditis usually causes the thyroid gland to swell rapidly resulting in pain and discomfort. Subsequently, the thyroid gland releases the thyroid hormone into the blood resulting in patients becoming hyperthyroid.

### What causes De Quervain’s Thyroiditis?

De Quervain’s thyroiditis is often brought on by a viral infection such as mumps, an upper respiratory tract infection, adenovirus or influenza. Some cases may develop following pregnancy and childbirth.

The symptoms may resolve themselves after a short period of time but can occasionally lead to an underactive thyroid, which may continue to be unsettled for many months before the gland returns to normal. In more severe cases patients can suffer from infectious thyroiditis or permanent hypothyroidism requiring thyroid hormone replacement.

### **What are the symptoms of De Quervain’s Thyroiditis?**

Symptoms vary depending on the patient and the severity of the condition but can include:

* fever
* pain in the neck, jaw and/or ear
* inflammation of the thyroid
* hyperthyroidism
* anxiety
* insomnia
* palpitations
* shakes

### **Testing**

It is essential to seek a professional diagnosis from your doctor or consultant. This may include a visual examination, blood test, ultrasound and/or fine-needle aspiration.

### **Treatment**

Treatment for De Quervain’s thyroiditis can vary dramatically depending on the individual patient’s needs. Some sufferers may simply require over the counter pain medication to manage a short-term attack. Salicylates and non-steroidal anti-inflammatory medications may also be used to treat mild to moderate cases. For more severe cases liothyronine (T3) or levothyroxine (T4) treatment might be considered and if extreme measures are required to benefit the patient’s health and wellbeing then a thyroidectomy may need to be performed.

### **Prognosis**

Prognosis of this condition varies massively between patients. De Quervain’s thyroiditis can be a reoccurring or permanent illness requiring long-term medication, but it is usually a short-term treatable complaint.

**EPIDEMIOLOGY**

Women are three to five times more likely to be affected than men. The average age of onset is 30 to 50 years. The disorder tends to be geographical and seasonal, occurring most often in the summer and fall.

**Microbial Inflammatory Thyroiditis**

## Acute Infectious Thyroiditis Symptoms

Acute infections, by definition, are infections that cause symptoms within a short period of time. If you or your child develop acute infectious thyroiditis, you can expect its effects to rapidly worsen.

Symptoms may include:

* Rapid onset of pain and tenderness in one side of your neck
* Fever and chills (a flu-like feeling)
* Enlarged thyroid gland or swelling in your neck area
* A movable lump in your neck
* A warm, red, or tender area in the neck
* Painful swallowing or difficulty swallowing
* Swollen lymph glands
* Hoarseness in your voice

You may also develop symptoms of hypothyroidism (low thyroid hormone function) or hyperthyroidism (excess thyroid hormone function), although your thyroid function is likely to remain stable during a bout of acute infectious thyroiditis.

### **Complications**

Acute infectious thyroiditis can produce a number of complications, the most common of which is an abscess—an encapsulated (closed-off) infection that requires immediate treatment, including with antibiotics and surgical drainage. A thyroid abscess typically presents with symptoms such as fever, neck pain, and a painful lump.

Other potential complications can include the following:

* Sepsis—poisoning of the blood with bacteria—rarely occurs when your existing infection spreads throughout the body.
* Bleeding into the thyroid gland can occur, resulting in swelling, possible respiratory symptoms, and damage to the thyroid gland.
* While it is uncommon, long-term thyroid dysfunction due to damage to the thyroid gland can occur after the infection is completely resolved.

## **What Causes Acute Infectious Thyroiditis?**

Infectious thyroiditis is usually caused by a bacterial infection. Most often, the culprit is a Gram-positive bacterium such as *S. aureus* or *Streptococci*. Gram-negative organisms involving the oropharynx can also be to blame. Less commonly, acute infectious thyroiditis can be caused by mycobacteria or fungi—this is rare, and typically only affects immunocompromised individuals.

Acute infectious thyroiditis is rare because the thyroid gland is inherently better protected from infection than most other regions of the body. There are some risk factors that can increase your chances of developing an acute thyroid infection.

**Risk factors include the following:**

* **Time of year**, as this infection is more common in the fall and winter, especially after an infection of the upper respiratory tract.
* **Age,** as only about 8% of acute infectious thyroiditis is estimated to occur in adults. Subacute thyroiditis is most common in young adulthood and middle age, and it decreases in frequency with increasing age.
* **A piriform sinus fistula**, which is a congenital (from birth) defect in the areas around the nose, mouth, and neck, leads to an increased risk of developing this infection. The fistula can permit bacterial organisms to have access to the thyroid gland.
* **A weakened immune system** can be caused by immunosuppressive medication, chemotherapy drugs, or a medical condition such as HIV.
* **Thyroid cancer** increases the risk of developing an acute thyroid infection.
* **Intravenous (IV) drug use** makes you more susceptible to developing a severe bacterial infection and has been associated with acute infectious thyroiditis.

While thyroid gland infection is rare, subacute or chronic thyroid infections are more common and less severe than acute infectious thyroiditis. Acute infectious thyroiditis is usually caused by bacteria, whereas subacute thyroid infections are usually caused by a virus, and are therefore treated with different medications.

## **Diagnosis**

If your healthcare provider suspects that you have acute infectious thyroiditis, you will need a medical evaluation to confirm the diagnosis and to identify any risk factors. Your healthcare provider will examine your neck and look for signs of infection elsewhere in the body.

### Physical Examination

The most common signs of acute infectious thyroiditis are a fever and neck tenderness.

Along with a thorough general physical examination, your healthcare provider will gently palpate (feel) your neck and thyroid gland, as well as nearby lymph nodes to check the size and texture of any growth.

### Diagnostic Imaging Tests

Your healthcare provider may order one or more imaging tests to visualize the structures in your neck. Diagnostic examinations may include a neck ultrasound, computerized tomography (CT) scan, magnetic resonance imaging (MRI), or a thyroid uptake scan.

These imaging tests can help identify whether your symptoms are caused by thyroiditis or by another infection or disease involving the neck. Anatomical variations, like a fistula, can be identified as well. However, imaging might not distinguish infectious thyroiditis from subacute (noninfectious) thyroiditis.

### Blood Tests

You may need blood tests. A complete cell count (CBC) can show an elevated white blood cell count with an infection. Thyroid function tests are usually altered by non-infectious inflammation of the thyroid gland, like non-infectious thyroiditis.

A blood culture may also be helpful in identifying bacteria or another microorganism that's causing your infection. Your healthcare provider may also run other blood tests to identify whether you have an undiagnosed problem with your immune system.

### Fine Needle Aspiration

Sometimes, an aspiration test can help identify whether thyroiditis is **suppurative** (contains pus) or **non-suppurative**. Suppurative infectious thyroiditis is usually more severe than non-suppurative thyroiditis.

Fine needle aspiration (FNA) is a procedure that involves withdrawing some of the fluid or tissue from your thyroid gland. In some cases, the FNA is guided by ultrasound to determine the position and location of an infection or abscess.

The sample will be analyzed using a culture, which is a material that allows infectious organisms to grow so that they can be identified. The culture results can help your healthcare provider choose the appropriate antibiotic and/or anti-fungal medication for treatment.

## **How Is Acute Infectious Thyroiditis Treated?**

The treatment of acute thyroiditis is focused on eliminating the infection and reducing symptoms while the infection resolves. Several treatments can be used, and, if you or your child has acute infectious thyroiditis, your healthcare providers will initiate treatment quickly.

The usual treatment for acute infectious thyroiditis is a combination of incision and drainage coupled with antibiotics.

In addition to treatment for your infection, you may also need medication to lower your fever and/or treatment for pain. If you are unable to eat, you may need IV fluids until you can resume eating.

### **Antibiotics**

**Oral antibiotics** can be used for the treatment of acute bacterial infectious thyroiditis. Some of the antibiotic medications that are commonly used for this type of infection include penicillin, clindamycin, or a combination of macrolide and metronidazole.

If your healthcare provider is concerned that you could have an **antibiotic-resistant infection**, another antibiotic may be selected. Antibiotic-resistant infections are bacteria that do not respond to standard antibiotics, often called "superbugs," and they require treatment with antibiotics that are stronger and/or more specifically directed.

You may need treatment with an **intravenous (IV) antibiotic** if your healthcare provider is concerned that your infection is progressing rapidly, you can't swallow oral medication, or you are vomiting so much that you can't absorb oral medication.

### **Procedures**

**Percutaneous drainage** is a procedure that your healthcare provider may use to remove the infectious fluid with a needle. You may have percutaneous drainage at the same time as your FNA. If you have this procedure, you will probably also receive antibiotic treatment.

Infrequently, **surgical drainage** of an infection or an abscess is required if your infection does not improve with percutaneous drainage and antibiotic therapy.

Rarely, surgical removal of part of the thyroid gland may be needed. In some cases, removal of half the thyroid gland, known as a hemithyroidectomy, may provide more effective treatment.

## **Epidemiology of Microbial (Acute Infectious) Thyroiditis**

* Rarity:  
  Acute infectious thyroiditis (AIT), a microbial inflammatory thyroiditis caused by bacterial, mycobacterial, or fungal infection, is very rare, accounting for approximately 0.1% to 0.7% of all thyroiditis cases.
* Incidence in Clinical Settings:  
  Large hospitals typically see only about two cases of AIT per year, highlighting its rarity.
* Age and Gender Distribution:  
  AIT commonly affects children and young adults, predominantly between ages 20 and 40, with about 92% of cases in children and young adults and 8% in older adults. Men and women are equally affected.
* Causative Microorganisms:  
  Most commonly caused by gram-positive bacteria such as *Staphylococcus* and *Streptococcus* species. Occasionally, mycobacteria and fungi (including *Pneumocystis*) may be involved.
* Geographic Variation:  
  Acute thyroiditis is more frequent in regions with less widespread antibiotic use. However, precise global incidence data are limited.
* Associated Conditions:  
  Microbial thyroiditis is rare compared to autoimmune thyroiditis, which is far more common worldwide. Autoimmune thyroiditis prevalence varies by region, with overall adult prevalence around 7.5%, higher in women (about four times more than men) and in low- and middle-income countries.
* Mortality:  
  If untreated, microbial thyroiditis carries a mortality risk of approximately 12%

**Invasive Fibrous Thyroiditis**

Riedel thyroiditis is a rare chronic inflammatory condition that affects the thyroid gland. It causes the thyroid gland to become replaced by fibrous tissue, leading to issues with thyroid function. This can impact overall health by affecting metabolism and hormone regulation, potentially resulting in various health complications.

## **What are the Symptoms of Riedel Thyroiditis**

Riedel thyroiditis is a rare condition that affects the thyroid gland. People with this condition typically experience symptoms related to the compression of nearby structures in the neck due to the enlarged thyroid gland. These symptoms can vary in severity and may impact the individual's quality of life. If you suspect you may have Riedel thyroiditis, it's important to seek medical advice for proper evaluation and management.

* Hoarseness
* Difficulty swallowing
* Neck pain
* Thyroid enlargement
* Hypothyroidism symptoms

## **Causes of Riedel Thyroiditis**

Riedel thyroiditis is a rare condition where the thyroid gland becomes replaced by scar-like tissue. The exact cause of Riedel thyroiditis is not fully understood, but several factors may contribute to its development. These factors include autoimmune reactions, genetic predisposition, and inflammation within the thyroid gland. Other potential triggers may involve previous infections or trauma to the thyroid area. The interplay of these various factors can lead to the development of Riedel thyroiditis, although more research is needed to fully understand its underlying causes.

* Autoimmune disorders
* Infections
* Trauma to the neck
* Inflammatory conditions
* Genetic factors

**Types of Riedel Thyroiditis**

Riedel's thyroiditis can manifest in different forms, each presenting distinct characteristics and symptoms. These variations in presentation can impact the diagnosis and treatment of the condition. Understanding the different types of Riedel's thyroiditis is crucial for healthcare professionals to effectively manage and care for patients with this rare thyroid disorder.

* Riedel's Thyroiditis: Also known as invasive fibrous thyroiditis, it is a rare form of chronic thyroiditis where the thyroid tissue is replaced by fibrous tissue, causing a hard, woody texture to the thyroid gland.
* Riedel's Struma: Characterized by extensive fibrosis that can extend beyond the thyroid gland, leading to compression of nearby structures in the neck and potentially causing symptoms such as difficulty swallowing or breathing.
* Fibrous Variant of Hashimoto's Thyroiditis: A subtype of Hashimoto's thyroiditis where fibrosis is a predominant feature, resulting in a firm and fixed thyroid gland.
* Idiopathic Fibrosclerosis of the Thyroid: A term used to describe cases of thyroid fibrosis with unknown underlying causes, often presenting with symptoms related to compression of surrounding tissues.
* Secondary Riedel's Thyroiditis: Refers to cases where fibrosis of the thyroid gland occurs as a secondary response to other conditions such as malignancies, infections, or autoimmune disorders, necessitating a thorough evaluation to determine the underlying cause.

## **Risk Factors**

Riedel thyroiditis is a rare condition that affects the thyroid gland. Certain factors can increase the risk of developing this condition. Understanding these risk factors is essential for early detection and management of Riedel thyroiditis.

* Female gender
* Middle aged adults
* Autoimmune diseases
* Previous history of thyroid disorders
* Family history of thyroid disorders
* Smoking
* Postpartum period

## **Diagnosis of Riedel Thyroiditis**

Riedel thyroiditis is typically diagnosed through a combination of physical exams, imaging tests, and laboratory studies. Healthcare providers will examine the neck for any abnormalities and may order ultrasound or CT scans to visualize the thyroid gland. Blood tests are also commonly performed to assess thyroid function and check for markers of inflammation. By analyzing these findings, doctors can make a diagnosis of Riedel thyroiditis.

* Physical examination
* Blood tests (thyroid function tests)
* Imaging studies (ultrasound, CT scan, MRI)
* Fine needle aspiration biopsy

## **Treatment for Riedel Thyroiditis**

Riedel thyroiditis is a rare condition that causes the thyroid gland to become inflamed and fibrotic. Treatment options for Riedel thyroiditis aim to manage symptoms and may include medications to reduce inflammation, relieve pain, and address thyroid dysfunction. In some cases, surgery may be necessary to remove part or all of the thyroid gland. Additionally, close monitoring by a healthcare provider is essential to track the progression of the condition and adjust treatment as needed.

* Corticosteroids: These are often prescribed to reduce inflammation and help manage symptoms in Riedel thyroiditis.
* Thyroid Hormone Replacement Therapy: This treatment option may be recommended to address any thyroid hormone imbalances that result from Riedel thyroiditis.
* Surgical Intervention: In severe cases or when other treatments are ineffective, surgery to remove the affected thyroid tissue may be necessary.
* Immunosuppressive Therapy: This approach aims to suppress the immune system's activity to alleviate the inflammation associated with Riedel thyroiditis.
* Pain Management: Depending on the patient's symptoms, pain relief medications may be prescribed to help manage discomfort associated with Riedel thyroiditis.

**When should I call my healthcare provider?**

Tell your healthcare provider if your symptoms get worse or you have new symptoms.

### **Is thyroiditis life-threatening?**

Thyroiditis generally isn’t life-threatening.

However, a life-threatening condition called thyroid storm can develop if you have long-term untreated or undertreated hyperthyroidism, which can develop from thyroiditis.

Symptoms of thyroid storm include:

* High fever — a temperature between 104 degrees to 106 degrees Fahrenheit is common.
* Rapid heart rate (tachycardia) that can exceed 140 beats per minute.
* Feeling agitated, irritable and/or anxious.
* Delirium.

If you’re experiencing these symptoms, call 911 or get to the nearest hospital as soon as possible.

If you’re experiencing symptoms of thyroiditis, it’s important to talk to your healthcare provider so they can order tests to diagnose it and treat it.

**CAUSES**

### **What causes thyroiditis?**

Thyroiditis is caused by an attack on your thyroid, causing inflammation (your body’s response to an injury) and damage to the thyroid cells. It has several different causes depending on the type.

The most common cause, or “attacker,” is an autoimmune disease, which is the result of your immune system accidentally attacking your body instead of protecting it. It's unclear why your immune system does this. Antibodies that attack your thyroid cause most types of thyroiditis.

*This chart lists the causes for each type of thyroiditis.*

| **Type of thyroiditis** | **Cause** |
| --- | --- |
| Hashimoto’s thyroiditis | Antithyroid antibodies, autoimmune disease. |
| Silent or painless thyroiditis | Antithyroid antibodies, autoimmune disease. |
| Postpartum thyroiditis | Antithyroid antibodies, autoimmune disease. |
| Subacute thyroiditis (de Quervain’s thyroiditis) | Likely a virus. |
| Acute infectious thyroiditis | Most commonly bacteria, but any infectious organism. |
| Radiation-induced thyroiditis | Follows treatment with radioactive iodine for hyperthyroidism or external beam radiation therapy for certain cancers. |
| Drug-induced thyroiditis | Certain medications, including amiodarone, lithium, interferons, interleukin-2 and checkpoint inhibitors. |
| Riedel thyroiditis | Fibrosis (thickening and scarring) of your thyroid. |

**RISK FACTORS**

Thyroiditis refers to a group of conditions that cause inflammation of the thyroid gland, and several risk factors are associated with its development. These include genetic and autoimmune factors, as well as environmental and medical influences.

Genetics and family history play a role, as individuals with a family history of thyroid disorders or other autoimmune diseases are at higher risk for Hashimoto's thyroiditis. Pregnancy can also be a risk factor, as changes in immune function during pregnancy may contribute to the development of Hashimoto's disease or postpartum thyroiditis. Excessive iodine intake may act as a trigger for those already at risk for Hashimoto's disease. Radiation exposure, such as from environmental radiation, increases the risk of developing Hashimoto's disease.

Autoimmune conditions are a significant risk factor for several types of thyroiditis. For example, Hashimoto's thyroiditis is an autoimmune condition where antithyroid antibodies attack the thyroid gland. Similarly, silent thyroiditis, postpartum thyroiditis, and subacute thyroiditis are also linked to autoimmune mechanisms. The presence of thyroid peroxidase antibodies or other autoimmune diseases increases the risk of postpartum thyroiditis.

Medical treatments can also contribute to the risk of thyroiditis. Radiation therapy, particularly for cancers of the head and neck, or treatment with radioactive iodine for hyperthyroidism, can lead to radiation-induced thyroiditis. Certain medications, such as amiodarone, lithium, interferons, and cytokines, are known to cause drug-induced thyroiditis.

**Infections, including viral or bacterial infections**, can also lead to thyroiditis. Subacute thyroiditis, for instance, is often associated with viral infections. Acute infectious thyroiditis is caused by bacterial or other infectious organisms.

In summary, the risk factors for thyroiditis include genetic predisposition, autoimmune conditions, pregnancy, excessive iodine intake, radiation exposure, certain medications, and infections.

### **SIGNS / SYMPTOMS**

### **What are the symptoms of thyroiditis?**

The symptoms of thyroiditis depend on the type of thyroiditis and its phase. Most types of thyroiditis cause thyrotoxicosis symptoms followed by hypothyroid symptoms.

Subacute thyroiditis and acute infectious thyroiditis usually also cause pain in your thyroid area. Some people with thyroiditis have an enlarged thyroid gland (goiter).

#### **Symptoms of thyrotoxicosis**

The thyrotoxic phase of thyroiditis is usually short, lasting one to three months. If your thyroid cells are damaged quickly and there’s a leak of excess thyroid hormone, you might experience symptoms of hyperthyroidism (overactive thyroid), which include:

* Fast heart rate.
* Increased appetite.
* Unexplained weight loss.
* Anxiety and nervousness.
* Irritability.
* Trouble sleeping
* Increased sweating and sensitivity to heat.
* Tremors.

#### **Symptoms of hypothyroidism**

The hypothyroid phase of thyroiditis can be long-lasting and may become permanent. If your thyroid cells are damaged and thyroid hormone levels fall, you might experience the symptoms of hypothyroidism, which include:

* Fatigue.
* Unexplained weight gain.
* Constipation.
* Depression.
* Dry skin.
* Increased sensitivity to cold.
* Muscle weakness.
* Decreased ability to concentrate and focus.

### **DIAGNOSIS METHODS**

### **How is thyroiditis diagnosed?**

Your healthcare provider will perform a physical exam, including assessing your thyroid, and ask you questions about your symptoms and medical history.

If they suspect you may have thyroiditis after, they’ll likely order any combination of the following tests to help diagnose it:

* Thyroid function tests: These are blood tests that measure the levels of thyroid-related hormones and thyroid hormones in your body, including thyroid-stimulating hormone (TSH), T3 (triiodothyronine) and T4 (thyroxine). TSH comes from your pituitary gland and stimulates your thyroid gland to produce the hormones T4 and T3, which together are called thyroid hormones.
* Thyroid ultrasound: Providers often use ultrasound to evaluate the anatomy of your thyroid gland. It can show a nodule (a growth) in your thyroid gland, a change in blood flow to your thyroid and the density of the gland.
* Thyroid antibody tests: These are blood tests that measure thyroid antibodies that include antithyroid (microsomal) antibodies (TPO) or thyroid receptor stimulating antibodies (TRAb). These antibodies could signal that you have a type of thyroiditis caused by autoimmune disease.
* Erythrocyte sedimentation rate (ESR or sed rate): This is a blood test that helps detect inflammation in your body. The ESR is high in subacute thyroiditis.
* C-reactive protein (CRP): This is a test that measures the level of c-reactive protein (CRP) in your blood. CRP increases when there's inflammation in your body, and it’s usually significantly elevated in acute infectious thyroiditis.
* Radioactive iodine uptake (RAIU) test: This test measures the amount of radioactive iodine (taken by mouth) that your thyroid gland absorbs. The amount is always low in the thyrotoxic phase of thyroiditis.

## **TREATMENT OPTIONS AND MANAGEMENT**

### **How is thyroiditis treated?**

The treatment for thyroiditis depends on the type and the symptoms.

#### **Thyrotoxicosis treatment for thyroiditis**

If you’re in the thyrotoxic phase of thyroiditis, your provider may prescribe beta-blockers to decrease palpitations (fast heart rate) and tremors.

As your symptoms improve, your provider will taper off the medication since the thyrotoxic phase is temporary.

#### **Hypothyroidism treatment for thyroiditis**

If you have Hashimoto’s thyroiditis, your provider will prescribe thyroid hormone replacement medication, such as levothyroxine. You’ll likely have to take this medication for the rest of your life since the hypothyroidism from Hashimoto’s thyroiditis is usually permanent.

If you have subacute, painless (silent) or postpartum thyroiditis and have hypothyroid symptoms, your provider will prescribe thyroid hormone replacement medication. You’ll likely have to take the medication for approximately six to 12 months and then taper off it to see if you have permanent hypothyroidism or not.

If the hypothyroidism is mild and you have few, if any, symptoms, then no medication may be necessary.

#### **Other treatments for thyroiditis**

If you have acute infectious thyroiditis, the infection will need to be treated. This will likely involve antibiotics. If an abscess forms on your thyroid, your provider may need to drain the fluid and pus with fine-needle aspiration (needle biopsy).

Drug-induced thyroiditis usually lasts as long as you’re taking the medication causing it. Your provider may switch you to a different but similar medication to treat the thyroiditis or they may prescribe levothyroxine (thyroid hormone medication) while you continue to take the medication causing thyroiditis.

The pain caused by acute infectious thyroiditis and subacute thyroiditis usually can be managed with nonsteroidal anti-inflammatory drugs (NSAIDs) such as aspirin or ibuprofen. In some cases, the pain can be severe and may require steroid therapy.

Riedel thyroiditis requires surgical treatment.

## **PREVENTION TIPS**

### **Can thyroiditis be prevented?**

Unfortunately, most cases of thyroiditis can’t be prevented.

If you have a condition that requires treatment using radioactive iodine or radiation therapy, talk to your healthcare provider about your risk of thyroiditis. You may be able to start with other treatments to avoid developing thyroiditis.

If you take prescription drugs that can cause thyroiditis, talk to your provider about your risk and if you can stop taking them. You still may not be able to avoid thyroiditis.

To prevent thyroiditis, it is important to focus on maintaining a healthy lifestyle and managing risk factors. While there is no guaranteed way to prevent thyroiditis, certain practices may help reduce the risk or manage its symptoms. Here are some prevention tips:

* **Maintain a healthy diet**: Eating a balanced diet rich in essential nutrients, including selenium, can support thyroid health. Selenium is particularly important for thyroid hormone metabolism and can be found in foods such as Brazil nuts, fish, and eggs. However, it is important to note that excessive selenium intake may pose risks, so it is advisable to consult a healthcare provider before taking supplements.
* **Exercise regularly**: Engaging in regular physical activity can help reduce inflammation and support overall health. The Physical Activity Guidelines for Americans recommend 150 minutes of moderate-intensity exercise per week, such as brisk walking, along with muscle-strengthening activities on two or more days.
* **Manage stress**: Chronic stress can affect the body's production of cortisol, which may interfere with thyroid function. Practicing stress-reduction techniques, such as meditation, yoga, or deep breathing, may help maintain hormonal balance.
* **Avoid excessive intake of goitrogens**: Goitrogens are substances found in certain foods, such as cruciferous vegetables (e.g., broccoli, cabbage, and kale), that can interfere with thyroid function if consumed in large amounts, especially in individuals with iodine deficiency. However, for most people, the benefits of these foods outweigh the risks, and they are generally safe in moderate amounts.
* **Limit exposure to environmental toxins**: Exposure to certain chemicals, such as perchlorates and fluoride, may affect thyroid function. It is advisable to be mindful of sources of these substances and, if necessary, consult a healthcare provider for guidance.
* **Monitor thyroid health**: Regular check-ups with a healthcare provider can help detect early signs of thyroid dysfunction. For individuals with a history of autoimmune conditions, such as Hashimoto's thyroiditis, regular monitoring of thyroid function is particularly important.
* **Avoid unnecessary radiation exposure**: Radiation exposure, particularly to the neck area, can increase the risk of thyroiditis. It is important to follow safety guidelines when undergoing medical procedures that involve radiation.
* **Be cautious with medications**: Some medications, such as amiodarone and lithium, can affect thyroid function. If you are taking these medications, it is important to monitor your thyroid health and discuss any concerns with your healthcare provider.

By adopting these lifestyle practices, individuals may reduce their risk of developing thyroiditis or manage its symptoms more effectively. However, it is always advisable to consult a healthcare provider for personalized recommendations.

**POSSIBLE COMPLICATIONS**

Thyroiditis can lead to several possible complications, depending on the type and severity of the condition. One of the most common complications is hypothyroidism, which may require long-term levothyroxine therapy in some cases. In subacute thyroiditis, there is a 5% possibility of developing permanent hypothyroidism. Additionally, acute infectious thyroiditis can result in complications such as an abscess, which requires immediate treatment with antibiotics and surgical drainage.

Thyroiditis can also cause transient or permanent hypo- or hyperthyroidism, and in some cases, patients may experience a triphasic sequence of hyperthyroidism followed by hypothyroidism and then euthyroidism. In rare cases, untreated or undertreated hyperthyroidism from thyroiditis can lead to a life-threatening condition called thyroid storm, characterized by high fever, rapid heart rate, and agitation.

Other complications may include difficulty swallowing or respiratory distress, particularly in cases of Riedel thyroiditis, which involves fibrosis of the thyroid gland. Patients with drug-induced thyroiditis may experience worsening hypothyroidism, especially if they have underlying conditions such as Hashimoto's thyroiditis or are pregnant.

## **OUTLOOK / PROGNOSIS**

### **What is the prognosis (outlook) for thyroiditis?**

The prognosis (outlook) for thyroiditis is generally good.

In the case of Hashimoto's thyroiditis, the resulting hypothyroidism is generally permanent, but it’s treatable with life-long thyroid hormone replacement therapy.

People who develop subacute thyroiditis usually have symptoms for one to three months, but complete recovery of thyroid function can take up to 12 to 18 months. These people have about a 5% chance of developing permanent hypothyroidism.

Full thyroid function recovery from postpartum and silent (painless) thyroiditis also takes about 12 to 18 months. People with these conditions have about a 20% chance of developing permanent hypothyroidism.

### **Who does thyroiditis affect?**

Thyroiditis can affect anyone, but it more commonly affects women.

Hashimoto’s thyroiditis is four to 10 times more common in women. It most often develops between the age of 30 to 50.

Silent or painless thyroiditis is also common in women and is the next common cause of thyroiditis after Hashimoto’s thyroiditis.

## **WHEN TO SEE A DOCTOR / RED FLAG**

### **When should I see my healthcare provider about thyroiditis?**

If you’ve been diagnosed with thyroiditis, you’ll need to see your healthcare provider regularly to monitor your symptoms and make sure your treatment is working.

If you develop worse or more concerning symptoms, call your provider as soon as possible.

## **EPIDEMIOLOGY**

### Frequency

*United States*

Studies in the United States and Western Europe report a prevalence of 1.2% in individuals aged 11-18 years. Approximately 25% of adults with type 1 diabetes have thyroiditis, about one half of whom have hypothyroidism. Approximately 10% of children with type 1 diabetes have antithyroid antibodies. Thirteen of 121 children with vitiligo were also found to have subsequent evidence of autoimmune thyroiditis. Similarly, a Korean study, by Bae et al, indicated that persons with vitiligo have an odds ratio for the autoimmune disease Hashimoto thyroiditis of 1.609.

The disease is also more common in children with Down syndrome or Turner syndrome. However, a study by Vassilatou et al indicated that the risk of autoimmune thyroiditis is not increased in psoriatic patients with or without psoriatic arthritis, finding the prevalence of autoimmune thyroiditis to be 20.2% in psoriatic patients (n = 114) and 19.6% in controls (n = 286). This contrasts with a study by Kiguradze et al, which reported an odds ratio of 2.49 for Hashimoto thyroiditis in persons with psoriasis.

Acute suppurative thyroiditis is rare in Western nations. Subacute thyroiditis is rare in childhood.

*International*

The prevalence of chronic autoimmune thyroiditis varies depending on screening procedures.

Chronic lymphocytic thyroiditis is the most common cause of hypothyroidism in the United States, and euthyroid persons with Hashimoto's disease develop hypothyroidism at a rate of approximately 5 percent per year. Up to 95 percent of cases of chronic lymphocytic thyroiditis occur in women, usually between 30 and 50 years of age. Chronic lymphocytic thyroiditis is also the most common cause of sporadic goiter in children. The incidence of Hashimoto's disease has risen exponentially over the past 50 years, and this increase may be related to an increased iodine content in the North American diet.

A genetic predisposition to thyroid auto-immunity exists; it is inherited as a dominant trait. Hashimoto's disease has been linked to other autoimmune diseases, including systemic lupus erythematosus, rheumatoid arthritis, pernicious anemia, diabetes mellitus and Sjögren's syndrome. A rare but serious complication of chronic autoimmune thyroiditis is thyroid lymphoma. These lymphomas, generally the B-cell, non-Hodgkin's type, tend to occur in women 50 to 80 years of age and are usually limited to the thyroid gland.

## **DIFFERENTIAL DIAGNOSIS**

* Hyperthyroidism and Thyrotoxicosis
* Hypothyroidism
* Pediatric Hyperthyroidism
* Pediatric Hypothyroidism
* Hashimoto’s thyroiditis (Chronic autoimmune thyroiditis)
* Silent (Painless) thyroiditis
* Postpartum thyroiditis
* Subacute thyroiditis (de Quervain’s thyroiditis, granulomatous thyroiditis)
* Acute (suppurative) infectious thyroiditis
* Radiation-induced thyroiditis
* Drug-induced thyroiditis (e.g., amiodarone, lithium, interferons, immune checkpoint inhibitors)
* Riedel’s thyroiditis (fibrous thyroiditis)
* Acute hemorrhage into thyroid cyst or nodule
* Thyroid nodules or malignancy (e.g., thyroid cancer)
* Tonsillitis or acute pharyngitis (mimicking thyroid pain)
* Trauma or palpation-induced thyroid pain
* Factitious thyrotoxicosis (exogenous thyroid hormone ingestion)
* Graves’ disease and toxic multinodular goiter (thyrotoxicosis with high radioactive iodine uptake, unlike thyroiditis)

**Not all patients you think have a large thyroid actually do.**

Overestimation of the size of the thyroid can result from:

* A more easily palpable thyroid in a thin patient with less overriding tissue
* A higher placed thyroid (normal variant)
* A long, curving neck that enhances prominence and palpation of the gland (Modigliani drawing)
* Lesion behind thyroid, pressing it forward
* Enlargement of adjacent structure, mistaken for thyroid

**Goiter: false negative**

**In some patients, you may miss detecting an enlarged thyroid.**

Underestimation of the size of the thyroid can result from:

* Inadequate physical examination (most common cause)
* Short thick neck in patients, seen most commonly in the obese, elderly or pts with COPD.
* Atypical placement of thyroid (retrosternal or lateral placement of lobes)

**Hypothyroidism**

Primary thyroid gland failure due to chronic autoimmune thyroiditis (Hashimoto's thyroiditis) is the most common cause of hypothyroidism. Other frequent causes are previous radioactive iodine therapy for hyperthyroidism and thyroid surgery. Subclinical hypothyroidism is most commonly due to autoimmune thyroiditis, or to inadequate replacement of hypothyroidism.

**Hypothyroidism**

The most common etiology of hyperthyroidism overall is Graves" Diseases, an immunologically mediated toxic goiter. The peak incidence is in patients in their 20's or 30's and is 5 times more likely in women than men. In the elderly, toxic nodular goiter (TNG) is more common than Graves' Disease. Other causes of hyperthyroidism include toxic adenoma, postpartum thyroiditis, subacute thyroiditis, and exogenous thyroid hormone ingestion.

Subacute thyroiditis is a self-limited disease of viral origin that often follows an URI. Transient postpartum thyroiditis, also a self-limited disease, occurs in approximately 5% of women in the first 3 to 6 months postpartum and increases the subsequent risk of developing primary hypothyroidism.

**Thyroid Cancer**

Thyroid cancer is rare (annual incidence of 0.004%) with low associated morbidity and mortality. In the US, there are 12,000 new cases of thyroid cancer and 1000 thyroid cancer related deaths annually. Almost all thyroid cancer (95%) presents as a thyroid nodule or neck mass.

**Type of Thyroid Cancers** (in order of decreasing frequency and increasing invasiveness)

* papillary (75%) - most common and least aggressive
* follicular (15%)
* medullary (5%)
* anaplastic (3%

*REFERENCES:*

[Thyroiditis Differential Diagnoses](https://emedicine.medscape.com/article/925249-differential?form=fpf)

[Thyroiditis: Types, Causes, Symptoms, Diagnosis & Treatment](https://my.clevelandclinic.org/health/diseases/15455-thyroiditis)

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[Thyroiditis Differential Diagnoses](https://emedicine.medscape.com/article/925249-differential?form=fpf)

**THYROID CANCER**

*ALTERNATIVE NAMES:* Thyroid cancer is also referred to by several alternative names based on the specific type of cells involved. The four main types of thyroid cancer include “**papillary thyroid cancer”, “follicular thyroid cancer”, “medullary thyroid cancer”, and “anaplastic thyroid cancer”**.

**DEFINITION / DESCRIPTION**

Thyroid cancer is a growth of cells that starts in the thyroid. The thyroid is a butterfly-shaped gland located at the base of the neck, just below Adam's apple. The thyroid produces hormones that regulate heart rate, blood pressure, body temperature and weight.

Thyroid cancer might not cause any symptoms at first. But as it grows, it can cause signs and symptoms, such as swelling in your neck, voice changes and difficulty swallowing.

Several types of thyroid cancer exist. Most types grow slowly, though some types can be very aggressive. Most thyroid cancers can be cured with treatment.

Thyroid cancer rates seem to be increasing. The increase may be caused by improved imaging technology that allows health care providers to find small thyroid cancers on CT and MRI scans done for other conditions (incidental thyroid cancers). Thyroid cancers found in this way are usually small cancers that respond well to treatments.

**CAUSES**

Thyroid cancer happens when cells in the thyroid develop changes in their DNA. A cell's DNA contains the instructions that tell the cell what to do. The changes, which doctors call mutations, tell the cells to grow and multiply rapidly. The cells go on living when healthy cells would naturally die. The accumulating cells form a mass called a tumor.

The tumor can grow to invade nearby tissue and can spread (metastasize) to the lymph nodes in the neck. Sometimes the cancer cells can spread beyond the neck to the lungs, bones and other parts of the body.

For most thyroid cancers, it's not clear what causes the DNA changes that cause the cancer.

### **Types of thyroid cancer**

Thyroid cancer is classified into types based on the kinds of cells found in the tumor. Your type is determined when a sample of tissue from your cancer is examined under a microscope. The type of thyroid cancer is considered in determining your treatment and prognosis.

Types of thyroid cancer include:

* **Differentiated thyroid cancers.** This broad category includes types of thyroid cancer that start in the cells that produce and store thyroid hormones. These cells are called follicular cells. Differentiated thyroid cancer cells appear similar to healthy cells when viewed under a microscope.
  + **Papillary thyroid cancer.** This is the most common type of thyroid cancer. It can happen at any age, but it most often affects people ages 30 to 50. Most papillary thyroid cancers are small and respond well to treatment, even if the cancer cells spread to the lymph nodes in the neck. A small portion of papillary thyroid cancers are aggressive and may grow to involve structures in the neck or spread to other areas of the body.
  + **Follicular thyroid cancer.** This rare type of thyroid cancer usually affects people older than 50. Follicular thyroid cancer cells don't often spread to the lymph nodes in the neck. But some large and aggressive cancers may spread to other parts of the body. Follicular thyroid cancer most often spreads to the lungs and bones.
  + **Hurthle cell thyroid cancer.** This rare type of thyroid cancer was once considered a type of follicular thyroid cancer. Now it is considered its own type because the cancer cells behave differently and respond to different treatments. Hurthle cell thyroid cancers are aggressive and can grow to involve structures in the neck and spread to other parts of the body.
  + **Poorly differentiated thyroid cancer.** This rare type of thyroid cancer is more aggressive than other differentiated thyroid cancers and often doesn't respond to the usual treatments.
* **Anaplastic thyroid cancer.** This rare type of thyroid cancer grows quickly and can be difficult to treat. However, treatments can help slow the progression of the disease. Anaplastic thyroid cancer tends to occur in people older than 60. It can cause severe signs and symptoms, such as neck swelling that worsens very quickly and may lead to difficulty breathing and swallowing.
* **Medullary thyroid cancer.** This rare type of thyroid cancer begins in thyroid cells called C cells, which produce the hormone calcitonin. Elevated levels of calcitonin in the blood can indicate medullary thyroid cancer at a very early stage. Some medullary thyroid cancers are caused by a gene called *RET* that's passed from parents to children. Changes in the *RET* gene can cause familial medullary thyroid cancer and multiple endocrine neoplasia, type 2. Familial medullary thyroid cancer increases the risk of thyroid cancer. Multiple endocrine neoplasia, type 2, increases the risk of thyroid cancer, adrenal gland cancer and other types of cancers.
* **Other rare types.** Other very rare types of cancer can start in the thyroid. These include thyroid lymphoma, which begins in the immune system cells of the thyroid, and thyroid sarcoma, which begins in the connective tissue cells of the thyroid.

**RISK FACTORS**

Factors that may increase the risk of thyroid cancer include:

* **Female sex.** Thyroid cancer occurs more often in women than in men. Experts think it may be related to the hormone estrogen. People who are assigned female sex at birth generally have higher levels of estrogen in their bodies.
* **Exposure to high levels of radiation.** Radiation therapy treatments to the head and neck increase the risk of thyroid cancer.
* **Certain inherited genetic syndromes.** Genetic syndromes that increase the risk of thyroid cancer include familial medullary thyroid cancer, multiple endocrine neoplasia, Cowden syndrome and familial adenomatous polyposis. Types of thyroid cancer that sometimes run in families include medullary thyroid cancer and papillary thyroid cancer.
* Between the ages of 25 and 65
* Exposed to radiation in the head or neck area
* Women (females are three times more likely than men to be diagnosed with this type of cancer.

**SIGNS / SYMPTOMS**

Most thyroid cancers don't cause any signs or symptoms early in the disease. As thyroid cancer grows, it may cause:

## A lump (nodule) that can be felt through the skin on your neck

## A feeling that close-fitting shirt collars are becoming too tight

## Changes to your voice, including increasing hoarseness

## Difficulty swallowing

## Swollen lymph nodes in your neck

## Pain in your neck and throat

The signs of thyroid cancer may include **a lump or swelling in the neck**, which is often painless and may grow over time. Other symptoms can include a hoarse voice, difficulty swallowing, and a sore throat. It is important to note that these symptoms can also be caused by non-cancerous conditions. In many cases, thyroid cancer does not cause symptoms in the early stages and is often discovered during a routine examination or imaging scans. If any of these symptoms are present, it is advisable to consult a doctor for further evaluation.

**Early signs and symptoms of thyroid cancer**

Although thyroid cancer may not cause symptoms until it's advanced, it's important to know that early signs may develop, including those listed below.

*Swollen lump on neck*

The most common early sign of thyroid cancer is an unusual lump, nodule or swelling in the neck. Patients who notice a new or growing lump should see a doctor, who can run additional tests to identify the cause and determine if it's a tumor. Most nodules on the thyroid are usually benign, but it's important to have any unusual growths examined by a health care professional.

***Fatigue***

Fatigue is a relatively common early sign of thyroid cancer, but because it's often caused by other conditions as well, it may be overlooked.

***Swollen glands in the neck***

If the thyroid cancer has spread to nearby lymph nodes, it may cause swelling in the lymph nodes in the neck.

***A persistent cough***

In some cases, thyroid cancer may cause nodules to grow on the thyroid, irritating the throat and causing a cough that won't subside, even after a cold or illness has passed.

***Neck pain***

In many cases, neck pain starts in the front of the neck. In some cases, the neck pain may extend all the way to the ears.

***Voice changes***

Experiencing hoarseness or other voice changes that do not go away could be a sign of thyroid cancer.

***Breathing problems***

Sometimes thyroid cancer patients say it feels like they are breathing through a straw. This breathing difficulty is often a symptom of the disease.

***Trouble swallowing***

A growth or nodule on the thyroid gland may interfere with swallowing.

**Recurrent thyroid cancer symptoms**

It may be possible for thyroid cancer to return after treatment, so it's important to look for any indication of recurrence. Signs and symptoms of thyroid cancer recurrence may include:

* Neck swelling or a lump in the neck that may grow rapidly
* Neck pain that starts in the front of the neck and sometimes extends to the ears
* Trouble breathing or swallowing
* Voice changes or hoarseness
* Continuous cough not related to a cold

Early thyroid cancer recurrence symptoms may not be apparent, so regular screenings and follow-up appointments are strongly recommended. At the follow-up appointments, the patient may undergo a physical exam, blood tests or imaging tests, such as radioiodine scans or ultrasounds. These tests are designed to screen for cancer recurrence and other health concerns. Make sure to discuss with the doctor any symptoms the patient may be experiencing. The timing and frequency of recommended follow-up appointments depend on many factors, including the stage and size of the original tumor.

**DIAGNOSIS METHODS**

Tests and procedures used to diagnose thyroid cancer include:

## Physical exam. Your health care provider will examine your neck to feel for changes in your thyroid, such as a lump (nodule) in the thyroid. The provider may also ask about your risk factors, such as past exposure to radiation and a family history of thyroid cancers.

## Thyroid function blood tests. Tests that measure blood levels of thyroid-stimulating hormone (TSH) and hormones produced by your thyroid gland might give your health care team clues about the health of your thyroid.

## Ultrasound imaging. Ultrasound uses high-frequency sound waves to create pictures of body structures. To create an image of the thyroid, the ultrasound transducer is placed on your lower neck. The way a thyroid nodule looks on an ultrasound image helps your provider determine if it's likely to be cancer. Signs that a thyroid nodule is more likely to be cancerous include calcium deposits (microcalcifications) within the nodule and an irregular border around the nodule. If there's a high likelihood that a nodule might be cancerous, additional tests are needed to confirm the diagnosis and determine what type of thyroid cancer is present. Your provider may also use ultrasound to create images of the lymph nodes in the neck (lymph node mapping) to look for signs of cancer.

## Removing a sample of thyroid tissue. During a fine-needle aspiration biopsy, your provider inserts a long, thin needle through your skin and into the thyroid nodule. Ultrasound imaging is typically used to precisely guide the needle. Your provider uses the needle to remove some cells from the thyroid. The sample is sent to a lab for analysis. In the lab, a doctor who specializes in analyzing blood and body tissue (pathologist) examines the tissue sample under a microscope and determines whether cancer is present. The results aren't always clear. Some types of thyroid cancer, particularly follicular thyroid cancer and Hurthle cell thyroid cancer, are more likely to have uncertain results (indeterminate thyroid nodules). Your provider may recommend another biopsy procedure or an operation to remove the thyroid nodule for testing. Specialized tests of the cells to look for gene changes (molecular marker testing) also can be helpful.

## An imaging test that uses a radioactive tracer. A radioactive iodine scan uses a radioactive form of iodine and a special camera to detect thyroid cancer cells in your body. It's most often used after surgery to find any cancer cells that might remain. This test is most helpful for papillary and follicular thyroid cancers. Healthy thyroid cells absorb and use iodine from the blood. Some types of thyroid cancer cells do this, too. When the radioactive iodine is injected in a vein or swallowed, any thyroid cancer cells in the body will take up the iodine. Any cells that take up the iodine are shown on the radioactive iodine scan images.

## Other imaging tests. You may have one or more imaging tests to help your provider determine whether your cancer has spread beyond the thyroid. Imaging tests may include ultrasound, CT and MRI.

## Genetic testing. A portion of medullary thyroid cancers are caused by inherited genes that are passed from parents to children. If you're diagnosed with medullary thyroid cancer, your provider may recommend meeting with a genetic counselor to consider genetic testing. Knowing that you have an inherited gene can help you understand your risk of other types of cancer and what your inherited gene may mean for your children.

## Thyroid cancer staging

## Your health care team uses information from your tests and procedures to determine the extent of the cancer and assign it a stage. Your cancer's stage tells your care team about your prognosis and helps them select the treatment that's most likely to help you.

## Cancer stage is indicated with a number between 1 and 4. A lower number usually means the cancer is likely to respond to treatment, and it often means the cancer only involves the thyroid. A higher number means the diagnosis is more serious, and the cancer may have spread beyond the thyroid to other parts of the body.

## Different types of thyroid cancer have different sets of stages. For instance, medullary and anaplastic thyroid cancers each have their own set of stages. Differentiated thyroid cancer types, including papillary, follicular, Hurthle cell and poorly differentiated, share a set of stages. For differentiated thyroid cancers, your stage may vary based on your age.

## **TREATMENT OPTIONS**

## Your thyroid cancer treatment options depend on the type and stage of your thyroid cancer, your overall health, and your preferences.

## Most people diagnosed with thyroid cancer have an excellent prognosis, as most thyroid cancers can be cured with treatment.

## **Treatment may not be needed right away**

## Treatment might not be needed right away for very small papillary thyroid cancers (papillary microcarcinomas) because these cancers have a low risk of growing or spreading. As an alternative to surgery or other treatments, you might consider active surveillance with frequent monitoring of the cancer. Your health care provider might recommend blood tests and an ultrasound exam of your neck once or twice a year.

## In some people, the cancer might never grow and never require treatment. In others, growth may eventually be detected and treatment can begin.

## **Surgery**

## Most people with thyroid cancer that requires treatment will undergo surgery to remove part or all of the thyroid. Which operation your health care team might recommend depends on your type of thyroid cancer, the size of the cancer and whether the cancer has spread beyond the thyroid to the lymph nodes. Your care team also considers your preferences when creating a treatment plan.

## **Operations used to treat thyroid cancer include:**

## Removing all or most of the thyroid (thyroidectomy). An operation to remove the thyroid gland might involve removing all of the thyroid tissue (total thyroidectomy) or most of the thyroid tissue (near-total thyroidectomy). The surgeon often leaves small rims of thyroid tissue around the parathyroid glands to reduce the risk of damage to the parathyroid glands, which help regulate the calcium levels in your blood.

## Removing a portion of the thyroid (thyroid lobectomy). During a thyroid lobectomy, the surgeon removes half of the thyroid. Lobectomy might be recommended if you have a slow-growing thyroid cancer in one part of the thyroid, no suspicious nodules in other areas of the thyroid and no signs of cancer in the lymph nodes.

## Removing lymph nodes in the neck (lymph node dissection). Thyroid cancer often spreads to nearby lymph nodes in the neck. An ultrasound examination of the neck before surgery may reveal signs that cancer cells have spread to the lymph nodes. If so, the surgeon may remove some of the lymph nodes in the neck for testing.

## To access the thyroid, surgeons usually make a cut (incision) in the lower part of the neck. The size of the incision depends on your situation, such as the type of operation and the size of your thyroid gland. Surgeons usually try to place the incision in a skinfold where it will be difficult to see as it heals and becomes a scar.

## Thyroid surgery carries a risk of bleeding and infection. Damage to your parathyroid glands also can occur during surgery, which can lead to low calcium levels in your body.

## There's also a risk that the nerves connected to your vocal cords might not work as expected after surgery, which can cause hoarseness and voice changes. Treatment can improve or reverse nerve problems.

## After surgery, you can expect some pain as your body heals. How long it takes to recover will depend on your situation and the type of surgery you had. Most people start to feel recovered in 10 to 14 days. Some restrictions on your activity might continue. For instance, your surgeon might recommend staying away from strenuous activity for a few more weeks.

## After surgery to remove all or most of the thyroid, you might have blood tests to see if all of the thyroid cancer has been removed. Tests might measure:

## Thyroglobulin — a protein made by healthy thyroid cells and differentiated thyroid cancer cells

## Calcitonin — a hormone made by medullary thyroid cancer cells

## Carcinoembryonic antigen — a chemical produced by medullary thyroid cancer cells

## These blood tests are also used to look for signs of cancer recurrence.

### **Thyroid hormone therapy**

## Thyroid hormone therapy is a treatment to replace or supplement the hormones produced in the thyroid. Thyroid hormone therapy medication is usually taken in pill form. It can be used to:

## Replace thyroid hormones after surgery. If your thyroid is removed completely, you'll need to take thyroid hormones for the rest of your life to replace the hormones your thyroid made before your operation. This treatment replaces your natural hormones, so there shouldn't be any side effects once your health care team finds the dose that's right for you. You might also need thyroid hormone replacement after having surgery to remove part of the thyroid, but not everyone does. If your thyroid hormones are too low after surgery (hypothyroidism), your health care team might recommend thyroid hormones.

## Suppress the growth of thyroid cancer cells. Higher doses of thyroid hormone therapy can suppress the production of thyroid-stimulating hormone (TSH) from your brain's pituitary gland. TSH can cause thyroid cancer cells to grow. High doses of thyroid hormone therapy might be recommended for aggressive thyroid cancers.

### **Radioactive iodine**

## Radioactive iodine treatment uses a form of iodine that's radioactive to kill thyroid cells and thyroid cancer cells that might remain after surgery. It's most often used to treat differentiated thyroid cancers that have a risk of spreading to other parts of the body.

## You might have a test to see if your cancer is likely to be helped by radioactive iodine, since not all types of thyroid cancer respond to this treatment. Differentiated thyroid cancer types, including papillary, follicular and Hurthle cell, are more likely to respond. Anaplastic and medullary thyroid cancers usually aren't treated with radioactive iodine.

## Radioactive iodine treatment comes as a capsule or liquid that you swallow. The radioactive iodine is taken up primarily by thyroid cells and thyroid cancer cells, so there's a low risk of harming other cells in your body.

## The side effect you experience will depend on the dose of radioactive iodine you receive. Higher doses may cause:

## Dry mouth

## Mouth pain

## Eye inflammation

## Altered sense of taste or smell

## Most of the radioactive iodine leaves your body in your urine in the first few days after treatment. You'll be given instructions for precautions you need to take during that time to protect other people from the radiation. For instance, you may be asked to temporarily avoid close contact with other people, especially children and pregnant women.

### **Injecting alcohol into cancers**

## Alcohol ablation, which is also called ethanol ablation, involves using a needle to inject alcohol into small areas of thyroid cancer. Ultrasound imaging is used to precisely guide the needle. The alcohol causes the thyroid cancer cells to shrink.

## Alcohol ablation may be an option to treat small areas of thyroid cancer, such as cancer that's found in a lymph node after surgery. Sometimes it's an option if you aren't healthy enough for surgery.

### **Treatments for advanced thyroid cancers**

## Aggressive thyroid cancers that grow more quickly may require additional treatment options to control the disease. Options might include:

## Targeted drug therapy. Targeted drug treatments focus on specific chemicals present within cancer cells. By blocking these chemicals, targeted drug treatments can cause cancer cells to die. Some of these treatments come in pill form and some are given through a vein. There are many different targeted therapy drugs for thyroid cancer. Some target the blood vessels that cancer cells make to bring nutrients that help the cells survive. Other drugs target specific gene changes. Your provider may recommend special tests of your cancer cells to see which treatments might help. Side effects will depend on the specific drug you take.

## Radiation therapy. External beam radiation uses a machine that aims high-energy beams, such as X-rays and protons, to precise points on your body to kill cancer cells. Radiation therapy might be recommended if your cancer doesn't respond to other treatments or if it comes back. Radiation therapy can help control pain caused by cancer that spreads to the bones. Radiation therapy side effects depend on where the radiation is aimed. If it's aimed at the neck, side effects might include a sunburn-like reaction on the skin, a cough and painful swallowing.

## Chemotherapy. Chemotherapy is a drug treatment that uses chemicals to kill cancer cells. There are many different chemotherapy drugs that can be used alone or in combination. Some come in pill form, but most are given through a vein. Chemotherapy may help control fast-growing thyroid cancers, such as anaplastic thyroid cancer. In certain situations, chemotherapy might be used for other types of thyroid cancer. Sometimes chemotherapy is combined with radiation therapy. Chemotherapy side effects depend on the specific drugs you receive.

## Destroying cancer cells with heat and cold. Thyroid cancer cells that spread to the lungs, liver and bones can be treated with heat and cold to kill the cancer cells. Radiofrequency ablation uses electrical energy to heat up cancer cells, causing them to die. Cryoablation uses a gas to freeze and kill cancer cells. These treatments can help control small areas of cancer cells.

### **Supportive (palliative) care**

## Palliative care is specialized medical care that focuses on providing relief from pain and other symptoms of a serious illness. Palliative care specialists work with you, your family and your health care team to provide an extra layer of support that complements your ongoing care.

## Palliative care can be used while undergoing other aggressive treatments, such as surgery, chemotherapy or radiation therapy. Increasingly, palliative care is being offered early in the course of cancer treatment.

## When palliative care is used along with all of the other appropriate treatments, people with cancer may feel better, have a better quality of life and live longer.

## Palliative care is provided by a team of doctors, nurses and other specially trained professionals. Palliative care teams aim to improve quality of life for people with cancer and their families.

### *Follow-up tests for thyroid cancer survivors*

## After your thyroid cancer treatment ends, your provider may recommend follow-up tests and procedures to look for signs that your cancer has returned. You may have follow-up appointments once or twice a year for several years after treatment ends.

## Which tests you need will depend on your situation. Follow-up tests may include:

## Physical exam of your neck

## Blood tests

## Ultrasound exam of your neck

## Other imaging tests, such as CT and MRI

## **POSSIBLE COMPLICATIONS**

### **Thyroid cancer that comes back**

Thyroid cancer can return despite successful treatment, and it can even come back if you've had your thyroid removed. This could happen if cancer cells spread beyond the thyroid before it's removed.

Most thyroid cancers aren't likely to recur, including the most common types of thyroid cancer — papillary thyroid cancer and follicular thyroid cancer. Your health care provider can tell you if your cancer has an increased risk of recurring based on the particulars of your cancer.

Recurrence is more likely if your cancer is aggressive or if it grows beyond your thyroid. When thyroid cancer recurrence happens, it's usually found in the first five years after your initial diagnosis.

Thyroid cancer that comes back still has a good prognosis. It's often treatable, and most people will have successful treatment.

Thyroid cancer may recur in:

* Lymph nodes in the neck
* Small pieces of thyroid tissue left behind during surgery
* Other areas of the body, such as the lungs and bones

Your health care provider may recommend periodic blood tests or thyroid scans to check for signs that your cancer has returned. At these appointments, your provider may ask if you've experienced any signs and symptoms of thyroid cancer recurrence, such as:

* Neck pain
* A lump in the neck
* Trouble swallowing
* Voice changes, such as hoarseness

### **Thyroid cancer that spreads (metastasizes)**

Thyroid cancer sometimes spreads to nearby lymph nodes or to other parts of the body. The cancer cells that spread might be found when you're first diagnosed or they might be found after treatment. The great majority of thyroid cancers don't ever spread.

When thyroid cancer spreads, it most often travels to:

* Lymph nodes in the neck
* Lungs
* Bones
* Brain
* Liver
* Skin

Thyroid cancer that spreads might be detected on imaging tests, such as CT and MRI, when you're first diagnosed with thyroid cancer. After successful treatment, your health care provider might recommend follow-up appointments to look for signs that your thyroid cancer has spread. These appointments might include nuclear imaging scans that use a radioactive form of iodine and a special camera to detect thyroid cancer cells.

**What are the complications of thyroid cancer?**

Thyroid cancer can spread (metastasize) to other parts of your body, such as your liver, lungs or bones. Detecting and treating thyroid cancer in the early stages reduces your risk for metastasis.

Thyroid cancer can recur (come back), even after treatment. Because thyroid cancer grows slowly, it could take up to 20 years to come back. Recurrence happens in up to 30% of thyroid cancer cases.

Overall, thyroid cancer prognosis (outlook) is positive. But it’s important to know that after thyroid surgery or treatments, your body still needs thyroid hormones to function. You’ll need thyroid hormone replacement therapy for life. Synthetic thyroid hormones, such as levothyroxine (Synthroid®), take over for the thyroid hormones that your body no longer naturally produces.

**How does thyroid cancer affect pregnancy?**

Thyroid cancer is the second most common cancer diagnosed in pregnancy (breast cancer is the first). Approximately 10% of thyroid cancers develop during pregnancy or within the first year after childbirth. Experts believe fluctuating hormone levels during pregnancy may trigger the cancer.

If you receive a thyroid cancer diagnosis during pregnancy, your healthcare provider can discuss treatment options. Depending on the cancer type and severity, your provider may recommend delaying treatment until after you deliver your baby. If treatment can’t wait, most people can safely undergo surgery to remove the cancerous gland. You shouldn’t have radioactive diagnostic tests or treatments when you’re pregnant or breastfeeding.

**PREVENTION TIPS**

Doctors aren't sure what causes the gene changes that lead to most thyroid cancers, so there's no way to prevent thyroid cancer in people who have an average risk of the disease.

### **Prevention for people with a high risk**

Adults and children with an inherited gene that increases the risk of medullary thyroid cancer may consider thyroid surgery to prevent cancer (prophylactic thyroidectomy). Discuss your options with a genetic counselor who can explain your risk of thyroid cancer and your treatment options.

### **Prevention for people near nuclear power plants**

A medication that blocks the effects of radiation on the thyroid is sometimes provided to people living near nuclear power plants in the United States. The medication (potassium iodide) could be used in the unlikely event of a nuclear reactor accident. If you live within 10 miles of a nuclear power plant and are concerned about safety precautions, contact your state or local emergency management department for more information.

**Can I prevent thyroid cancer?**

Many people develop thyroid cancer for no known reason, so prevention isn’t really possible. But if you know you’re at risk for thyroid cancer, you may be able to take steps to prevent it. These include:

* **Preventive (prophylactic) surgery:** Genetic tests can determine if you carry an altered gene (a mutation) that increases your risk for medullary thyroid cancer or multiple endocrine neoplasia. If you have the faulty gene, you may opt to have preventive (prophylactic) surgery to remove your thyroid gland before cancer develops.
* **Potassium iodide:** If you’ve had radiation exposure during a nuclear disaster, such as the 2011 incident at Fukushima, Japan, taking potassium iodide within 24 hours of exposure can lower your risk of eventually getting thyroid cancer. Potassium iodide (Pima®) blocks your thyroid gland from absorbing too much radioiodine. As a result, your gland stays healthy.

**OUTLOOK / PROGNOSIS**

**Certain factors affect prognosis (chance of recovery) and treatment options.**

The prognosis and treatment options depend on the following:

* The age of the patient at the time of diagnosis.
* The type of thyroid cancer.
* The stage of the cancer.
* Whether the cancer was completely removed by surgery.
* Whether the patient has multiple endocrine neoplasia type 2B (MEN 2B).
* The patient's general health.
* Whether the cancer has just been diagnosed or has recurred (come back).

**What’s the thyroid cancer survival rate?**

Eight out of 10 people who have thyroid cancer develop the papillary type. Papillary thyroid cancer has a five-year survival rate of almost 100% when the cancer is in their gland (localized). Even when the cancer spreads (metastasizes), the survival rate is close to 80%. This rate means that, on average, you’re about 80% as likely to live for at least five years after diagnosis as someone who doesn’t have metastatic papillary thyroid cancer.

Five-year survival rates for other thyroid cancer types include:

* **Follicular:** Close to 100% for localized; around 63% for metastasized.
* **Medullary:** Close to 100% for localized; around 40% for metastasized.
* **Anaplastic:** Close to 31% for localized; 4% for metastasized.

**Is thyroid cancer curable?**

Yes, most thyroid cancers are curable with treatment, especially if the cancer cells haven’t spread to distant parts of your body. If treatment doesn’t fully cure thyroid cancer, your healthcare provider can design a treatment plan to destroy as much of the tumor as possible and prevent it from growing back or spreading.

**WHEN TO SEE A DOCTOR / RED FLAG**

If you experience any signs or symptoms that worry you, make an appointment with your healthcare provider.

**When should I see my healthcare provider?**

You should call your healthcare provider if you have thyroid cancer and you experience:

* A new lump in your neck.
* Rapid heart rate.
* Unexplained weight loss or gain.
* Extreme fatigue.

**What questions should I ask my doctor?**

If you have thyroid cancer, you may want to ask your healthcare provider:

* Why did I get thyroid cancer?
* What type of thyroid cancer do I have?
* Has the cancer spread outside of my thyroid gland?
* What’s the best treatment for this type of thyroid cancer?
* What are the treatment risks and side effects?
* Will I need thyroid replacement hormone therapy?
* Is my family at risk for developing this type of thyroid cancer? If so, should we get genetic tests?
* Can I get thyroid cancer again?
* Am I at risk for other types of cancer?
* What type of follow-up care do I need after treatment?
* Should I look out for signs of complications?

**DIFFERENTIAL DIAGNOSIS**

Papillary thyroid cancer must be differentiated from other diseases that cause neck mass, such as branchial cleft cyst, thyroglossal duct cyst, cystic metastasis, and multiple neurofibromas.

For example, follicular thyroid cancer presents as a solid hypoechoic nodule with a peripheral halo indicating a fibrous capsule, while medullary thyroid cancer may present with systemic symptoms due to hormonal secretion by the tumor. Anaplastic thyroid cancer is characterized by a rapidly enlarging thyroid mass and an infiltrative pattern on microscopy.

Follicular adenoma is typically a solitary, spherical, and encapsulated lesion, while multinodular goiter involves multiple nodules with variable sized follicles. Thyroid lymphoma may present as a rapidly enlarging mass with a hypoechogenic appearance and is often associated with preexisting chronic autoimmune thyroiditis.

Additionally, papillary thyroid cancer must be distinguished from other thyroid cancers as well as other disorders such as Hashimoto's thyroiditis and thyroid lymphoma. The differential diagnosis of thyroid cancer also includes considering other types of thyroid malignancies, such as follicular thyroid cancer, medullary thyroid cancer, and anaplastic thyroid cancer.

**EPIDEMIOLOGY**

Close to 53,000 Americans receive a thyroid cancer diagnosis every year. Treatments for most thyroid cancers are very successful. Still, about 2,000 people die from the disease every year.

Women are three times more likely to get thyroid cancer compared to men. The disease is commonly diagnosed in women in their 40s and 50s and men in their 60s and 70s. Even children can develop the disease.

Studies from a few of the countries with detailed registries show that almost the entire increase in incidence has been due to increased diagnosis of papillary thyroid cancer. The size of the cancers that are now being detected is also notable: most of the increase in incidence has come from the detection of papillary thyroid cancers less than or equal to 2 cm in diameter. Given that cancers of this size are usually difficult to detect through physical examination (palpation), the increased incidence of these small cancers is most likely to be due to increased use of sensitive imaging technologies. The implicated technologies include ultrasonography and cross-sectional imaging that includes the neck, which is driven largely by practice patterns of health-care providers.

Recent studies have shown that a large fraction of thyroid cancer diagnoses in high-income countries are likely to be due to the diagnosis of lesions of no clinical significance. In women, this fraction could be as high as 70–80% in Australia, France, Italy, and the USA and 90% in the Republic of Korea. In men, the estimated fraction is 70% in France, Italy, and the Republic of Korea and 45% in Australia and the USA.

During the same period, thyroid cancer mortality rates have not increased proportionally. This pattern of dramatically increasing incidence of thyroid cancer worldwide, particularly of small papillary thyroid cancers, with largely stable mortality rates suggests that the main cause is the diagnosis of lesions that pose no significant risk to the person. For overdiagnosis to occur, three factors must be present: (i) subclinical disease that is detectable by the screening test, (ii) a mechanism by which the tumours can be identified, and (iii) health-care activities that lead to the detection. The necessary components for overdiagnosis of thyroid cancer are all present, as explained below.

Thyroid cancer is a disease that is readily detected subclinically. Papillary thyroid cancer is commonly found at autopsy in people who died of other causes. Depending on the method of examination of the thyroid, about 4% (partial examination) to 11% (whole examination) of thyroid glands can be shown to contain differentiated thyroid cancer, and this rate has been stable over time. The high prevalence at autopsy explains the increasing identification of these smaller tumours.

The mechanism is increasingly sensitive to imaging studies. Asymptomatic thyroid nodules are very common and are easily seen on medical imaging studies: up to 16% of computed tomography (CT) scans and magnetic resonance imaging (MRI) scans that include the thyroid gland show thyroid nodules, and with ultrasonography about two thirds of people will be found to have at least one nodule

**How common is thyroid cancer recurrence?**

Up to 30 percent of thyroid cancer patients may develop cancer recurrence. Of these patients, an estimated 80 percent develop thyroid cancer recurrence only in the neck area. The other 20 percent diagnosed with recurrent disease develop distant metastases, tumors that form in other areas of the body, such as the lungs, liver and bone. A number of thyroid cancer treatment options are available for primary and recurrent thyroid cancer, but early detection is key.

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**HYPERTHYROIDISM**

*ALTERNATIVE NAMES:* Hyperthyroidism is also known as “overactive thyroid”, or “hyperthyreosis”.

**DEFINITION / DESCRIPTION**

Hyperthyroidism, which is also called overactive thyroid, is a condition that occurs when the thyroid gland makes too much thyroid hormone, which is usually more than the body needs. This condition also is called ***“overactive thyroid”.*** Hyperthyroidism speeds up the body's metabolism. That can cause many symptoms, such as weight loss, hand tremors, and rapid or irregular heartbeat.

Several treatments are available for hyperthyroidism. Anti-thyroid medicines and radioiodine can be used to slow the number of hormones the thyroid gland makes. Sometimes, hyperthyroidism treatment includes surgery to remove all or part of the thyroid gland. In some cases, depending on what's causing it, hyperthyroidism may improve without medication or other treatment.

. Thyroid hormones control the way the body uses energy, so they affect nearly every organ in your body, even the way your heart beats. With too much thyroid hormone, many of your body’s functions speed up.

**CAUSES**

Hyperthyroidism can be caused by several medical conditions that affect the thyroid gland. The thyroid is a small, butterfly-shaped gland at the base of the neck. It has a big impact on the body. Every part of metabolism is controlled by hormones that the thyroid gland makes.

The thyroid gland produces two main hormones: thyroxine (T-4) and triiodothyronine (T-3). These hormones affect every cell in the body. They support the rate at which the body uses fats and carbohydrates. They help control body temperature. They have an effect on heart rate. And they help control how much protein the body makes.

Hyperthyroidism happens when the thyroid gland puts too much of those thyroid hormones into the bloodstream. Conditions that can lead to hyperthyroidism include:

* **Graves' disease.** Graves' disease is an autoimmune disorder that causes the immune system to attack the thyroid gland. That prompts the thyroid to make too much thyroid hormone. Graves' disease is the most common cause of hyperthyroidism.
* **Overactive thyroid nodules.** This condition also is called toxic adenoma, toxic multinodular goiter and Plummer disease. This form of hyperthyroidism happens when a thyroid adenoma makes too much thyroid hormone. An adenoma is a part of the gland that is walled off from the rest of the gland. It forms noncancerous lumps that can make the thyroid bigger than usual.
* **Thyroiditis.** This condition happens when the thyroid gland becomes inflamed. In some cases, it's due to an autoimmune disorder. In others, the reason for it is unclear. The inflammation can cause extra thyroid hormone stored in the thyroid gland to leak into the bloodstream and cause symptoms of hyperthyroidism.
* **Thyroid nodules,** which are growths on your thyroid. They are usually benign (not cancer). But they may become overactive and make too much thyroid hormone. Thyroid nodules are more common in older adults.
* **Thyroiditis,** inflammation of the thyroid. It causes stored thyroid hormone to leak out of your thyroid gland.
* Too much iodine. Iodine is found in some medicines, cough syrups, seaweed and seaweed-based supplements. Taking too much of them can cause your thyroid to make too much thyroid hormone.
* **Too much thyroid medicine.** This can happen if people who take thyroid hormone medicine for hypothyroidism (underactive thyroid) take too much of it.

**Graves’ disease**

Graves’ disease, the most common cause of hyperthyroidism, is an autoimmune disorder. With this disease, your immune system attacks the thyroid and causes it to make too much thyroid hormone.

**Overactive thyroid nodules**

Overactive thyroid nodules, or lumps in your thyroid, are common and usually not cancerous. However, one or more nodules may become overactive and produce too much thyroid hormone. Overactive nodules are found most often in older adults.

**Thyroiditis**

Thyroiditis is inflammation of your thyroid gland. Some types of thyroiditis can cause thyroid hormone to leak out of your thyroid gland into your bloodstream. As a result, you may develop symptoms of hyperthyroidism.

The types of thyroiditis that can cause hyperthyroidism include

* subacute thyroiditis, which involves a painfully inflamed and enlarged thyroid.
* postpartum thyroiditis, which can develop after a woman gives birth.
* painless thyroiditis, which is similar to postpartum thyroiditis, but occurs in the absence of pregnancy. Your thyroid may be enlarged. Experts think painless thyroiditis is probably an autoimmune condition.

Thyroiditis can also cause symptoms of hypothyroidism, or underactive thyroid. In some cases, after your thyroid is overactive for a period of time, it may become underactive.

**Too much iodine**

Your thyroid uses iodine to make thyroid hormone. How much iodine you consume affects how much thyroid hormone your thyroid makes. In some people, consuming large amounts of iodine may cause the thyroid to make too much thyroid hormone.

Some cough syrups and medicines, including some heart medicines, may contain a lot of iodine. Seaweed and seaweed-based supplements also contain a lot of iodine.

**Too much thyroid hormone medicine**

Some people who take thyroid hormone medicine for hypothyroidism may take too much. If you take thyroid hormone medicine, see your doctor at least once a year to have your thyroid hormone levels checked. You may need to adjust your dose if your doctor finds your thyroid hormone level is too high.

Some other medicines may also interact with thyroid hormone medicine and raise hormone levels. If you take thyroid hormone medicine, ask your doctor about interactions when starting new medicines.

**Noncancerous tumor**

In some rare cases, a noncancerous tumor of the pituitary gland, located at the base of the brain, can cause hyperthyroidism.

**How do doctors diagnose hyperthyroidism?**

A blood test might confirm a diagnosis of hyperthyroidism.

Your doctor will take a medical history and perform a physical exam. A hyperthyroidism diagnosis can’t be based on symptoms alone because many of its symptoms are the same as those of other diseases. That’s why your doctor may use several thyroid blood tests and imaging tests to confirm the diagnosis and find its cause.

Because hyperthyroidism can cause fertility problems, women who have trouble getting pregnant often get tested for thyroid problems.

**How do doctors treat hyperthyroidism?**

Your doctor will treat your hyperthyroidism to bring your thyroid hormone levels back to normal. Treating the disease will prevent long-term health problems, and it will relieve uncomfortable symptoms. No single treatment works for everyone.

Your treatment depends on what’s causing your hyperthyroidism and how severe it is. When recommending a treatment, your doctor will consider

* your age
* possible allergies to or side effects of the medicines
* other conditions, such as pregnancy or heart disease
* whether you have access to an experienced thyroid surgeon

**Treatment options**

Hyperthyroidism is usually treated with medicines, radioiodine therapy, or thyroid surgery.

**Medicines**

**Radioiodine therapy**

**Thyroid surgery**

Researchers are looking into new ways to treat hyperthyroidism. An example is radiofrequency ablation (RFA), a new approach to treating thyroid nodules that cause hyperthyroidism.5,6 RFA is used mainly in cases where medicines or surgery won’t help, and is not yet widely available.

**How does eating, diet, and nutrition affect hyperthyroidism?**

Your thyroid uses iodine to make thyroid hormones. If you have Graves’ disease or another autoimmune thyroid disorder, you may be sensitive to harmful side effects from iodine. Eating foods that have large amounts of iodine—such as kelp, dulse, or other kinds of seaweed—may cause or worsen hyperthyroidism. Taking iodine supplements can have the same effect. Talk with members of your health care team about

* what foods to limit or avoid
* any iodine supplements you take
* any cough syrups or multivitamins you take because they may contain iodine

**Clinical Trials for Hyperthyroidism**

The NIDDK conducts and supports clinical trials in many diseases and conditions, including endocrine diseases. The trials look to find new ways to prevent, detect, or treat disease and improve quality of life.

**RISK FACTORS**

Risk factors for hyperthyroidism include:

* A family history of thyroid disease, particularly Graves' disease.
* A personal history of certain chronic illnesses, including pernicious anemia and primary adrenal insufficiency.
* A recent pregnancy, which raises the risk of developing thyroiditis. This can lead to hyperthyroidism.

**Risk for hyperthyroidism**

You are at higher risk for hyperthyroidism if you:

* Are a woman
* Are older than age 60
* Have been pregnant or had a baby within the past 6 months
* Have had thyroid surgery or a thyroid problem, such as goiter
* Have a family history of thyroid disease
* Have pernicious anemia, in which the body cannot make enough healthy red blood cells because it does not have enough vitamin B12
* Have type 1 diabetes or primary adrenal insufficiency, a hormonal disorder
* Get too much iodine, from eating large amounts of foods containing iodine or using iodine-containing medicines or supplements

**SIGNS / SYMPTOMS**

Hyperthyroidism sometimes looks like other health problems. That can make it hard to diagnose. It can cause many symptoms, including:

* Losing weight without trying.
* Fast heartbeat, a condition called tachycardia.
* Irregular heartbeat, also called arrhythmia.
* Pounding of the heart, sometimes called heart palpitations.
* Increased hunger.
* Nervousness, anxiety and irritability.
* Tremor, usually a small trembling in the hands and fingers.
* Sweating.
* Changes in menstrual cycles.
* Increased sensitivity to heat.
* Changes in bowel patterns, especially more-frequent bowel movements.
* Enlarged thyroid gland, sometimes called a goiter, which may appear as a swelling at the base of the neck.
* Tiredness.
* Muscle weakness.
* Sleep problems.
* Warm, moist skin.
* Thinning skin.
* Fine, brittle hair.

Older adults are more likely to have symptoms that are hard to notice. These symptoms may include an irregular heartbeat, weight loss, depression, and feeling weak or tired during ordinary activities.

The symptoms of hyperthyroidism can vary from person to person and may include:

* Nervousness or irritability
* Fatigue
* Muscle weakness
* Trouble tolerating heat
* Trouble sleeping
* Tremor, usually in your hands
* Rapid and irregular heartbeat
* Frequent bowel movements or diarrhea
* Weight loss
* Mood swings
* Goiter, an enlarged thyroid that may cause your neck to look swollen. Sometimes it can cause trouble with breathing or swallowing.

Adults over age 60 may have different symptoms than younger adults. For example, they may lose their appetite or withdraw from other people. Sometimes this can be mistaken for depression or dementia.

**What other problems can hyperthyroidism cause?**

If hyperthyroidism isn't treated, it can cause some serious health problems, including:

* An irregular heartbeat that can lead to blood clots, stroke, heart failure, and other heart problems
* An eye disease called Graves' ophthalmopathy. It can cause double vision, light sensitivity, and eye pain. In rare cases, it can lead to vision loss.
* Thinning bones and osteoporosis
* Fertility problems in women
* Complications in pregnancy, such as premature birth, low birth weight, high blood pressure in pregnancy, and miscarriage

**DIAGNOSIS METHODS**

Hyperthyroidism is diagnosed with a medical history, physical exam and blood tests. Depending on the results of the blood tests, you may need other tests too.

* **Medical history and physical exam.** During the exam, your health care provider may check for:
  + Slight tremor in your fingers and hands.
  + Overactive reflexes.
  + Rapid or irregular pulse.
  + Eye changes.
  + Warm, moist skin.

Your provider also examines your thyroid gland as you swallow to see if it's larger than usual, bumpy or tender.

* **Blood tests.** Blood tests that measure the hormones T-4 and T-3 and thyroid-stimulating hormone (TSH) can confirm a diagnosis of hyperthyroidism. A high level of T-4 and a low level of TSH is common in people with hyperthyroidism.

Blood tests are particularly important for older adults because they may not have classic symptoms of hyperthyroidism.

Thyroid blood tests may give false results if you take biotin. Biotin is a B vitamin supplement that also may be found in multivitamins. Tell your health care provider if you are taking biotin or a multivitamin with biotin. To make sure your blood test is accurate, your health care provider may ask you to stop taking biotin 3 to 5 days before the test.

If blood test results show hyperthyroidism, your health care provider may suggest one of the following tests. They can help find out why your thyroid is overactive.

* **Radioiodine scan and uptake test.** For this test, you take a small dose of radioactive iodine, called radioiodine, to see how much of it collects in your thyroid gland and where it collects in the gland.

If your thyroid gland takes in a high amount of radioiodine, that means your thyroid gland is making too much thyroid hormone. The most likely cause is either Graves' disease or overactive thyroid nodules.

If your thyroid gland takes in a low amount of radioiodine, that means hormones stored in the thyroid gland are leaking into the bloodstream. In that case, it's likely that you have thyroiditis.

* **Thyroid ultrasound.** This test uses high-frequency sound waves to make images of the thyroid. Ultrasound may be better at finding thyroid nodules than are other tests. There's no exposure to radiation with this test, so it can be used for people who are pregnant or breastfeeding, or others who can't take radioiodine.

**TREATMENT OPTIONS**

There are several treatments available for hyperthyroidism. The best approach for you depends on your age and health. The underlying cause of hyperthyroidism and how severe it is, makes a difference too. Your personal preference also should be considered as you and your health care provider decide on a treatment plan. Treatment may include:

* **Anti-thyroid medicine.** These medications slowly ease symptoms of hyperthyroidism by preventing the thyroid gland from making too many hormones. Anti-thyroid medications include methimazole and propylthiouracil. Symptoms usually begin to improve within several weeks to months.

Treatment with antithyroid medicine typically lasts 12 to 18 months. After that, the dose may be slowly decreased or stopped if symptoms go away and if blood test results show that thyroid hormone levels have returned to the standard range. For some people, anti-thyroid medicine puts hyperthyroidism into long-term remission. But other people may find that hyperthyroidism comes back after this treatment.

Although rare, serious liver damage can happen with both anti-thyroid medications. But because propylthiouracil has caused many more cases of liver damage, it's generally used only when people can't take methimazole. A small number of people who are allergic to these medicines may develop skin rashes, hives, fever or joint pain. They also can raise the risk of infection.

* **Beta blockers.** These medicines don't affect thyroid hormone levels. But they can lessen symptoms of hyperthyroidism, such as a tremor, rapid heart rate and heart palpitations. Sometimes, health care providers prescribe them to ease symptoms until thyroid hormones are closer to a standard level. These medicines generally aren't recommended for people who have asthma. Side effects may include fatigue and sexual problems.
* **Radioiodine therapy.** The thyroid gland takes up radioiodine. This treatment causes the gland to shrink. This medicine is taken by mouth. With this treatment, symptoms typically lessen within several months. This treatment usually causes thyroid activity to slow enough to make the thyroid gland underactive. That condition is hypothyroidism. Because of that, over time, you may need to take medicine to replace thyroid hormones.
* **Thyroidectomy.** This is surgery to remove part of or all of the thyroid gland. It is not used often to treat hyperthyroidism. But it may be an option for people who are pregnant. It also may be a choice for those who can't take anti-thyroid medicine and don't want to or can't take radioiodine therapy.

Risks of this surgery include damage to the vocal cords and parathyroid glands. The parathyroid glands are four tiny glands on the back of the thyroid. They help control the level of calcium in the blood.

People who have a thyroidectomy or radioiodine therapy need lifelong treatment with the medicine levothyroxine (Levoxyl, Synthroid, others). It supplies the body with thyroid hormones. If the parathyroid glands are removed during surgery, medicine also is needed to keep blood calcium in a healthy range.

**Thyroid eye disease**

If you have thyroid eye disease, you may be able to manage mild symptoms with self-care steps, such as artificial tear drops and lubricating eye gels. Avoiding wind and bright lights can help too.

More-severe symptoms may need treatment with medicine called corticosteroids, such as methylprednisolone or prednisone. They can lessen swelling behind the eyeballs. The medicine teprotumumab (Tepezza) also may be used to control moderate to severe symptoms. If those medicines don't ease symptoms, other medicines are sometimes used to treat thyroid eye disease. They include, tocilizumab (Actemra), rituximab (Rituxan) and mycophenolate mofetil (Cellcept).

In some cases, surgery may be needed to treat thyroid eye disease, including:

* **Orbital decompression surgery.** In this surgery, the bone between the eye socket and the sinuses is removed. This surgery can improve vision. It also gives the eyes more room, so they can go back to their usual position. There is a risk of complications with this surgery. If you have double vision before the surgery, it may not go away afterward. Some people develop double vision after the surgery.
* **Eye muscle surgery.** Sometimes scar tissue from thyroid eye disease can cause one or more eye muscles to be too short. This pulls the eyes out of alignment, causing double vision. Eye muscle surgery may correct double vision by cutting the muscle from the eyeball and attaching it again farther back.

**Lifestyle and home remedies**

Once you begin treatment, symptoms of hyperthyroidism likely will get better. Along with your treatment, your health care provider might suggest that you reduce iodine in your diet. It can make hyperthyroidism worse. Kelp, dulse and other types of seaweed contain a lot of iodine. Cough syrup and multivitamins also may contain iodine.

**Graves' disease**

If you have Graves' disease that causes eye or skin problems, taking the following steps may help ease symptoms:

* **Don't smoke.** Smoking has been linked to the development of thyroid eye disease. It also can make that condition worse. And smoking can cause symptoms to come back after treatment.
* **Keep your eyes lubricated.** Eye drops may help relieve dryness and scratchiness. A cool compress also can provide moisture. If your eyes don't completely close, a lubricating gel at bedtime may help keep the cornea from drying out. Some people also tape their eyelids shut while they sleep.
* **Protect your eyes.** Wear sunglasses to help protect your eyes from the sun and wind.
* **Keep your head up.** Raising the head of your bed may lessen swelling and ease pressure on your eyes.
* **Use creams for swollen skin.** Creams containing hydrocortisone that you can buy without a prescription (Cortizone 10, others) may help ease swollen skin on the shins and feet. For help finding these creams, ask a pharmacist.

**PREVENTION TIPS**

To reduce the risk of developing hyperthyroidism, it is important to maintain a healthy lifestyle. This includes reducing the intake of sugar and processed foods, ensuring adequate iodine intake, and engaging in regular exercise.

Additionally, avoiding smoking is crucial, as smokers are more likely to develop Graves' disease, a leading cause of hyperthyroidism.

It is also advisable to manage stress effectively and maintain regular checkups with a healthcare provider, especially if there are risk factors for thyroid disease.

Furthermore, individuals should be cautious with iodine intake, as excessive iodine can exacerbate hyperthyroidism, particularly in those with underlying thyroid conditions.

**POSSIBLE COMPLICATIONS**

Hyperthyroidism can lead to the following complications.

**Heart problems**

Some of the most serious complications of hyperthyroidism involve the heart, including:

* A heart rhythm disorder called atrial fibrillation that increases the risk of stroke.
* Congestive heart failure, a condition in which the heart can't circulate enough blood to meet the body's needs.

**Brittle bones**

Untreated hyperthyroidism can lead to weak, brittle bones. This condition is called osteoporosis. The strength of bones depends, in part, on the amount of calcium and other minerals in them. Too much thyroid hormone makes it hard for the body to get calcium into bones.

**Vision problems**

Some people with hyperthyroidism develop a problem called thyroid eye disease. It's more common in people who smoke. This disorder affects the muscles and other tissues around the eyes.

Symptoms of thyroid eye disease include:

* Bulging eyes.
* Gritty sensation in the eyes.
* Pressure or pain in the eyes.
* Puffy or retracted eyelids.
* Reddened or inflamed eyes.
* Light sensitivity.
* Double vision.

Eye problems that go untreated may cause vision loss.

**Discolored, swollen skin**

In rare cases, people with Graves' disease develop Graves' dermopathy. This causes the skin to change colors and swell, often on the shins and feet.

**Thyrotoxic crisis**

This rare condition also is called thyroid storm. Hyperthyroidism raises the risk of a thyrotoxic crisis. It causes severe, sometimes life-threatening symptoms. It requires emergency medical care. Symptoms may include:

* Fever.
* Fast heartbeat.
* Nausea.
* Vomiting.
* Diarrhea.
* Dehydration.
* Confusion.
* Delirium.

**What are the complications of hyperthyroidism?**

If your hyperthyroidism is not treated, these complications may happen:

* Thyroid crisis, when symptoms get worse because of stress or illness
* Heart problems, such as an abnormal rhythm or heart failure
* Weak, brittle bones (osteoporosis)
* Pregnancy problems, such as miscarriage, early delivery, and preeclampsia or high blood pressure

**Complications of hyperthyroidism**

Untreated, hyperthyroidism can cause serious health problems, including

* an irregular heartbeat that can lead to blood clots, stroke, heart failure, and other heart-related problems
* an eye disease called Graves’ ophthalmopathy
* thinning bones, osteoporosis, and muscle problems
* menstrual cycle and fertility issues

**OUTLOOK / PROGNOSIS**

Hyperthyroidism from toxic multinodular goiter and toxic adenoma is permanent and usually occurs in adults. After normalization of thyroid function with antithyroid medications, radioactive iodine ablation usually is recommended as the definitive therapy. Long-term, high-dose antithyroid medication is not recommended. Toxic multinodular goiters and toxic adenomas probably will continue to grow slowly in size during antithyroid pharmacotherapy.

Generally, the thyrotoxic areas are ablated, and patients may remain euthyroid. Those who become hypothyroid after radioactive iodine therapy are easily maintained on thyroid hormone replacement therapy, with T4 taken once daily.

Patients with Graves’ disease may become hypothyroid in the natural course of their disease, regardless of whether treatment involves radioactive iodine or surgery. Eye disease may develop at a time distant from the initial diagnosis and therapy. Generally, after the diagnosis, the ophthalmopathy slowly improves over years.

Thyroid hormone excess causes left ventricular thickening, which is associated with an increased risk of heart failure and cardiac-related death. Thyrotoxicosis has been associated with dilated cardiomyopathy,right heart failure with pulmonary hypertension, and diastolic dysfunction and atrial fibrillation.

An increase in the rate of bone resorption occurs. Bone loss, measured by bone mineral densitometry, can be seen in severe hyperthyroidism at all ages and in both sexes.

**WHEN TO SEE A DOCTOR / RED FLAG**

If you lose weight without trying, or if you notice a rapid heartbeat, unusual sweating, swelling at the base of your neck or other symptoms of hyperthyroidism, make an appointment with your healthcare provider. Tell your provider about all the symptoms you've noticed even if they are minor.

After a diagnosis of hyperthyroidism, most people need regular follow-up visits with their health care provider to monitor the condition.

Tell your healthcare provider if your symptoms get worse or you have new symptoms. If you are a woman of childbearing age and want to become pregnant, talk with your provider first.

**DIFFERENTIAL DIAGNOSIS**

*Diagnostic Considerations*

Diagnostic considerations include factitious hyperthyroidism, which is hyperthyroidism secondary to intentional consumption of thyroid hormone. In this condition, thyroid hormone consumption causes suppression of thyroglobulin secretion by the thyroid. Factitious hyperthyroidism is common in medical personnel, who have easy access to medication containing thyroid hormone and may abuse it for weight loss or an energy boost.

**Differential Diagnoses**

* Diffuse Toxic Goiter (Graves’ Disease)
* Euthyroid Hyperthyroxinemia
* Goiter
* Graves’ Disease
* Struma Ovarii
* Thyrotoxicosis Imaging

**RECENT GUIDELINES OR UPDATES**

* Beta-adrenergic blockade is recommended in all patients with symptomatic thyrotoxicosis, especially elderly patients and thyrotoxic patients with resting heart rates in excess of 90 beats per minute or coexistent cardiovascular disease
* Patients with overt Graves hyperthyroidism should be treated with any of the following modalities: radioactive iodine therapy, antithyroid drugs, or thyroidectomy
* If methimazole is chosen as the primary therapy for Graves’ disease, the medication should be continued for approximately 12-18 months and then discontinued if the serum thyrotropin and thyrotropin receptor antibody levels are normal at that time
* If surgery is chosen as the primary therapy for Graves’ disease, near-total or total thyroidectomy is the procedure of choice
* If surgery is chosen as treatment for toxic multinodular goiter, near-total or total thyroidectomy should be performed
* If surgery is chosen as the treatment for toxic adenoma, a thyroid sonogram should be done to evaluate the entire thyroid gland; an ipsilateral thyroid lobectomy (or isthmusectomy, if the adenoma is in the thyroid isthmus), should be

**EPIDEMIOLOGY**

Graves’ disease is the most common form of hyperthyroidism in the United States, causing approximately 60-80% of cases of thyrotoxicosis. The annual incidence of Graves’ disease was found to be 0.5 cases per 1000 population during a 20-year period, with the peak occurrence in people aged 20-40 years.

Toxic multinodular goiter (15-20% of thyrotoxicosis) occurs more frequently in regions of iodine deficiency. Most persons in the United States receive sufficient iodine, and the incidence of toxic multinodular goiter in the US population is lower than that in areas of the world with iodine deficiency. Toxic adenoma is the cause of 3-5% of cases of thyrotoxicosis.

The incidences of Graves’ disease and toxic multinodular goiter change with iodine intake. Compared with regions of the world with less iodine intake, the United States has more cases of Graves’ disease and fewer cases of toxic multinodular goiters.

Race-, sex-, and age-related demographics

Autoimmune thyroid disease occurs with the same frequency in Caucasians, Hispanics, and Asians but at lower rates in African Americans.

All thyroid diseases occur more frequently in women than in men. Graves autoimmune disease has a male-to-female ratio of 1:5-10. The male-to-female ratio for toxic multinodular goiter and toxic adenoma is 1:2-4.

**How common is hyperthyroidism?**

About 1 out of 100 Americans ages 12 years and older have hyperthyroidism.1

**Who is more likely to develop hyperthyroidism?**

Hyperthyroidism is more common in women and people older than 60.2 You are more likely to have hyperthyroidism if you

* have a family history of thyroid disease
* have other health problems, including
  + pernicious anemia *NIH external link*, a condition caused by a vitamin B12 deficiency
  + type 1 or type 2 diabetes
  + primary adrenal insufficiency, a disorder of hormones
* eat large amounts of food containing iodine, such as kelp
* use medicines that contain iodine
* use nicotine products3
* were pregnant within the past 6 months

**Is hyperthyroidism during pregnancy a problem?**

Mild hyperthyroidism during pregnancy is usually not a problem. But severe hyperthyroidism during pregnancy, when untreated, can affect both the mother and the baby. If you have hyperthyroidism and plan to get pregnant or become pregnant, work with your doctor to get the disease under control.

Be sure your hyperthyroidism is under control before becoming pregnant.

**What are the symptoms of hyperthyroidism?**

Symptoms of hyperthyroidism can vary from person to person and may include4

* weight loss despite an increased appetite
* rapid or irregular heartbeat
* nervousness, irritability, trouble sleeping, fatigue
* shaky hands, muscle weakness
* sweating or trouble tolerating heat
* frequent bowel movements
* an enlargement in the neck, called a goiter

In older adults, hyperthyroidism is sometimes mistaken for depression, or dementia. Older adults may have different symptoms, such as loss of appetite or withdrawal from people, than younger adults with hyperthyroidism. You may want to ask your doctor about hyperthyroidism if you or your loved one shows these symptoms.

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**HYPOPITUITARISM**

*ALTERNATIVE NAMES:* Hypopituitarism is also known as “pituitary insufficiency”, “panhypopituitarism”, and “anterior hypopituitarism”.

**DEFINITION / DESCRIPTION**

Hypopituitarism is a rare condition in which the pituitary gland doesn't make one or more hormones or doesn't make enough hormones.

The pituitary gland is a kidney-bean-sized gland at the base of your brain. It is part of the body's system of glands that make hormones, called the endocrine system. The pituitary gland makes several hormones. They act on nearly every part of the body

Hypopituitarism is when there isn't enough of one or more of the pituitary hormones. This lack of hormones, called a deficiency, can affect how the body works in many ways. These include growth, blood pressure and the ability to have children, among others. Symptoms depend on which hormones are missing.

People who have hypopituitarism usually need to take medicines for the rest of their lives. These medicines replace the missing hormones, which helps control symptoms.

The condition can happen suddenly after an injury or develop slowly over months or years. People with it often need to take medication for the rest of their lives to manage symptoms. Your healthcare provider will watch you closely to make sure you get the right treatment.

**Types of hypopituitarism**

There are three different kinds of hypopituitarism based on the number of hormones that are lacking (deficient):

* Isolated pituitary deficiency: Affects one pituitary hormone.
* Multiple pituitary hormone deficiency: Affects two or more pituitary hormones.
* Panhypopituitarism: Affects all pituitary hormones.

There are three kinds of hypopituitarism based on its cause and how it affects your pituitary gland or hormones:

* Primary hypopituitarism: Damage to or disorders of your pituitary gland.
* Secondary hypopituitarism: Damage to or disorders of your hypothalamus.
* Idiopathic hypopituitarism: Cause remains undetermined.

**CAUSES**

Hypopituitarism has a number of causes. One common cause is a tumor of the pituitary gland. As a pituitary tumor grows, it can press on and damage pituitary tissue. This disrupts the pituitary gland's ability to make hormones. A tumor also can press on the optic nerves, causing vision problems.

Other **potential causes** of damage to the pituitary gland that may lead to hypopituitarism include:

* Lack of blood flow to the brain or pituitary gland, known as a stroke, or bleeding, called hemorrhage, into the brain or pituitary gland.
* Certain medicines, such as narcotics, high-dose steroids or certain cancer medicines called checkpoint inhibitors.
* Swelling, known as inflammation, of the pituitary gland caused by an unusual immune system response, called hypophysitis.
* Infections of the brain, such as meningitis, or infections that can spread to the brain, such as tuberculosis or syphilis.
* Significant blood loss during childbirth, which can damage the front part of the pituitary gland. This condition is known as Sheehan syndrome or postpartum pituitary necrosis.

In some cases, a change in a gene causes hypopituitarism. That change is heredity, which means it is passed down in families. The genetic change affects the pituitary gland's ability to make one or more of its hormones. This often starts at birth or in early childhood.

Tumors or diseases of a part of the brain that's just above the pituitary, called the hypothalamus, also can cause hypopituitarism. The hypothalamus makes hormones that affect how the pituitary gland works.

**Conditions that affect your pituitary gland or hypothalamus**

Conditions that can cause pressure on these areas of your brain, possibly leading to hypopituitarism, include:

* Pituitary adenomas: A benign tumor on your pituitary gland that can change the way it releases hormones.
* Brain tumors: A brain tumor near your hypothalamus and/or pituitary gland can affect hormone production.
* Lymphocytic hypophysitis (LH): This is a rare condition where lymphocytes invade your pituitary gland.
* Pituitary or hypothalamus sarcoidosis: Sarcoidosis is a disease that causes inflammation.

Injuries that cause damage to your pituitary gland or hypothalamus

Examples of situations that can cause pituitary or hypothalamus damage include:

* Surgery: Complications from brain surgery (especially surgery to remove a pituitary adenoma).
* Radiation therapy: Prior cancer radiation therapy or radiation used to treat a pituitary adenoma.
* Traumatic brain injury: Situations like a vehicle accident, a fall or contact sports.
* Pituitary apoplexy: Sudden destruction of pituitary gland tissue.

**Rare conditions**

Examples of rare conditions that can cause the condition include:

* Hereditary hemochromatosis: This genetic condition causes too much iron in your bloodstream. It can damage your pituitary gland.
* Bacterial meningitis: Although it’s rare, hypopituitarism can be a complication of bacterial meningitis.
* Genetic mutations: Some rare genetic conditions can cause deficiencies in pituitary hormones.

Sometimes, the cause of hypopituitarism isn't known.

**RISK FACTORS**

Most people with hypopituitarism don't have any factors that put them at higher risk of developing the condition. But the following may raise the risk of developing hypopituitarism:

* A head injury.
* Brain surgery.
* Radiation treatment to the head or neck.
* Diseases that affect more than one part of the body. These include an inflammatory disease that affects various organs, called sarcoidosis; a disease in which unusual cells cause scarring, called Langerhans cell histiocytosis; and a disease that causes too much iron in the liver and other tissues, called hemochromatosis.

The following conditions or situations may be risk factors for hypopituitarism:

* A history of cancer and radiation therapy.
* Head or brain trauma: Approximately 27% to 32% of people who experience a traumatic brain injury (TBI) develop hypopituitarism.
* Sickle cell anemia: Sickle cell anemia can cause a deficiency of pituitary hormones.
* Type 1 diabetes: Nerve and vascular damage from unmanaged Type 1 diabetes can contribute to the condition.
* Pregnancy and giving birth: Severe blood loss (hemorrhaging) after childbirth can result in pituitary damage. This is known as Sheehan syndrome.

**SIGNS / SYMPTOMS**

The symptoms of hypopituitarism usually start slowly and get worse over time. They might not be noticed for months or even years. But for some people, symptoms start suddenly.

Symptoms of hypopituitarism vary from person to person. Symptoms depend on what hormones are missing and how little of the hormone is being made. There might be more than one hormone that's low. A second hormone deficiency might increase the symptoms of the first one. Or sometimes, it might hide those symptoms.

*Growth hormone (GH) deficiency*

In children, GH deficiency can cause growth problems and short stature. Most adults who have GH deficiency don't have symptoms. But some adults have:

* Fatigue.
* Muscle weakness.
* Changes in body fat.
* Loss of interest in activities.
* Lack of social contacts.

*Luteinizing hormone (LH) and follicle-stimulating hormone (FSH) deficiency*

A lack of these hormones, called gonadotropins, affects the reproductive system.

The lack of hormones keeps the ovaries from making enough eggs and estrogen. It keeps the testicles from making enough sperm and testosterone. This can lower sex drive and cause tiredness. It also can make it hard or impossible to have children — a condition called infertility. In children, the physical changes to an adult body, known as puberty, may not occur or may be late.

Some people might have symptoms such as:

* Hot flashes.
* Irregular periods or no periods.
* Loss of pubic hair.
* Not being able to make milk for breastfeeding.
* Not being able to get or keep an erection, known as erectile dysfunction.
* Decreased facial or body hair.
* Mood changes.
* Fatigue.

**Thyroid-stimulating hormone (TSH) deficiency**

This hormone controls the thyroid gland. Too little TSH leads to low levels of thyroid hormones. This condition is called hypothyroidism. It causes symptoms such as:

* Tiredness.
* Weight gain.
* Dry skin.
* Constipation.
* Sensitivity to cold or trouble staying warm.

**Adrenocorticotropic hormone (ACTH) deficiency**

This hormone helps the adrenal glands work correctly. It also helps the body react to stress. Symptoms of ACTH deficiency include:

* Severe tiredness.
* Low blood pressure.
* Many and lasting infections.
* Nausea, vomiting or abdominal pain.
* Confusion.

**Antidiuretic hormone (ADH) deficiency**

This hormone, which also is called vasopressin, helps the body balance its fluid levels. An ADH deficiency can lead to a disorder called diabetes insipidus, which can cause:

* Urinating more than usual.
* Extreme thirst.
* Imbalances in minerals such as sodium and potassium, known as electrolytes.

**Prolactin deficiency**

Prolactin is the hormone that tells the body when to start making breast milk. Low levels of prolactin can cause problems with making milk for breastfeeding.

**DIAGNOSIS METHODS**

Several tests can check hormone levels in the body and look for the cause of problems with the way the pituitary is working. These include:

* **Blood tests.** These tests measure levels of the hormones made in the pituitary gland and those made in glands that the pituitary controls, such as the thyroid gland. Blood tests can show if low hormone levels are due to the pituitary not working as it should.
* **Stimulation or dynamic testing.** A clinic that specializes in endocrine conditions can run these tests to measure hormone levels. These tests check the body's hormone levels before and after taking medicines that cause the body to make hormones.
* **Brain imaging.** MRI or CT scans of the brain can show a pituitary tumor or other pituitary gland problems.

**TREATMENT OPTIONS**

Hypopituitarism is treated with medicines that raise hormone levels. This is called hormone replacement. Doses are set to match the amount of hormones that the body would make if it didn't have a pituitary problem. In some cases, people with hypopituitarism may need to take this medicine for the rest of their lives.

Sometimes, treatment of a condition causing hypopituitarism may restore the body's ability to make pituitary hormones, either fully or in part.

**Medications**

Hormone replacement medicines might include:

* **Cortisol replacement.** These medicines include hydrocortisone (Cortef) or prednisone (Rayos). Taken by mouth, they replace the adrenal hormones needed because of a lack of adrenocorticotropic hormone (ACTH).
* **Levothyroxine (Levoxyl, Synthroid, others).** This medicine treats the low thyroid hormone levels, known as hypothyroidism, from a lack of thyroid-stimulating hormone (TSH).
* **Sex hormones.** These include testosterone, estrogen and progesterone. Testosterone is given by a shot, pills, patch or gel. Estrogen and progesterone usually are given in pills, gels or patches.
* **Growth hormone.** Also called somatotropin (Genotropin, Humatrope, others), growth hormone is given by a shot under the skin. It promotes growth, which helps children grow taller. Adults who lack growth hormone also can benefit from growth hormone, but they won't get taller.
* **Fertility hormones.** Gonadotropins can be given by a shot to help ovulation and sperm production.

**Monitoring hormone replacement**

A specialist in endocrine disorders, called an endocrinologist, may keep an eye on symptoms and hormone levels in the blood. This is to ensure that the right amount of medicine is given.

People who take cortisol replacement need to work with a health care provider to adjust the dose during times of major stress. Under stress, the body usually makes extra cortisol to help manage the stress.

Having the flu, diarrhea or vomiting, or having surgery or dental work might mean the dose needs to be changed. The same might be true during pregnancy or with big changes in body weight.

**Surgery or other procedures**

If a tumor in or around the pituitary gland is the cause of hypopituitarism, surgery might be needed to remove the growth. Some tumors also can be treated with medicines or radiation therapy.

**In case of emergency**

People with hypopituitarism need to wear a medical alert bracelet or necklace and carry a card telling others of the condition. This is especially important for those taking cortisol replacement for a lack of ACTH.

**PREVENTION TIPS**

There are no specific prevention tips for hypopituitarism because it is typically caused by underlying conditions or damage to the pituitary gland or hypothalamus, which are not always preventable. However, managing risk factors and seeking prompt medical care for conditions that may lead to hypopituitarism can help reduce the likelihood of developing the condition. For example, managing diabetes, avoiding head trauma, and treating infections promptly may help lower the risk.

Additionally, individuals with a history of brain surgery or radiation therapy should be monitored closely for potential pituitary dysfunction.

In most cases, the disorder is not preventable. Awareness of risk, such as from taking certain medicines, may allow early diagnosis and treatment.

**OUTLOOK / PROGNOSIS**

*What is the prognosis (outlook) for hypopituitarism?*

The outlook varies and depends on the following:

* How old you were when your symptoms began.
* What caused your condition.
* How much your affected hormone(s) are lacking.
* How your body responds to treatment.

While many people with hypopituitarism lead healthy lives, long-term pituitary damage can lower your life expectancy compared to people without the condition of the same age.

In complex situations, a diagnosis of hypopituitarism may be overlooked or delayed, especially when normal pituitary hormone levels are misinterpreted within the context of suboptimal target organ hormone levels. However, clinical treatment should be initiated in cases of suspected adrenal insufficiency without waiting for definitive biochemical evidence.

The differential diagnoses that may be considered when assessing for hypopituitarism in patients include primary hypothyroidism, Kallmann syndrome, pituitary macroadenomas, hyponatremia, and autoimmune polyglandular syndrome types 1, 2, and 3.

**What is the life expectancy of someone with this condition?**

Your life expectancy depends on the hormone deficiency type, its severity and your overall health. People who follow their treatment plans typically don’t have a lower life expectancy.

**Can I die from hypopituitarism?**

Although it’s not as common, a sudden and severe onset of hypopituitarism can result in a medical emergency and death if it’s not treated. Be sure to call your healthcare provider or go to the nearest emergency room if you’re experiencing symptoms.

Patients in stable condition and can adhere to hormone replacement therapy typically have a favorable prognosis. Mortality rates increase in patients experiencing acute decompensation and critical states. The extent of morbidity varies and is contingent on the hormone deficiency type.

The systemic effects of hypopituitarism vary depending on the extent of pituitary involvement. Certain clinical states that result from the acute decline in pituitary production may increase the mortality risk. For instance, ACTH deficiency can lead to an adrenal crisis, whereas TSH deficiency may cause myxedema coma, potentially resulting in death.

**POSSIBLE COMPLICATIONS**

Hormonal deficiencies that accompany hypopituitarism can lead to the development of other conditions. The exact effects vary depending on which hormone is lacking. Some examples are:

* GH deficiency can lead to obesity, high cholesterol and metabolic syndrome.
* Estrogen deficiency (from FSH deficiency) can lead to osteoporosis in females.
* ACTH deficiency can lead to an adrenal crisis.

Side effects of medicines to treat hypopituitarism can develop. However, do not stop any medicine on your own without talking with your provider first.

Other hormonal deficiencies that often accompany hypopituitarism can contribute to developing secondary diseases. For instance, a human GH (HGH) deficiency is associated with obesity, elevated cholesterol levels, and metabolic syndrome. Likewise, estradiol deficiency can potentially lead to osteoporosis.

**WHEN TO SEE A DOCTOR / RED FLAG**

See your health care provider if you develop any symptoms of hypopituitarism.

Contact your health care provider right away if symptoms of hypopituitarism start suddenly or come with a bad headache, changes in vision, confusion or a drop in blood pressure. These could be symptoms of sudden damage to the pituitary gland tissue. This condition is known as pituitary apoplexy.

Bleeding into the pituitary gland can cause pituitary apoplexy. Pituitary apoplexy is a medical emergency and needs medical attention quickly.

In most cases, hypopituitarism requires close, lifelong monitoring of the hormones affected. Be sure to see your healthcare provider regularly to make sure your treatment plan is working. If you’re experiencing new or concerning symptoms, contact your healthcare provider as soon as possible.

**DIFFERENTIAL DIAGNOSIS**

In complex situations, a diagnosis of hypopituitarism may be overlooked or delayed, especially when normal pituitary hormone levels are misinterpreted within the context of suboptimal target organ hormone levels. However, clinical treatment should be initiated in cases of suspected adrenal insufficiency without waiting for definitive biochemical evidence.

The differential diagnoses that may be considered when assessing for hypopituitarism in patients include primary hypothyroidism, Kallmann syndrome, pituitary macroadenomas, hyponatremia, and autoimmune polyglandular syndrome types 1, 2, and 3.

**EPIDEMIOLOGY**

Hypopituitarism is categorized as a rare disorder by the National Institute of Health (NIH), with limited data available on the incidence and prevalence of the condition. A study conducted by Regal et al in Northwestern Spain reported a prevalence of 45.5 cases per 100,000 population.

Hypopituitarism is considered to be a rare disorder, with less than 200,000 patients in the United States.

On a global basis, the incidence is estimated to be 4.2 cases per 100,000 per year, and the prevalence is approximately 45.5 cases per 100,000 people.

These figures are indicative of the general population and have not been adjusted for gender or specific groups at risk.

The first scientific study to investigate the prevalence and incidence of hypopituitarism was carried out by Regal et al in Spain with a sample population size of 146,000. In this group of people, the prevalence of hypopituitarism was found to be 45.5 cases per 100,000.

The study population comprised adults residing in South Galicia (north-western Spain). The diagnosis of hypopituitarism was made on baseline and hormonal dynamic tests. The first survey found the prevalence of hypopituitarism to be 29 per 100,000. The second survey found it to be closer to 45.5 per 100,000.

Traumatic brain injury (TBI) was also found as an important cause of hypopituitarism. It has been shown that between 5% and 70% of the TBI patients suffer from hypopituitarism.

This large variation in the prevalence may be explained by diverse diagnostic criteria used in different studies, different time points of interventions after TBI, severity of trauma etc.

Patients with hypopituitarism show higher rates of mortality associated with cardiovascular and cerebrovascular causes when compared to the general population. This is usually thought to be linked to a deficiency in growth hormone (GH), although other pituitary hormones may also be involved.

The annual incidence of hypopituitarism remained stable during the study period. The average annual incidence rate of hypopituitarism was 4.21 cases per 100,000.

The incidence increased with age.

The causes of hypopituitarism were pituitary tumorous (61%), non-pituitary lesions (9%), and non-cancerous causes (30%), including 11% idiopathic cases.

Some medical scientists have expressed that the true prevalence of the disorder is likely to be considerably greater than indicated in these studies, due to the known difficulties in diagnosing the condition.

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**MENSTRUAL DISORDER**

*ALTERNATIVE NAMES*: Menstrual disorders refer to a range of conditions that affect a woman's normal menstrual cycle. These disorders can include heavy, painful, or irregular periods, as well as the absence of periods. Some alternative names and descriptions for menstrual disorders include:

*Menorrhagia:* Unusually long and/or heavy periods.

*Menometrorrhagia:* Heavy bleeding during menstrual periods and bleeding that occurs frequently and irregularly between periods.

*Dysmenorrhea:* Severe, frequent cramping during menstruation.

*Amenorrhea:* The absence of a menstrual period in a woman of reproductive age.

*Irregular menstruation:* Variation in menstrual cycle length of more than approximately 8 days for a woman.

*Metrorrhagia:* Irregular menstruation that occurs between the expected menstrual periods.

*Heavy menstrual bleeding:* A condition characterized by excessively heavy or prolonged menstrual bleeding.

*Irregular periods:* Periods that come early, late, or not at all, or when the length of the menstrual cycle changes.

**IRREGULAR PERIODS (MENSTRUAL DISORDER)**

Most women have menstrual periods that last four to seven days. Your period usually occurs every 28 days, but normal menstrual cycles can range from 21 days to 35 days. In fact, the average cycle length is 29 days. Many things cause irregular periods (or irregular menstruation) such as changes in hormone levels, stress, certain health conditions, medications and more.

Your period is still considered “regular” even if it varies slightly from cycle to cycle. Examples of irregular menstruation include:

* Periods that occur fewer than 21 days or more than 35 days apart.
* Missing three or more periods in a row.
* Menstrual flow (bleeding) that’s much heavier or lighter than usual.
* Periods that last longer than seven days.
* Length of time between cycles varies by more than nine days. For example, one cycle is 28 days, the next is 37 days and the next is 29 days.
* Periods that are accompanied by severe pain, cramping, nausea or vomiting.
* Bleeding or spotting that happens between periods, after menopause or after sexual intercourse.
* Soaking through one or more tampons or sanitary pads in an hour.

Your menstrual cycle may not always be predictable — and that may be OK. It’s normal to have slight variations in cycle length or have a menstrual period that seems slightly heavier or lighter in flow than your previous period. Menstrual irregularities are fairly common, and you don’t have to be able to predict your cycle to the exact day for it to be considered “normal.”

Conditions related to irregular menstruation

* *Amenorrhea:* A condition where your periods have stopped completely. The absence of a period for 90 days or more is considered abnormal unless you’re pregnant, breastfeeding or going through menopause (which generally occurs between ages 45 and 55). If you haven’t started menstruating by age 15 or 16 or within three years of your breasts developing, you may also have amenorrhea.
* *Oligomenorrhea:* A condition where your periods occur infrequently. You may go more than 35 days between periods or have six to eight periods a year.
* *Dysmenorrhea:* A medical term for painful periods and severe menstrual cramps. Some discomfort during your cycle is normal.
* *Abnormal uterine bleeding:* Abnormal uterine bleeding is bleeding between monthly periods, prolonged bleed**ing or an extremely heavy period.**

**Hormones involved in the menstrual cycle**

* Gonadotropin-releasing hormone (GnRH): It is released from the hypothalamus in the brain and acts upon the pituitary gland to stimulate the release of pituitary sex hormones: FSH and LH.
* Follicular stimulating hormone (FSH): Released from the pituitary gland in the brain, it acts upon ovarian follicles, causing maturation of the egg.
* Luteinizing hormone (LH): Released from the pituitary gland, it acts upon the ovary and causes the release of the egg from the ovary, known as ovulation.
* Estrogen: Produced in the ovaries, it plays a role in the maturation of the egg, prepares the uterus, and has other effects on different body functions as well.
* Progesterone: It is produced from the ruptured follicle (corpus luteum). Progesterone also thickens the uterine endometrium and makes it suitable for the implantation of the embryo.

**Phases of the menstrual cycle**

* Menstruation: The menstrual cycle begins on the first day of menstruation. This phase marks the shedding of the uterine lining that was prepared in the previous cycle for a potential pregnancy. The shedding consists of blood, endometrial tissues, and mucus which is discharged from the vagina.
* Follicular phase: It starts after menstruation. FSH encourages the growth of several ovarian follicles, each containing an immature egg. Only one follicle fully matures, and the rest degenerate. Simultaneously, the uterus is being prepared for the implantation of a fertilized egg.
* Ovulation: It occurs in the mid of the cycle when the follicle ruptures and the egg is released into the uterine tube. It requires an LH surge to cause ovulation. The egg is viable for fertilization for about 12-24 hours. If it combines with sperm, fertilization will occur.
* Luteal phase: It starts after ovulation and continues until menstrual periods. The ruptured follicle transforms into the corpus luteum, which releases progesterone and some estrogen. These hormones maintain the thickened uterine lining, preparing it for implantation.

**Types of menstrual disorders**

There are many types of menstrual disorders that affect women of reproductive age:

***Amenorrhea***

Amenorrhea refers to the complete absence of periods. There are two types of amenorrhea:

* Primary amenorrhea: This occurs when a girl is above the age of 16 and has not yet experienced her first period. It can be due to various reasons, including genetic and hormonal factors.
* Secondary amenorrhea: This is the absence of periods for three consecutive months or more. It occurs in females who previously had their normal periods.

While amenorrhea is an abnormal condition, there are certain normal conditions where there is an absence of periods, which include pregnancy and breastfeeding.

**Oligomenorrhea**

Oligomenorrhea refers to infrequent periods that have a length greater than 35 days, or less than a total of nine periods in a year. In oligomenorrhea, the bleeding might also be light. It can be due to hormonal issues, thyroid disorders, or other medical conditions.

**Menorrhagia**

Menorrhagia refers to abnormally heavy or prolonged bleeding during menstruation. In menorrhagia despite having a regular cycle, the amount of blood loss is considerably higher. It mostly occurs in the perimenopausal phase (the time before the start of menopause) and is often accompanied by dysmenorrhea because passing large clots can cause painful cramps. Menorrhagia is a type of abnormal uterine bleeding.

Abnormal uterine bleeding refers to bleeding that does not follow the normal pattern of menstruation. It is mainly due to ovulatory dysfunction, a disorder where ovulation does not occur predictably or at all. It can manifest in various other disorders:

* *Metrorrhagia:* It refers to irregular bleeding in between normal menstrual periods. The blood flow can vary, the timing is irregular, and not associated with a predictable menstrual cycle.
* *Menometrorrhagia:* It refers to abnormally heavy bleeding both during and in between menstrual periods. It can be particularly disturbing to a woman’s routine and may suggest an underlying medical condition.

**Dysmenorrhea**

Dysmenorrhea refers to pain and discomfort during periods. Mild pain is normal during periods, but intense pain along with other symptoms signifies some serious underlying cause. There are two types of dysmenorrhea:

* Primary dysmenorrhea: This refers to painful periods in the absence of any underlying disease. It is a normal physiological response to the menstrual cycle and occurs due to prostaglandins that cause contraction of the uterus muscles. Contracting muscles constrict blood vessels and block blood flow to the uterus, resulting in ischemia of the endometrium which stimulates pain.
* Secondary dysmenorrhea: This type of dysmenorrhea refers to painful periods due to the presence of some underlying pelvic disease. Along with pain, symptoms such as irregular periods, heavy bleeding, and spotting between periods may be experienced.

**Premenstrual syndrome (PMS)**

Premenstrual syndrome includes physical and psychological symptoms occurring one or two weeks before the onset of menstrual periods. It is mainly caused by fluctuating hormonal levels that affect body systems. These hormones also have psychological impacts.

* *Premenstrual dysphoric disorder (PMDD)*: It is a severe and more complex form of premenstrual syndrome. PMDD is characterized by extreme mood swings, depression, anxiety, and irritability that occur during the week or two before menstruation and usually improve once the menstrual period begins.

**SYMPTOMS OF MENSTRUAL DISORDERS**

Symptoms vary depending on the specific condition, but generally, the common symptoms of menstrual disorders are:

* Absence of periods
* Increased or decreased length of cycle
* Heavy menstrual bleeding
* Pelvic pain
* Breast tenderness
* Irritability
* Spotting between periods
* Bleeding during pregnancy
* Extreme mood swings.

These are some common symptoms experienced during menstrual disorders, however, there are certain symptoms specific to different disorders. These include:

**Amenorrhea**

* Complete absence of periods
* Hair loss
* Excessive facial hair
* Headache
* Milky nipple discharge
* Vision problems.

**Oligomenorrhea**

* Infrequent menstrual periods, often with cycles longer than 35 days
* Difficulty in conceiving due to less frequent ovulation
* Acne
* Hair loss or excessive body hair growth.

**Menorrhagia**

* Prolonged or heavy bleeding (you may need to change pads or tampons every hour)
* Passing of blood clots
* Painful menstrual cramps
* Headaches
* Nausea
* Symptoms of anemia (tiredness, exhaustion, and shortness of breath).

**Metrorrhagia and menometrorrhagia**

* More frequent periods
* Intermenstrual bleeding
* Heavy bleeding
* Irregular bleeding.

**Dysmenorrhea**

* Pain in the pelvis, lower back, and inner thighs
* Vomiting
* Nausea
* Dizziness
* Fainting
* Headache
* Diarrhea.

**Premenstrual syndrome**

* Bloating
* Breast tenderness
* Headache and body pains
* Fatigue
* Mood swings
* Irritability and anxiety
* Food cravings.

**CAUSES OF MENSTRUAL DISORDERS**

Menstrual disorders, as a whole, have multiple causes ranging from hormonal issues to structural defects. We will discuss the causes of each major disorder separately.

**Amenorrhea**

*Causes of primary amenorrhea*

* **Delayed puberty:** The normal age for the beginning of the menstrual period is 9 to 15 years. Delayed puberty means periods occur after 16 years of age.
* **Genetic disorders:**
  + Turner’s syndrome (the ovaries in such females are not completely developed. As a result, they may not produce the necessary hormones to initiate the menstrual cycle, leading to amenorrhea).
  + Kallmann syndrome (a disorder characterized by delayed or absent puberty. Hypothalamus fails to produce enough GnRH for stimulating the release of FSH and LH, resulting in failure to begin the menstrual cycle).
  + Congenital adrenal hyperplasia (a condition that leads to overproduction of male sex hormones, androgens. Increased levels of androgen inhibit the release of GnRH, causing the absence of menstruation).
* **Hormonal problems:** Hormonal imbalances involving the hypothalamus, pituitary gland, and ovaries can disrupt the normal onset of menstruation. It also includes thyroid disorders.
* **Structural abnormalities:**
  + Imperforate hymen (hymen is a membrane that partially covers the vaginal opening. Imperforate hymen completely obstructs the vaginal canal, leading to blockage of menstrual flow).
  + Mullerian agenesis (underdevelopment of the uterus, fallopian tubes, and vagina lead to amenorrhea).
  + Cervical stenosis (it refers to the narrowing of the cervix and can cause amenorrhea by obstructing the outflow of menstrual blood from the uterus).
  + Vaginal atresia (vagina is either abnormally short or completely absent which can lead to amenorrhea).

*Causes of secondary amenorrhea*

* **Polycystic ovary syndrome (PCOS):** It is characterized by the presence of multiple cysts on ovaries, irregular periods, and excess of male hormones (androgen).
* **Thyroid disorders:** Over or under-functioning thyroid also results in the disruption of ovulation leading to amenorrhea.
* **Hypothalamic dysfunction:** This condition occurs when the function of the hypothalamus is impaired. It regulates the key functions of the body by releasing certain hormones including gonadotropin-releasing hormone (GnRH) which in return disrupts the normal menstrual cycle. Weight loss, eating disorders, and stress affect the hypothalamus, resulting in disrupted hormonal release.
* **Hyperprolactinemia:** Increased prolactin levels, a hormone from the pituitary gland, inhibit the release of GnRH. It causes anovulation and amenorrhea.
* **Primary ovarian insufficiency:** This is a condition in which ovaries stop working before the age of 40 years, causing amenorrhea and infertility.
* **Medications:** Certain medications cause amenorrhea, which include hormonal contraceptives, anti-psychotics, and chemotherapy drugs.
* **Other illnesses:** Epilepsy, diabetes, chronic kidney disease, celiac sprue, and cushing syndrome can cause amenorrhea.

**Oligomenorrhea**

**Hormonal imbalance**

Mainly, diseases associated with hormonal imbalance cause oligomenorrhea. All the reproductive hormones including gonadotropin-releasing hormone, follicle-stimulating hormone (FSH), luteinizing hormone (LH), estrogen, and progesterone are secreted in a regulated way in the normal menstrual cycle. Any aberration in their release or action disrupts normal cyclic events and may result in oligomenorrhea. The conditions that cause hormonal imbalances are:

* **Polycystic ovary syndrome:** There is increased secretion of androgens that results in hormonal imbalance leading to irregular periods, weight gain, hirsutism, and acne.
* **Thyroid disorders:** Increase or decrease levels of thyroid hormones (T3, T4) alter levels of menstrual hormones resulting in irregular periods.
* **Pituitary tumors:** The pituitary gland releases several hormones that regulate the menstrual cycle. Pituitary tumors cause abnormalities in the production and release of various hormones, including prolactin and FSH.
* **Androgen-secreting tumors:** Androgen-secreting tumors of the ovary and adrenal glands cause excessive androgen secretion that disturbs the normal menstrual cycle.
* **Cushing syndrome:** It is characterized by increased levels of the cortisol hormone. Elevated cortisol suppresses the release of menstrual hormones from the pituitary and ultimately leads to oligomenorrhea.
* **Prolactinoma:** It is a benign tumor of the pituitary gland that causes hyperprolactinemia. Increased prolactin suppresses FSH and LH secretion, disturbing the menstrual cycle.

**Other medical conditions**

* **Pelvic inflammatory disease:** It is marked by infection and inflammation of female reproductive organs due to sexually transmitted bacteria, viruses, or fungi. It also results in oligomenorrhea.
* **Premature ovarian failure:** Also known as primary ovarian syndrome. Normally, the menstrual cycle ceases in the 40s or 50s, but in this condition, there is dysfunction or depletion of ovarian follicles before the age of 40. It can cause infrequent or very light menstruation.
* **Asherman’s syndrome:** The uterus gets obstructed by scar tissue and adhesions that ultimately ends up causing irregular menstrual cycles.
* **Eating disorders:** Anorexia nervosa, which causes a decrease in estrogen, and bulimia nervosa, which results in electrolyte imbalance, impacts the menstrual cycle and disrupts it.
* **Diabetes mellitus:** Uncontrolled type 1 and type 2 diabetes mellitus also lead to oligomenorrhea.

**Particular medications**

Certain medications cause oligomenorrhea, which includes hormonal contraceptives, anti-psychotics, and antiepileptics.

**Menorrhagia**

*Causes of menorrhagia include:*

* **Uterine polyps:** These are overgrowths of uterine endometrial tissue. As compared to the normal smooth endometrium, polyps increase the amount of tissue to be shed, leading to heavy menstrual bleeding. The presence of polyps also interferes with normal contractions, preventing the efficient shedding of the endometrial tissue and leading to prolonged and heavy bleeding.
* **Uterine fibroids:** They are non-cancerous growths that develop within or on the muscular walls of the uterus. Just like polyps, fibroids also increase the surface area and ultimately, the tissue that is shed during periods. They also disrupt hormonal balance, causing prolonged and heavy bleeding.
* **Adenomyosis:** It is a condition in which the tissue that normally lines the inside of the uterus grows into the muscular wall of the uterus. Adenomyosis increases the size of the uterus, leading to more tissue sloughing off during periods. It also increases blood flow to the uterus, which ultimately increases the blood flow during menstruation.
* **Ovulatory dysfunction:** It causes menorrhagia due to hormonal imbalances, particularly unopposed estrogen. Without normal ovulation, progesterone levels decrease, leading to excessive endometrial growth. Prolonged estrogen stimulation and delayed periods contribute to heavy and prolonged bleeding. Hormonal irregularities disrupt the normal shedding of the endometrial lining, causing menorrhagia.
* **Coagulopathy:** This includes diseases affecting the body’s ability to control bleeding. Coagulopathy causes menorrhagia by impairing blood clotting mechanisms, leading to prolonged and heavy menstrual bleeding.
* **Hormonal imbalance:** Conditions such as estrogen dominance and less progesterone can also lead to menorrhagia
* **Endometrial hyperplasia:** This is an abnormal excessive thickening of the endometrium. Endometrial hyperplasia causes menorrhagia by creating an abnormally thickened uterine lining, which sheds over a longer time with increased period flow.
* **Pelvic inflammatory disease:** It causes inflammation and infection of the uterus and fallopian tubes. This results in irregular shedding of the uterine lining during menstruation and causes heavy and prolonged menstrual bleeding.
* **Intrauterine device:** The presence of an IUD in the uterus can lead to irritation and inflammation of the uterine lining, resulting in increased shedding during menstruation. Also, some IUDs increase uterine contractions, leading to menorrhagia.
* **Uterine cancer:** It can cause menorrhagia due to the abnormal growth of endometrial cells. As the cancer progresses, it disrupts the normal hormonal balance, leading to irregular and excessive growth of the uterine lining. This results in heavy and prolonged menstrual bleeding.

**Dysmenorrhoea**

*Causes of primary dysmenorrhea*

* **Prostaglandins:** They are mainly responsible for causing pain during periods. Prostaglandins trigger uterine muscular contractions which lead to the obstruction of blood flow to uterine tissue. This causes oxygen deprivation (ischemia) and stimulates pain receptors.
* **Lifestyle factors:** Stress, nutritional deficiency, smoking, alcohol, and a sedentary lifestyle increase the risk of dysmenorrhea.
* **Genetics:** Genes play a huge part in this; those whose siblings or mothers have painful periods are at a higher risk of having primary dysmenorrhea.
* **Age:** Primary dysmenorrhea occurs in adolescence and decreases with age.

*Causes of secondary dysmenorrhea*

* **Endometriosis:** A condition in which endometrial tissue grows in places other than the uterus, like ovaries or fallopian tubes. This tissue also responds to hormonal fluctuations and sheds like the normal endometrium, resulting in pain and inflammation.
* **Uterine fibroids:** These are noncancerous growths of uterine tissue that cause pain and heavy bleeding.
* **Adenomyosis:** In adenomyosis, endometrial tissue grows into the muscular wall of the uterus, causing the uterus to enlarge. This also causes painful periods.
* **Ovarian cysts:** They form on the ovaries and if they become large or rupture, they can cause pain.
* **Pelvic inflammatory disease:** This is an infection and inflammation of the female reproductive organs.
* **Intrauterine device:** In some cases, an IUD can cause painful periods.
* **Cervical stenosis:** Narrowing of the cervix halts the menstrual bleeding, causing pain.

**Premenstrual syndrome**

*Causes of premenstrual syndrome include:*

* **Increase hormonal sensitivity:** Some females have increased sensitivity to fluctuating hormones during the menstrual cycle. The bodies of such females respond greatly to changing hormonal levels by altering neurotransmitter levels, affecting mood, behavior, and other physical activities.
* **Decreased serotonin levels:** During the menstrual cycle, there are fluctuations in estrogen and progesterone levels, which can affect serotonin levels in the brain. Serotonin regulates mood, and altered levels lead to low mood, anxiety, and irritability.
* **Genetics:** Certain females have genes inherited from their parents that increase the susceptibility of being affected by premenstrual syndrome. Such genes affect hormonal levels and neurotransmitter functioning.
* **Nutritional deficiency:** Magnesium and calcium deficiencies can cause PMS by disrupting the balance of hormones and neurotransmitters, leading to increased sensitivity to hormonal fluctuations and enhancing PMS symptoms. These minerals play essential roles in hormone regulation, muscle function, and neurotransmitter activity, and their deficiency can contribute to mood swings and other PMS-related issues.
* **Stress:** It triggers the release of stress hormones like cortisol, which can disrupt the normal menstrual cycle and alter hormone levels, exacerbating emotional and physical PMS symptoms.
* **Environmental factors:** Exposure to environmental toxins and pollutants may affect hormone regulation and contribute to PMS.

**RISK FACTORS FOR MENSTRUAL DIAGNOSIS**

*Risk factors for developing menstrual disorders include:*

* **Perimenopausal phase:** As women approach menopause, the menstrual cycle starts to become irregular with the development of various disorders. This happens due to fluctuations in reproductive hormones, mainly estrogen and progesterone.
* **Early menarche:** Girls who had their menarche before the age of 11 years are at a higher risk. Early menarche has been linked with an increased risk for premenstrual syndrome, PCOS, endometriosis, and dysmenorrhea. Also, girls who had their first period earlier usually experience irregular periods at the beginning.
* **Over/under Weight:** Weight plays an important role in hormonal balance. Extreme changes in weight disturb this delicate balance of hormones, causing reproductive system problems. Obesity increases the likelihood of getting PCOS, amenorrhea, and irregular periods.
* **Intense exercise:** Exercise is good for health but intense exercise can disturb menstrual hormones. It also decreases body energy and stimulates stress response, further exacerbating menstrual abnormalities. Severe exercise can cause amenorrhea, irregular periods, and oligomenorrhea.
* **Smoking:** The chemicals present in smoke have negative effects on hormonal balance and reproductive health. Women who smoke may have a longer or shorter length of cycle than normal. Smoking has been associated with an increased risk of premature ovarian failure. Smoking can decrease fertility by affecting both the quantity and quality of eggs in women.
* **Stress:** Stress causes the release of the stress hormone, cortisol, from the adrenal glands. These stress hormones affect the reproductive hormone release and action. Stress also exacerbates premenstrual syndrome. Chronic stress can cause the stoppage of periods, known as stress-induced amenorrhea.
* **Medication:** Chemotherapy may disrupt the menstrual cycle temporarily or permanently.

**MENSTRUAL DISORDER DIAGNOSIS METHODS**

Diagnosing any menstrual disorder requires a proper procedure step by step.

* **Medical history:** The doctor will take a detailed medical history from you, including your menstrual cycle history. He/She will ask you about cycle patterns, family history, menstrual hygiene history, medications, and contraceptives. This will help in evaluating the underlying condition.
* **Physical examination:** The medical history is followed by a physical examination. This usually involves a thorough examination of your abdomen and pelvis to detect any abnormalities that could be contributing to your symptoms.
* **Blood tests:** Blood tests will be done to determine hormonal levels.
* **Imaging studies:** This includes an ultrasound of the pelvis and sonohysterography. These can help diagnose uterine fibroids, endometriosis, and other structural abnormalities of the reproductive organs.
* **Endometrial biopsy:** This involves removing a small tissue sample from the endometrium for microscopic analysis. The procedure may help in locating the underlying cause of irregular menstrual cycles, abnormal uterine bleeding, or other menstrual problems.
* **Hysteroscopy:** In order to observe the inside of the uterus, a thin hysteroscope is inserted through the cervix and vagina. The gynecologist may thoroughly inspect the uterine cavity with the help of the hysteroscope’s camera, which projects real-time images onto a display. Hysteroscopy can detect the presence of uterine fibroids and polyps.
* **Laparoscopy:** This is a minimally invasive technique that involves making small incisions in the abdominal wall through which a laparoscope and other specialized instruments are inserted to examine the pelvic organs. Laparoscopy is used to detect and treat endometriosis.
* **Dilation and curettage:** Dilation and curettage is a slightly invasive procedure and requires general anesthesia. It is carried out to investigate serious underlying conditions that could be causing abnormal bleeding. Dilation and curettage serve dual purposes: it allows the extraction of tissue samples for further examination and can also relieve heavy menstrual bleeding in some cases.

**MANAGEMENT OF MENSTRUAL DIAGNOSIS**

Lifestyle modifications

* Eat a healthy diet, consisting of vegetables and fruits. Have nuts and seeds. Omega fatty acids are great for menstrual health
* Food rich in iron helps in the prevention of iron deficiency anemia
* Stay away from alcohol and smoking
* Limit caffeine intake
* Exercise regularly
* Maintain proper weight
* Reduce stress with various stress-reducing techniques such as meditation and yoga
* Apply heating pads for cramps
* Take care of your menstrual hygiene.

**MEDICATIONS**

* **Oral contraceptives:** They are commonly known as birth control pills and consist of synthetic hormones. They are available as progestin-only or progestin and estrogen combined pills. Oral contraceptives are used to regulate the menstrual cycle and address specific menstrual disorders. They might not be safe for everyone and imply some side effects. Side effects include nausea, headache, menstrual irregularities, and weight changes.
* **Nonsteroidal anti-inflammatory drugs (NSAIDs):** They work by inhibiting the production of prostaglandins, thereby reducing inflammation and pain. NSAIDs include ibuprofen and naproxen.
* **Acetaminophen:** It is commonly known under the brand name Tylenol and is a widely used analgesic that helps manage pain caused by dysmenorrhea or other menstrual disorders.
* **GnRH agonists**: They are used for the treatment of hormone-dependent disorders. GnRH agonists work by acting on GnRH receptors in the pituitary gland, either by stimulating or suppressing the release of menstrual hormones. It is specifically used for managing endometriosis. Common side effects include hot flashes, mood swings, osteoporosis, and vaginal dryness.
* **Tranexamic acid:** It works by preventing the breakdown of blood clots, helpful in heavy bleeding.

**SURGICAL INTERVENTIONS**

When medical treatments have failed or when specific conditions are present, certain surgical procedures may be considered. These procedures include:

* **Endometrial ablation:** It is a surgical procedure that removes or destroys the uterine lining (endometrium) to address excessive or irregular uterine bleeding. With this surgery, severe or prolonged bleeding can be reduced or stopped in women without the necessity for a hysterectomy (the removal of the uterus).
* **Uterine artery embolization:** It is a minimally invasive procedure used to treat symptomatic uterine fibroids.
* **Myomectomy:** This is a surgical procedure to remove uterine fibroids while conserving the uterus as a whole. It is an alternative to hysterectomy for women who want to remain fertile.
* **Hysterectomy:** Hysterectomy is considered a last resort when other procedures have failed. It involves the removal of the uterus, which leads to the cessation of menstrual periods.
* **Hysteroscopy:** It can be performed as both a diagnostic and therapeutic procedure. In therapeutic procedures, it is used for removing uterine polyps or fibroids.

**Treating the underlying condition**

When a menstrual disorder is caused by an underlying disease or condition, it is necessary to treat the actual cause to completely cure the menstrual disorder. Only providing symptomatic relief without treating the underlying condition is not a permanent solution.

**POSSIBLE COMPLICATIONS OF MENSTRUAL DISORDERS**

If menstrual disorders are not treated timely, various complications can arise:

* **Anaemia:** Menstrual disorders that lead to excessive blood loss can contribute to iron deficiency anemia, which occurs when the body does not have enough iron to produce adequate amounts of hemoglobin.
* **Osteoporosis:** It is a condition characterized by the weakening of bones, making them more prone to fractures and breaks. A low level of estrogen increases the risk of osteoporosis over time.
* **Infertility:** Certain menstrual disorders interfere with the ability of ovaries to form an egg, resulting in difficulty conceiving. The common disorders that can cause infertility include endometriosis, PCOS, and fibroids.
* **Psychosocial impact:** Hormonal imbalances that underlie irregular periods can have widespread effects on other body functions, resulting in symptoms such as acne, hirsutism (excessive hair growth), low mood, anxiety, and irritability.

**WHEN TO SEE A DOCTOR / RED FLAG**

You should seek medical advice if:

* Your periods are consistently very heavy or prolonged
* You are experiencing severe pain during your menstrual cycle that is not relieved by painkillers
* Your periods have been skipped for more than three months, and you are not pregnant
* You are experiencing irregular bleeding in between normal menstrual periods
* You are observing mood swings, depression, anxiety, or other emotional changes that interfere with your daily life
* You are experiencing menopause symptoms such as hot flashes, night sweats, or vaginal dryness, while you are under 40 years.

**CAUSES OF MENSTRUAL DISORDERS**

*Which infections cause menstrual disorders?*

Menstrual disorders can result from various types of infections, including pelvic inflammatory disease, urinary tract infections, vaginal infections, and sexually transmitted diseases.

*Which foods cause heavy periods?*

There are no particular foods that directly cause heavy periods. However, some foods can worsen menstrual symptoms and contribute indirectly to heavy periods. These include processed and salty foods, alcohol, and caffeine.

**RECOMMENDATIONS (RECENT GUIDELINES / UPDATES)**

Heavy menstrual bleeding has a major impact on a woman’s quality of life. The patient’s assessment of treatment response is paramount. Medical management should be the first line treatment for the majority of women. Considerations include, the woman’s needs and preferences, future fertility wishes, previous treatments and their effects, and any potential contraindications to treatments.

Pharmacological Managements Pharmacological treatments should be considered for all women, with the exception of levonorgestrel intrauterine system (LNG-IUS) where rates of expulsion are higher with fibroids >3 cm, particularly where there is distortion of the uterine cavity. When a first pharmaceutical treatment has proven to be ineffective, a second pharmaceutical treatment can be considered rather than immediate referral for additional review.

Pharmacological (non-hormonal) Tranexamic Acid 1g TID oral with menstruation, max 3-4 days.

• It is an anti-fibrinolytic and reduces bleeding by approximately 50%.

• Suitable as a long term treatment but alternative treatments should be considered if no improvement after 3 cycles.

• Not suitable for patients with a personal history of venous thromboembolic disease.

• Suitable for use where fertility is desired.

NSAIDS:

• Naproxen, ibuprofen and mefenamic acid have similar efficacy in the treatment of HMB and can reduce bleeding by 20-50%

• Mefenamic acid is licenced for the treatment of HMB, where the other NSAIDS are licenced for menstrual bleeding associated with pain.

• NSAIDs can be used in conjunction with Tranexamic Acid.

• NSAIDs are not suitable for patients who are sensitive to their effects e.g. gastric ulcers, aspirin sensitive asthma

• Suggested regimes include

• Naproxen 500mg oral initially, followed by 250mg 6-8 hourly (max 1.25g/day) with menstruation or

• Ibuprofen 300–400 mg 3–4 times a day with menstruation or

• Mefenamic Acid 500mg TID oral with menstruation. Pharmacological (Hormonal) Levonorgestrel Intrauterine System (LNG-IUS, Mirena ®)

• Reduces menstrual loss by up to 90% after 6 months of use.

• Can be initiated as a first line option if at least one year of use is expected.

• Erratic vaginal bleeding is common in the first 4-6 months of use but rarely heavy or painful.

• There are very few contraindications to LNG-IUS.

• Systemic effects are uncommon and often improve after the first 2-3 months.

• LNG-IUS is a highly effective contraceptive and can also be used as the progestogen component of Hormone replacement therapy (5 years).

• Expulsion is higher where there are fibroids >3 cm. Combined Hormonal Contraception

• Highly effective in reducing menstrual blood loss and associated menstrual pain.

• Tailored regimes with shorter hormone free intervals (HFI) have shown a greater improvement in symptoms of HMB.

*Progestogens The progesterone only pill (POP)*

• Can be used where oestrogen is contra-indicated.

• Irregular bleeding is common.

• Desogestrel preparations (e.g.Cerazette®, Cerelle®) appear to be more effective in reducing menstrual loss and for contraceptive protection than other progesterone only preparations. Progestogen-only injectables: depot medroxyprogesterone acetate (DMPA)

• Many women are rendered amenorrhoic by DMPA (e.g. Depo Provera® 150mg, 12 weekly as an intramuscular injection).

• Erratic bleeding is common in the first few months of use however often improves with time. CSM advice The CSM has advised that:

• In adolescents DMPA is used only when other methods of contraception are inappropriate.

• In all women, benefits of using DMPA beyond 2 years should be evaluated against risks.

• In women with risk factors for osteoporosis a method of contraception other than DMPA should be considered. Cyclical Progestogens

• Norethisterone (5 mg TID, days 5 to 26 of the menstrual cycle)

• Can significantly reduce menstrual loss.

• Can inhibit ovulation, but should not be considered an effective form of contraception.

• Use limited by the common progestogenic side effects such as breast tenderness, bloating and acne.

• There is an effect on clotting and high dose progestins are contraindicated for patients at high risk for VTE. (10-20mg of Norethisterone a day equates to 20-30g ethinylestradiol) Surgical Management - Normal pelvic anatomy or fibroids <3 cm with no distortion of endometrial cavity Endometrial Ablation

• Successful reduction in menstrual blood loss in up to 90% of women, with 25-35% of women experiencing amenorrhoea.

• Suitable for women with a uterus sounded at 10cm size with fibroids of up to 3 cm which do not distort the cavity.

• Can be performed as an outpatient or day case procedure.

• This procedure should only be considered in women who have completed their family and contraception should be continued post procedure.

• Women with a previous caesarean delivery should have a scar thickness measured with transvaginal ultrasound of ≥8mm. Where scar is ≤7mm, it is possible to treat, the technique is described in endometrial ablation guideline.

• An endometrial biopsy should be obtained ideally in advance of the procedure. Hysterectomy

• Total hysterectomy is the only procedure that will guarantee amenorrhoea and has high patient satisfaction rates.

• Hysterectomy has a 4 in 100 risk of major complication.

• Preoperative consideration should be given to smear history (where a subtotal procedure is required) and previous surgery particularly caesarean delivery.

• Oophorectomy should not be performed routinely if ovaries are healthy.

• Patients should be advised that ovarian failure is earlier following hysterectomy.

• Where there is a suggestion of ovarian dysfunction e.g. premenstrual syndrome, a trial of pharmaceutical ovarian suppression for at least 3 months should be used as a guide to the need for oophorectomy.

• The optimal surgical approach (abdominal, vaginal or laparoscopic) will depend on discussion between the patient and her gynaecologist.

• Ensure the patient understands the differences between sub-total, total hysterectomy and hysterectomy with bilateral salpingo-oophorectomy (BSO). Pharmacological Hormonal Management - Fibroids 3 cm or more in diameter, normal endometrial histology Gonadotrophin Releasing Hormone Analogues (GnRHa)

• The use of GnRHa may be considered prior to surgery or when all other treatment options for uterine fibroids are contraindicated.

• These preparations will stop the menstrual cycle as they induce a temporary menopause.

• Vasomotor symptoms are very common but add-back HRT can be used to treat side effects.

• These preparations are only licensed for 6 months of use and should only be used in the context of a formal management plan following discussion with a consultant. Surgical Management - Fibroids 3 cm or more in diameter, normal endometrial histology Women who wish to preserve their uterus

• Hysteroscopic Resection of submucous fibroids

• Referral to gynaecologist with special interest for management

• Myomectomy • Suitable for women who wish to preserve her fertility.

• There is a small risk that emergency hysterectomy may be performed.

• Consider pretreatment with a GnRHa for 3 to 4 months.

• The uterus and fibroids should be assessed by ultrasound prior to the procedure, with MRI considered where information about fibroid position, size, number and vascularity is required Uterine Artery Embolisation (UAE).

• Women who wish to avoid surgery should be referred to interventional radiology for assessment.

• There is a small (about 10%) risk of ovarian failure due to the effect of embolisation on the collateral supply of the ovary.

• It is useful to organise MRI imaging at the same time as referring to the interventional radiology team as it allows full counseling and assessment. Hysterectomy •

• Pretreatment before hysterectomy with a GnRHa for 3 to 4 months should be considered particularly where uterine fibroids are causing an enlarged or distorted uterus

**Patients With Physical or Cognitive Disabilities or Both**

Menstrual suppression is a safe and viable option for patients with physical or cognitive disabilities or both who need or want to have fewer or no menses. Although suppression should not be started until menarche, anticipatory guidance before menarche can be very useful and may lessen anxiety felt by patients and caregivers.

Patients with cognitive delay may have trouble comprehending menstruation or may face challenges maintaining personal hygiene during menstruation. In this setting, the approach to menstrual suppression should be comparable with that in patients who are neurotypical (ie, without a defined neurologic difference) by starting with the lowest-risk and reversible options.

Gynecologists should educate patients as much as possible based on their cognitive abilities, maintain respect, maximize autonomy, avoid harm, and address patient and caregiver concerns.

**Drug Interactions**

Gynecologists should conduct a thorough review of a patient’s use of over-the-counter and prescribed medications to address any potential drug interactions with hormonal medications for menstrual suppression.

**EPIDEMIOLOGY OF MENSTRUAL DISORDERS**

* Prevalence Range:  
  The prevalence of menstrual disorders varies widely across populations, ranging from 3% to 87% depending on the type of disorder and study population.
* Common Disorders and Their Prevalence:
  + Dysmenorrhea: Reported in 46% to 76% of women, making it the most common menstrual disorder globally and in specific populations like medical students
  + Premenstrual Syndrome (PMS): Prevalence ranges from 40% to 71%
  + Polycystic Ovary Syndrome (PCOS): Less common, with prevalence estimates between 3% and 14.14% in Indian populations.
  + Heavy Menstrual Bleeding (HMB): Increases with age; reported prevalence rises from 17.6% at age 22 to 32.1% at age 48 in Australian women.
* Associated Risk Factors:  
  Lifestyle and demographic factors influencing menstrual disorders include:
  + Sedentary lifestyle and lack of exercise
  + Obesity and high body mass index (BMI)
  + Inadequate diet and high consumption of junk food
  + Psychological stress, especially related to academic pressure or life events
  + Smoking and family history of menstrual disorders
  + Age at menarche and marriage
  + Place of residence (urban vs rural differences)
* Impact on Quality of Life and Health:  
  Menstrual disorders are linked to significant morbidity, including:
  + Increased depressive symptoms and mental health burden
  + School and work absenteeism, with pooled menstrual-related absenteeism estimated at 15% globally, highest in South Asia (~20%)
  + Reduced physical and mental health-related quality of life, especially in women experiencing heavy menstrual bleeding
* Health-Seeking Behavior:  
  Approximately one-third of women with menstrual disorders seek medical treatment, indicating a gap in awareness, access, or social stigma that may hinder care
* Global and Regional Context:
  + Menstrual health education and hygiene remain inadequate worldwide, with only about 39% of schools globally providing menstrual health education
  + Access to menstrual products and sanitation facilities is limited in many low- and middle-income countries, impacting menstrual health management

**DIFFERENTIAL DIAGNOSIS OF MENSTRUAL DISORDERS**

1. Amenorrhea (Absence of Menstruation)

* Primary Amenorrhea (no menses by age 16):
  + Anatomical defects: Müllerian agenesis (Mayer-Rokitansky-Küster-Hauser syndrome), imperforate hymen, transverse vaginal septum
  + Gonadal dysgenesis: Turner syndrome (45,X), Swyer syndrome (46,XY)
  + Hypogonadotropic hypogonadism: Kallmann syndrome, functional hypothalamic amenorrhea (stress, exercise, eating disorders)
  + Pituitary causes: Prolactinoma, hypopituitarism
  + Enzyme deficiencies: 17,20-desmolase deficiency
  + Androgen insensitivity syndrome
* Secondary Amenorrhea (cessation of menses after menarche):
  + Pregnancy (most common cause)
  + Hypothalamic dysfunction (stress, weight loss, excessive exercise)
  + Pituitary disorders (prolactinoma, Sheehan syndrome)
  + Ovarian failure (premature ovarian insufficiency)
  + Polycystic ovary syndrome (PCOS)
  + Thyroid disorders (hypo- or hyperthyroidism)
  + Hyperprolactinemia
  + Uterine causes (Asherman syndrome)

2. Heavy Menstrual Bleeding (Menorrhagia)

* Structural causes (PALM):
  + Polyps
  + Adenomyosis
  + Leiomyoma (fibroids)
  + Malignancy and hyperplasia
* Non-structural causes (COEIN):
  + Coagulopathy (e.g., von Willebrand disease)
  + Ovulatory dysfunction (anovulation, PCOS)
  + Endometrial disorders
  + Iatrogenic (medications, devices)
  + Not yet classified

3. Irregular/Uterine Bleeding (Metrorrhagia, Menometrorrhagia)

* Ovulatory dysfunction (PCOS, thyroid disease, hyperprolactinemia)
* Endometrial pathology (hyperplasia, polyps)
* Infection (endometritis)
* Cervical or vaginal lesions
* Perimenopausal hormonal fluctuations

4. Dysmenorrhea (Painful Periods)

* Primary dysmenorrhea: No pelvic pathology; related to prostaglandin excess
* Secondary dysmenorrhea: Due to pelvic pathology such as:
  + Endometriosis
  + Adenomyosis
  + Pelvic inflammatory disease (PID)
  + Uterine fibroids
  + Congenital anomalies

5. Premenstrual Syndrome (PMS) and Premenstrual Dysphoric Disorder (PMDD)

* Cyclic physical and emotional symptoms related to luteal phase
* Must differentiate from mood disorders, thyroid disease, and other psychiatric conditions

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[**Irregular Periods (Abnormal Menstruation): Causes & Treatment**](https://my.clevelandclinic.org/health/diseases/14633-abnormal-menstruation-periods)

# **TOXIC MULTINODULAR GOITER**

## *ALTERNATIVE NAMES: “*Toxic multinodular goiter”, “Plummer disease”, “Thyrotoxicosis - nodular goiter”, “Overactive thyroid - toxic nodular goiter”, “Hyperthyroidism - toxic nodular goiter”, “Toxic multinodular goiter”, “MNG”

**DEFINITION / DESCRIPTION**

Toxic nodular goiter involves an enlarged thyroid gland. The gland contains areas that have increased in size and formed nodules. One or more of these nodules produce too much thyroid hormone.

A toxic nodular goiter (TNG) is a thyroid gland that contains autonomously functioning thyroid nodules, with resulting hyperthyroidism. There are distinct considerations if the patient has a single solitary toxic nodule (see Solitary Thyroid Nodule). TNG, or Plummer disease, was first described by Henry Plummer, in 1913.

TNG is the second most common cause of hyperthyroidism in the Western world, after Graves’ disease.[[1](about:blank)]In elderly individuals and in areas of endemic iodine deficiency, TNG is the most common cause of hyperthyroidism.

Toxic multinodular goiter (TMNG), also known as multinodular toxic goiter (MNTG), is **an active multinodular goiter associated with hyperthyroidism**. It is a common cause of hyperthyroidism in which there is excess production of thyroid hormones from functionally autonomous thyroid nodules, which do not require stimulation from thyroid-stimulating hormone (TSH). It is the second most common cause of hyperthyroidism (after Graves' disease) in the developed world.

Toxic multinodular goiter **involves an enlarged thyroid gland that contains one or more nodules, which produce too much thyroid hormone**. These nodules are typically benign growths and can lead to hyperthyroidism. The condition is more common in individuals over 60 years of age and in females.

The development of toxic multinodular goiter is often linked to a long-standing simple goiter, and it is characterized by the autonomous activity of the nodules, independent of pituitary TSH feedback. This can result in a net overproduction of thyroid hormone, leading to hyperthyroidism.

Symptoms of toxic multinodular goiter include those of hyperthyroidism, such as a rapid heart rate, but do not include the protruding eyeballs seen in Graves' disease. Diagnosis typically involves a physical examination, thyroid scan, and blood tests to measure thyroid hormone levels and TSH.

Toxic multinodular goiter is also referred to as **Plummer's disease**. It is considered to be the second most common cause of hyperthyroidism, with Graves' disease being the first.

**TOXIC NODULE OR TOXIC MULTINODULAR GOITER**

Toxic nodule or toxic multinodular goiter refers to one or more nodules (typically benign growths) in the thyroid gland that make thyroid hormone without responding to the signal to keep thyroid hormone balanced. The end result is that too much thyroid hormone can be produced and released into the bloodstream, resulting in hyperthyroidism.

**CAUSES**

Toxic multinodular goiter starts from an existing simple goiter. It occurs most often in older adults. Risk factors include being female and over 55 years old. This disorder is rare in children. Most people who develop it have had a goiter with nodules for many years. Sometimes the thyroid gland is only slightly enlarged, and the goiter was not already diagnosed.

Sometimes, people with toxic multinodular goiter will develop high thyroid hormone levels for the first time after:

* Taking iodine through a vein (intravenously) or by mouth. The iodine may be used as contrast for a CT scan or heart catheterization (most common)
* Taking medicines that contain iodine, such as amiodarone
* Moving from a country with iodine deficiency to a country with a lot of iodine in the diet

Toxic multinodular goiter (TMNG) is primarily caused by a **chronic lack of dietary iodine**, which leads to decreased thyroid hormone production. In response, the anterior pituitary releases thyroid-stimulating hormone (TSH), causing thyroid hypertrophy and hyperplasia. However, some parts of the thyroid gland are more responsive to TSH, leading to uneven growth and the formation of nodules. Over time, some of these nodules may develop autonomous function due to somatic mutations in the thyrotropin (TSH) receptor, resulting in excessive thyroid hormone production and hyperthyroidism. Additionally, iodine deficiency can cause goiter, and within a goiter, nodules can develop, increasing the risk of TMNG. Other factors, such as iodine supplementation or iodinated contrast agents, can also trigger hyperthyroidism in individuals with underlying nontoxic multinodular goiter.

Factors contributing to its development include iodine deficiency, genetics, aging, and autoimmune conditions like Hashimoto's thyroiditis.  These nodules become autonomous and produce hormones independently of the body's regulatory mechanisms, resulting in hyperthyroidism.

* Excessive iodine intake, whether through diet or medications, can lead to the development of toxic multinodular goiter.
* Aging is a common cause of toxic multinodular goiter, as the thyroid gland may develop nodules and become overactive over time.
* Genetics plays a role in the development of toxic multinodular goiter, with a family history of thyroid disorders increasing the risk.
* Autoimmune conditions such as Hashimoto's thyroiditis or Graves' disease can trigger the formation of toxic nodules in the thyroid gland.
* Environmental factors, such as exposure to radiation or certain chemicals, can contribute to the development of toxic multinodular goiter in susceptible individuals.

**Types Of Toxic Multinodular Goiter**

* Plummer's disease is a type of toxic multinodular goiter characterized by the presence of multiple overactive nodules in the thyroid gland, leading to excessive production of thyroid hormones.
* Marine-Lenhart syndrome is a rare form of toxic multinodular goiter where the thyroid nodules exhibit autonomy in hormone production, causing symptoms of hyperthyroidism.
* Adenomatous toxic multinodular goiter refers to a condition where one or more nodules in the thyroid gland become hyperfunctional, resulting in the overproduction of thyroid hormones and subsequent hyperthyroid symptoms.
* Toxic adenoma is a type of toxic multinodular goiter in which a single nodule in the thyroid gland becomes autonomously hyper

**RISK FACTORS**

Toxic multinodular goiter (TMNG) has several risk factors. These include **advanced age, particularly in individuals over 60 years old, and being female**.

Other risk factors include a family history of thyroid disorders, iodine deficiency, and exposure to radiation.

Additionally, smoking and certain medications can contribute to the development of this condition. Secondary factors such as elevated thyroid-stimulating hormone (TSH), smoking, stress, certain drugs, and other thyroid-stimulating factors also play a role.

Risk factors for toxic multinodular goiter include older age, female gender, a family history of thyroid disorders, iodine deficiency, and exposure to radiation. Smoking and certain medications can also contribute to the development of this condition. Proper management and regular monitoring are crucial for individuals with these risk factors to prevent complications and optimize treatment outcomes.

* Advanced age, particularly in individuals over 60 years old, is a significant risk factor for developing toxic multinodular goiter.
* A family history of thyroid disorders, including multinodular goiter, can increase the likelihood of developing the toxic form of the condition.
* Exposure to excessive amounts of iodine through diet or medications is a known risk factor for the development of toxic multinodular goiter.
* Women are more likely than men to develop toxic multinodular goiter, with hormonal factors playing a role in this increased risk.
* Previous radiation exposure to the neck or chest area, such as in the treatment of other conditions, can predispose individuals to developing toxic multinodular goiter.

## **SIGNS / SYMPTOMS**

Symptoms may include any of the following:

* Fatigue
* Frequent bowel movements
* Heat intolerance
* Increased appetite
* Increased sweating
* Irregular menstrual period (in women)
* Muscle cramps
* Nervousness
* Restlessness
* Weight loss

Older adults may have symptoms that are less specific. These may include:

* Weakness and fatigue
* Palpitations and chest pain or pressure
* Changes in memory and mood

Toxic nodular goiter does not cause the bulging eyes that can occur with Graves’ disease. Graves’ disease is an autoimmune disorder that leads to an overactive thyroid gland (hyperthyroidism).

## **DIAGNOSIS METHODS**

## **Exams and Tests**

A physical exam may show one or many nodules in the thyroid. The thyroid is often enlarged. There may be a rapid heart rate or shaking hands (tremor).

Other tests that may be done include:

* Serum thyroid hormone levels (T3, T4)
* Serum TSH (thyroid stimulating hormone)
* Thyroid uptake and scan
* Thyroid ultrasound

These tests help to confirm the presence of enlarged nodules in your thyroid gland that are producing excess thyroid hormones. Based on these results, your doctor will create a treatment plan tailored to your specific condition.

* Blood tests to measure thyroid hormone levels and thyroid-stimulating hormone (TSH) can help diagnose toxic multinodular goiter.
* Imaging tests such as ultrasound, CT scans, or MRIs may be used to visualize the thyroid gland and identify nodules in cases of toxic multinodular goiter.
* Fine-needle aspiration biopsy can help determine if the nodules in the thyroid gland are cancerous or benign.
* Radioactive iodine uptake test can evaluate the function of the thyroid gland and detect any areas of increased activity, common in cases of toxic multinodular goiter.
* Thyroid scan using radioactive iodine can provide information on the size and activity of nodules in the thyroid gland, aiding.

## **TREATMENT OPTIONS**

Beta-blockers can control some of the symptoms of hyperthyroidism until thyroid hormone levels in the body are under control.

Certain medicines can block or change how the thyroid gland uses iodine. These may be used to control the overactive thyroid gland in any of the following cases:

* Before surgery or radioiodine therapy occurs
* As a long-term treatment

Radioiodine therapy may be used. Radioactive iodine is given by mouth. It concentrates in the overactive thyroid tissue and causes damage. In rare cases, thyroid replacement is needed afterward.

Surgery to remove the thyroid may be done when:

* A very large goiter or a goiter is causing symptoms by making it hard to breathe or swallow
* Thyroid cancer is present
* Rapid treatment is needed

Patients at the stage of subclinical hyperthyroidism can be monitored without intervention, with the recommendation to avoid excessive iodine intake in the form of supplements and medications and avoid iodinated contrast media for radiological studies if possible. Patients with risk factors for atrial fibrillation or with atrial fibrillation, patients with osteoporosis, and women with osteopenia should be treated, even if they have subclinical hyperthyroidism due to toxic multinodular goiter.

**Surgery:** Surgical treatment is the mainstay therapy for toxic MNG. It provides rapid resolution with low morbidity and mortality. A selective strategy avoids remnant nodules and preserves a normal functional remnant. It led to low morbidity and increased recurrence compared to radical resection, which is associated with increased morbidity but less recurrence. Clinical recurrence may occur in some patients after surgery, but it is rare after 10 years. Patients are expected to have post-treatment hypothyroidism after surgery. Total, near-total, or subtotal thyroidectomy may be done according to the disease state. Surgical treatment may lead to complications, including:

* Unilateral or bilateral vocal cord paralysis
* Hypoparathyroidism
* Significant postoperative bleeding or infection
* Tracheostomy

**Radioactive iodine ablation (RIA):** RIA (sodium iodide-131) is indicated in treating Plummer disease. It has no absolute contraindication except for pregnancy. A single dose is usually required, and recent studies suggest customized dose calculation and not a fixed-dose formula. RAI is a safe and effective treatment but does not entirely resolve the disease, and the results are delayed. There is also an increased risk for the development of secondary cancers because of radioactive iodine treatment. Complications of RAI include:

* Hypothyroidism
* Mild thyrotoxic symptoms
* Exacerbation of congestive cardiac failure and atrial fibrillation
* Tracheal compression
* Thyroid storm (rare)

**Antithyroid drugs:** Propylthiouracil and methimazole are used in the period of waiting until RAI is given and for surgery preparation. Propylthiouracil is preferred over methimazole in pregnant patients during the first trimester. Long-term methimazole therapy is safe in patients with Plummer disease. Methimazole therapy converts the hot thyroid nodule to hypofunctioning nodule over time, according to studies using scintigrams.

**Ethanol ablation:**Percutaneous ethanol ablation is a minimally invasive procedure for hyperfunctioning nodules. It can be performed in the outpatient department. Before careful ultrasound assessment, thyroid scintigraphy and thyroid FNA cytology for cold nodules should rule out malignancy before ethanol injection of hot nodules. Ethanol ablation is favorable for patients who are unfit to undergo surgery. It should be noted that this is not a routine treatment as it must be done weekly for several sessions. This treatment shows good short-term outcomes, but the long-term outcomes are unsatisfactory.

**Other drugs:**Cardiovascular effects such as hypertension and tachycardia should be treated with beta-blockers.

## **OUTLOOK / PROGNOSIS**

Toxic nodular goiter is mainly a disease of older adults. So, other chronic health problems may affect the outcome of this condition. An older adult may be less able to tolerate the effect of the disease on the heart. However, the condition is often treatable with medicines.

Some toxic multinodular goiters do not need treatment if they are not causing any symptoms or if the degree of hyperthyroidism is at the subclinical level (normal T4, T3, and low TSH). Symptomatic multinodular goiters need surgical resection or radioactive ablation. Disease recurrence is very low after surgery. Overall, Plummer disease has a good prognosis.

Most treated patients have a good prognosis. A worse prognosis is related to untreated hyperthyroidism. Patients should understand the gravity of hyperthyroidism. If left untreated, hyperthyroidism may lead to osteoporosis, arrhythmia, heart failure, coma, and death. Regular assessment of thyroid function is important in monitoring disease.

Iodine-131 (131I) ablation may result in continued hyperthyroidism, with some patients (up to 73% in some studies, depending on the size of the goiter and dosing of radioiodine) requiring repeated treatment or surgical removal of the gland. Hypothyroidism after radioiodine ablation has been reported in 0-35% of individuals.

Surgical treatment usually consists of a lobectomy of the hyperfunctioning nodule. The rate of hypothyroidism associated with this procedure is very low. Rates of hyperthyroidism recurrence with surgery have been reported to be as low as 0-9%. Larger, multinodular goiters may require total thyroidectomy.

**POSSIBLE COMPLICATIONS**

Heart complications:

* Heart failure
* Irregular heartbeat (atrial fibrillation)
* Rapid heart rate

Other complications:

* Bone loss leading to osteoporosis

Thyroid crisis or storm is a sudden worsening of hyperthyroidism symptoms. It may occur with infection or stress. Thyroid crisis may cause:

* Abdominal pain
* Decreased mental alertness
* Fever

People with this condition need to go to the hospital right away.

Complications of having a very large goiter may include difficulty breathing or swallowing. This is due to pressure on the airway passage (trachea) or esophagus, which lies behind the thyroid.

Plummer disease may lead to a variety of complications, including:

* Progression of hyperthyroidism with hyperthyroid signs and symptoms. Toxic MNG may cause osteoporosis, bone fractures, tachycardia, arrhythmia, atrial fibrillation, or heart failure. Thyrotoxicosis may exacerbate underlying coronary heart disease by increasing the oxygen demand and may also cause worsening asthma symptoms, COPD, atherosclerotic cardiovascular disease, and congestive heart failure.
* A decrease in bone density, hypercalciuria, hypercalcemia, and accelerated bone loss may occur. Studies show variable results regarding the reversibility of bone changes. Plummer disease also increases the risk of fractures.
* The thyroid gland in Plummer disease may harbor malignancy. Hyperthyroidism, along with malignancy, has been reported in 1.2% to 13.3% of surgeries for both causes.
* Pain over the thyroid area can occur if there is any hemorrhage, especially in 1 of the cystic nodules if coincidentally present in a toxic multinodular goiter.
* A thyroid storm may be precipitated by triggering factors like infection or stress, causing the worsening of symptoms, fever, abdominal pain, and decreased mental alertness. The frequency of thyroid storms is lower in toxic multinodular goiter than in Graves’ disease.
* An increase in the size of the thyroid gland due to Plummer disease may compress the trachea and esophagus, causing dyspnea, voice hoarseness (due to compression of the recurrent laryngeal nerve), dysphagia, tracheomalacia, and asphyxiation.

## **WHEN TO SEE A DOCTOR / RED FLAG**

Contact your health care provider if you have symptoms of this disorder listed above. Follow your provider's instructions for follow-up visits.

## **PREVENTION TIPS**

To prevent toxic nodular goiter, treat hyperthyroidism and simple goiter as your provider suggests.

Toxic multinodular goiter is a condition characterized by the presence of multiple nodules in the thyroid gland that produce excess thyroid hormone, leading to hyperthyroidism. While the exact causes of toxic multinodular goiter are not fully understood, certain preventive measures can help reduce the risk or manage the condition effectively. Here are some prevention tips:

Iodine Intake: Iodine deficiency is a known risk factor for goiter, including toxic multinodular goiter. Consuming a diet that includes iodized salt, fish, and dairy products can help prevent iodine deficiency.

However, it is important to note that excessive iodine intake can also be harmful, especially for individuals with pre-existing thyroid conditions.

* Regular Medical Check-ups: Regular visits to a healthcare provider are essential for monitoring thyroid health. Early detection and management of thyroid disorders can prevent the progression of conditions like toxic multinodular goiter.
* Treatment of Hyperthyroidism: Prompt and effective treatment of hyperthyroidism can help prevent the development of toxic multinodular goiter. This may include medications, radioactive iodine therapy, or surgery, depending on the severity and underlying causes.
* Avoiding Environmental Triggers: Exposure to certain environmental factors, such as radiation, can increase the risk of thyroid disorders. Avoiding unnecessary radiation exposure and maintaining a healthy lifestyle can contribute to thyroid health.
* Genetic Counseling: Given the potential genetic factors involved in the development of toxic multinodular goiter, individuals with a family history of thyroid disorders may benefit from genetic counseling and regular screening.
* Managing Chronic Conditions: Managing other chronic health conditions, such as autoimmune thyroid diseases, can help reduce the risk of developing toxic multinodular goiter. Conditions like Hashimoto's thyroiditis and Graves' disease are associated with an increased risk of thyroid nodules and goiters.

By following these prevention tips, individuals can reduce their risk of developing toxic multinodular goiter and maintain overall thyroid health. It is always advisable to consult a healthcare provider for personalized recommendations and regular monitoring.

## **EPIDEMIOLOGY**

### *United States statistics*

Toxic nodular goiter accounts for approximately 15-30% of cases of hyperthyroidism in the United States, second only to Graves’ disease.

### *International statistics*

In areas of endemic iodine deficiency, TNG accounts for approximately 58% of cases of hyperthyroidism, 10% of which are from solitary toxic nodules. Graves’ disease accounts for 40% of cases of hyperthyroidism. In patients with underlying nontoxic multinodular goiter, initial iodine supplementation (or iodinated contrast agents) can lead to hyperthyroidism (Jod-Basedow effect). Iodinated drugs, such as amiodarone, may also induce hyperthyroidism in patients with underlying nontoxic multinodular goiter. Roughly 3% of patients treated with amiodarone in the United States (more in areas of iodine deficiency) develop amiodarone-induced hyperthyroidism.

### *Sex- and age-related demographics*

TNG occurs more commonly in women than in men. In women and men older than 40 years, the prevalence rate of palpable nodules is 5-7% and 1-2%, respectively.

Most patients with TNG are older than 50 years.

Thyrotoxicosis often occurs in patients with a history of longstanding goiter. Toxicity occurs in a subset of patients who develop autonomous function. This toxicity usually peaks in the sixth and seventh decades of life, especially in persons with a family history of multinodular goiter or TNG, suggesting a genetic component.

Plummer disease (toxic multinodular goiter) is considered to be the second most common cause of hyperthyroidism (the first being Graves’ disease). It is more common among females. It is also prevalent in the 50 and above age group, both males and females. In comparison to Plummer disease, Graves’ disease occurs among younger age groups. Thyrotoxicosis occurs in Plummer disease after long-standing goiter, and it peaks in the sixth or seventh decade of life, especially in patients with a family history of toxic multinodular goiter.

## **DIFFERENTIAL DIAGNOSIS**

* Diffuse Toxic Goiter (Graves’ Disease)
* Goiter
* Graves’ Disease
* Nontoxic Goiter
* Papillary Thyroid Carcinoma
* Riedel Thyroiditis
* Struma Ovarii
* Thyroid Nodule
* Subacute Thyroiditis
* Hashimoto thyroiditis at the Hashitoxicosis stage
* Nontoxic (euthyroid) multinodular goiter

*REFERENCES*

[Toxic Nodular Goiter: Background, Pathophysiology, Etiology](https://emedicine.medscape.com/article/120497-overview#a6)

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**Types of Endocrine Disorders**

There are many different types of endocrine disorders. Diabetes is the most common endocrine disorder diagnosed in the U.S.

*Other endocrine disorders include:*

**Adrenal insufficiency:** The adrenal gland releases too little of the hormone cortisol and sometimes, aldosterone. Symptoms include fatigue, stomach upset, dehydration, and skin changes. Addison's disease is a type of adrenal insufficiency.

**Cushing's disease:** The overproduction of a pituitary gland hormone leads to an overactive adrenal gland. A similar condition called Cushing's syndrome may occur in people, particularly children, who take high doses of corticosteroid medications.

**Gigantism (acromegaly) and other growth hormone problems:** If the pituitary gland produces too much growth hormone, a child's bones and body parts may grow abnormally fast. If growth hormone levels are too low, a child can stop growing in height.

**Hyperthyroidism:** The thyroid gland produces too much thyroid hormone, leading to weight loss, fast heart rate, sweating, and nervousness. The most common cause for an overactive thyroid is an autoimmune disorder called Grave's disease.

**Hypothyroidism:** The thyroid gland does not produce enough thyroid hormone, leading to fatigue, constipation, dry skin, and depression. The underactive gland can cause slowed development in children. Some types of hypothyroidism are present at birth.

**Hypopituitarism:** In this condition, the pituitary gland releases little or no hormones. It may be caused by several different diseases. Women with this condition may stop getting their periods.

**Multiple endocrine neoplasia type 1 and 2 (MEN1 and MEN2):** These rare, genetic conditions are passed down through families. They cause tumors of the parathyroid, adrenal, and thyroid glands, leading to overproduction of hormones.

**Polycystic ovary syndrome (PCOS):** The overproduction of androgens interferes with the development of eggs and their release from the female ovaries. PCOS is a leading cause of infertility.

**Precocious puberty:** This refers to abnormally early puberty that occurs when glands tell the body to release sex hormones too soon in life.

**Endocrine Disorder Causes**

Endocrine disorders are typically grouped into two categories:

* Endocrine diseases that result when a gland produces too much or too little of an endocrine hormone which are sometimes known as a hormone imbalance.
* Endocrine diseases that happen due to the development of lesions (such as nodules or tumors) in the endocrine system, which may or may not affect hormone levels.

The endocrine feedback system helps control the balance of hormones in the bloodstream. If your body has too much or too little of a certain hormone, the feedback system signals the proper gland or glands to correct the problem. A hormone imbalance may occur if this feedback system has trouble keeping the right level of hormones in the bloodstream, or if your body doesn't clear them out of the bloodstream properly.

Increased or decreased levels of endocrine hormone may be caused by:

* A problem with the endocrine feedback system
* Disease
* Failure of a gland to stimulate another gland to release hormones (for example, a problem with the hypothalamus can disrupt hormone production in the pituitary gland)
* A genetic disorder, such as multiple endocrine neoplasia (MEN) or congenital hypothyroidism
* Infection
* Injury to an endocrine gland
* Tumor of an endocrine gland

Most endocrine tumors and nodules (lumps) are noncancerous. They usually don't spread to other parts of the body. However, a tumor or nodule on the gland may interfere with the gland's hormone production.

**Symptoms of Endocrine Disorders**

The symptoms of an endocrine disorder vary widely and depend on the specific gland involved. However, most people with endocrine disease complain of fatigue and weakness. Certain symptoms may make you think you have a different disease or disorder. Some symptoms that are worth talking to your doctor about include:

* Changes in your heart rate
* Changes to your skin or eyes
* Bone fractures
* High blood sugar levels
* High calcium levels
* Low or high blood pressure
* Unexplained changes in your weight
* Loss of sex drive
* Infertility
* Menstrual cycle disorders

**Testing for Endocrine Disorders**

If you have an endocrine disorder, your doctor may refer you to a specialist called an endocrinologist. An endocrinologist is specially trained in problems with the endocrine system.

Blood and urine tests to check your hormone levels can help your doctors determine if you have an endocrine disorder. Imaging tests may be done to help locate or pinpoint a nodule or tumor.

Treatment of endocrine disorders can be complicated, as a change in one hormone level can throw off another. Your doctor or specialist may order routine blood work to check for problems or to determine if your medication or treatment plan needs to be adjusted.

*REFERENCE:*

<https://www.webmd.com/diabetes/endocrine-system-disorders>

<https://www.webmd.com/diabetes/endocrine-system-disorders>

**GOITER**

*ALTERNATIVE NAMES:* Goiters are also known as “struma”, “enlarged thyroid”, “swelling of the neck”, “neck swelling”, “thyromegaly”, “colloid goiter”, or “endemic goiter”.

**DEFINITION / DESCRIPTION**

A goiter (GOI-tur) is the irregular growth of the thyroid gland. The thyroid is a butterfly-shaped gland located at the base of the neck just below Adam's apple.

A goiter may be an overall enlargement of the thyroid, or it may be the result of irregular cell growth that forms one or more lumps (nodules) in the thyroid. A goiter may be associated with no change in thyroid function or with an increase or decrease in thyroid hormones.

The most common cause of goiters worldwide is a lack of iodine in the diet. In the United States, where the use of iodized salt is common, goiters are caused by conditions that change thyroid function or factors that affect thyroid growth.

Treatment depends on the cause of the goiter, symptoms, and complications resulting from the goiter. Small goiters that aren't noticeable and don't cause problems usually don't need treatment.

Goiter happens when your thyroid gland grows larger. It has several possible causes and may or may not be associated with abnormal thyroid hormone levels. It’s treatable.

Goiter is a condition where your thyroid gland grows larger. Your entire thyroid can grow larger, or it can develop one or more small lumps called thyroid nodules.

Your thyroid gland is a small, butterfly-shaped endocrine gland located in your neck, below your Adam's apple. It produces the hormones thyroxine (also called T4) and triiodothyronine (also called T3). These hormones play a role in certain bodily functions, including:

* Metabolism.
* Body temperature.
* Mood and excitability.
* Pulse and heart rate.
* Digestion.

Goiter may be associated with an irregular amount of thyroid hormone in your body (hyperthyroidism or hypothyroidism) or with normal levels of thyroid hormone (euthyroid).

Goiter has several possible causes. Depending on the cause, it may or may not require treatment.

**Types of goiters**

Goiter can be classified in a few different ways, including the way by which it grows and if your thyroid hormone levels are irregular or not.

Classifications for goiter based on how it enlarges include:

* **Simple (diffuse) goiter**: This type of goiter happens when your entire thyroid gland swells and feels smooth to the touch.
* **Nodular goiter**: This type of goiter happens when a solid or fluid-filled lump called a nodule develops within your thyroid and makes it feel lumpy.
* **Multinodular goiter**: This type of goiter happens when there are many lumps (nodules) within your thyroid. The nodules may be visible or only discovered through examination or scans.

*Classifications of goiter based on thyroid hormone levels include:*

* **Toxic goiter**: This goiter happens when your thyroid is enlarged and produces too much thyroid hormone.
* **Nontoxic goiter**: If you have an enlarged thyroid but normal thyroid levels (euthyroid), it’s a nontoxic goiter. In other words, you don’t have hyperthyroidism (overactive thyroid) or hypothyroidism (underactive thyroid).

Healthcare providers combine these descriptors to classify certain types of goiters when diagnosing them. For example, a toxic multinodular goiter happens when there’s more than one nodule on your thyroid — usually several — producing an extra amount of thyroid hormone.

**CAUSES**

### **How the thyroid gland works**

Two hormones produced by the thyroid are thyroxine (T-4) and triiodothyronine (T-3). When the thyroid releases T-4 and T-3 into the bloodstream, they play a role in many functions in the body, including the regulation of:

* The conversion of food into energy (metabolism).
* Body temperature.
* Heart rate.
* Blood pressure.
* Other hormone interactions.
* Growth during childhood.

The thyroid gland also produces calcitonin, a hormone that helps regulate the amount of calcium in the blood.

### **How the thyroid is regulated**

The pituitary gland and hypothalamus control the rate at which T-4 and T-3 are produced and released.

The hypothalamus is a specialized region at the base of the brain. It acts as a thermostat for maintaining balance in multiple body systems. The hypothalamus signals the pituitary gland to make a hormone known as thyroid-stimulating hormone (TSH).

The pituitary gland — located below the hypothalamus — releases a certain amount of TSH, depending on how much T-4 and T-3 are in the blood. The thyroid gland, in turn, regulates its production of hormones based on the amount of TSH it receives from the pituitary gland.

### **Causes of goiter**

A number of factors that influence thyroid function or growth can result in a goiter.

* **Iodine deficiency.** Iodine is essential for the production of thyroid hormones. If a person does not get enough dietary iodine, hormone production drops and the pituitary gland signals the thyroid to make more. This increased signal results in thyroid growth. In the United States, this cause is uncommon because of iodine added to table salt.
* **Hashimoto's disease.** Hashimoto's disease is an autoimmune disorder, an illness caused by the immune system attacking healthy tissues. The damaged and inflamed tissues of the thyroid don't produce enough hormones (hypothyroidism). When the pituitary gland detects the decline and prompts the thyroid to create more hormones, the thyroid can become enlarged.
* **Graves' disease.** Another autoimmune disorder called Graves' disease occurs when the immune system produces a protein that mimics TSH. This rogue protein prompts the thyroid to overproduce hormones (hyperthyroidism) and can result in thyroid growth.
* **Thyroid nodules.** A nodule is the irregular growth of thyroid cells that form a lump. A person may have one nodule or several nodules (multinodular goiter). The cause of nodules is not clear, but there may be multiple factors — genetics, diet, lifestyle and environment. Most thyroid nodules are noncancerous (benign).
* **Thyroid cancer.** Thyroid cancer is less common than other cancers and generally treatable. About 5% of people with thyroid nodules are found to have cancer.
* **Pregnancy.** A hormone produced during pregnancy, human chorionic gonadotropin (HCG), may cause the thyroid gland to be overactive and enlarge slightly.
* **Inflammation.** Thyroiditis is inflammation of the thyroid caused by an autoimmune disorder, bacterial or viral infection, or medication. The inflammation may cause hyperthyroidism or hypothyroidism.

**What causes goiter?**

Goiter is an adaptive reaction of the cells in your thyroid to any process that blocks thyroid hormone production. While the most common cause of goiter worldwide is iodine deficiency, many conditions can cause it.

Causes of goiter include:

* **Iodine deficiency:** Your thyroid needs iodine to produce thyroid hormone. If you don’t get enough iodine in your diet, your thyroid makes more cells (and grows) to try to make more thyroid hormone. While this is the most common cause of goiter worldwide, it’s not common in the United States. You can get the recommended amount of iodine in your diet by including seafood, dairy products and iodized salt in your diet. Supplementation with iodine is not recommended for most people in the U.S. and may have unintended negative effects on your health.
* **Graves' disease:** Graves' disease is an autoimmune disease in which your immune system attacks your thyroid, causing it to grow larger. Graves’ disease also causes hyperthyroidism, which requires treatment.
* **Hashimoto's disease:**This is an autoimmune disease that causes inflammation of your thyroid gland. Some people with Hashimoto's disease develop a compensatory increase in the thyroid gland's size. This type of goiter usually gets better on its own over time. Some cases of Hashimoto’s disease require treatment with thyroid hormone.
* **Thyroid cancer:** Cancer of your thyroid gland often enlarges your thyroid.
* **Pregnancy**: Human chorionic gonadotropin, a hormone that a person produces during pregnancy, can cause their thyroid to grow.
* **Thyroiditis:** Inflammation of the thyroid gland itself can cause your thyroid gland to grow. This can happen for several reasons.

Sporadic goiters, in most cases, have no known cause. In some cases, certain drugs can cause this type of goiter. For example, the drug lithium, which is used to treat certain mental health conditions, as well as other medical conditions, can cause this type of goiter.

**RISK FACTOR**

Anyone can develop a goiter. It may be present at birth or occur at any time throughout life. Some common risk factors for goiters include:

* **A lack of dietary iodine.** Iodine is found primarily in seawater and in the soil in coastal areas. In the developing world in particular, people who don't have enough iodine in their diets or access to food supplemented with iodine are at increased risk. This is rare in the United States.
* **Being female.** Women are more likely to develop a goiter or other thyroid disorders.
* **Pregnancy and menopause.** Thyroid problems in women are more likely to occur during pregnancy and menopause.
* **Age.** Goiters are more common after age 40.
* **Family medical history.** Family medical history of goiters or other thyroid disorders increases the risk of goiters. Also, researchers have identified genetic factors that may be associated with an increased risk.
* **Medications.** Some medical treatments, including the heart drug amiodarone (Pacerone) and the psychiatric drug lithium (Lithobid), increase your risk.
* **Radiation exposure.** Your risk increases if you've had radiation treatments to your neck or chest area.

**SIGNS / SYMPTOMS**

Most people with goiters have no signs or symptoms other than a swelling at the base of the neck. In many cases, the goiter is small enough that it's only discovered during a routine medical exam or an imaging test for another condition.

Other signs or symptoms depend on whether thyroid function changes, how quickly the goiter grows and whether it obstructs breathing.

### 

### **Underactive thyroid (hypothyroidism)**

Signs and symptoms of hypothyroidism include:

* Fatigue.
* Increased sensitivity to cold.
* Increased sleepiness.
* Dry skin.
* Constipation.
* Muscle weakness.
* Problems with memory or concentration.

### 

### **Overactive thyroid (hyperthyroidism)**

Signs and symptoms of hyperthyroidism include:

* Weight loss.
* Rapid heartbeat (tachycardia).
* Increased sensitivity to heat.
* Excess sweating.
* Tremors.
* Irritability and nervousness.
* Muscle weakness.
* Frequent bowel movements.
* Changes in menstrual patterns.
* Sleep difficulty.
* High blood pressure.
* Increased appetite.

*Children with hyperthyroidism might also have the following:*

* Rapid growth in height.
* Changes in behavior.
* Bone growth that outpaces expected growth for the child's age.

### 

### **Obstructive goiter**

The size or position of a goiter may obstruct the airway and voice box. Signs and symptoms may include:

* Difficulty swallowing.
* Difficulty breathing with exertion.
* Cough.
* Hoarseness.
* Snoring.

**Symptoms of goiter**

The size of a goiter can range from very small and barely noticeable to very large. Most goiters are painless, but if you have thyroiditis (an inflamed thyroid gland), it can be painful.

The main symptoms of goiter include:

* A lump in the front of your neck, just below your Adam's apple.
* A feeling of tightness in your throat area.
* Hoarseness (scratchy voice).
* Neck vein swelling.
* Dizziness when you raise your arms above your head.

Other, less common symptoms include:

* Difficulty breathing (shortness of breath).
* Coughing.
* Wheezing (due to squeezing of your windpipe).
* Difficulty swallowing (due to squeezing of your esophagus).

Some people who have a goiter may also have hyperthyroidism (overactive thyroid). Symptoms of hyperthyroidism include:

* Rapid heart rate (tachycardia).
* Unexplained weight loss.
* Diarrhea.
* Sweating without exercise or increased room temperature.
* Shaking.
* Agitation.

Some people with goiter may also have hypothyroidism (underactive thyroid). Symptoms of hypothyroidism include:

* Fatigue (feeling tired).
* Constipation.
* Dry skin.
* Unexplained weight gain.
* Abnormal menstruation (periods).

**DIAGNOSIS METHODS**

A goiter is often discovered during a routine physical exam. By touching your neck, your health care provider may detect an enlargement of the thyroid, an individual nodule or multiple nodules. Sometimes a goiter is found when you are undergoing an imaging test for another condition.

Your healthcare provider usually diagnoses goiter when they perform a physical examination and feel that you have an enlarged thyroid. However, the presence of a goiter indicates that there’s an issue with your thyroid gland. They’ll need to figure out what the issue is.

Your provider can use several tests to diagnose and evaluate goiter, including the following:

* **Physical exam:**Your provider may be able to tell if your thyroid gland is enlarged by feeling your neck area for nodules and signs of tenderness.
* **Thyroid blood test:**This blood test measures thyroid hormone levels, which reveal if your thyroid is working properly.
* **Antibody test:**This blood test looks for certain antibodies that are produced in some forms of goiter. An antibody is a protein made by white blood cells. Antibodies help defend against invaders (for example, viruses) that cause disease or infection in your body.
* **Thyroid ultrasound:**Ultrasound is a procedure that sends high-frequency sound waves through body tissues. The echoes are recorded and transformed into video or photos. Your provider can “see” your thyroid to check its size and if it has nodules.
* **Biopsy:** A biopsy is the removal of a sample of tissue or cells to be studied in a laboratory. You may need a thyroid biopsy if there are large nodules in your thyroid gland. A biopsy is taken to rule out cancer.
* **Thyroid uptake and scan:**This imaging test provides information on the size and function of your thyroid. In this test, a small amount of radioactive material is injected into a vein to produce an image of your thyroid on a computer screen. Providers don’t order this test very often, since it’s only useful in certain circumstances.
* **CT scan or MRI (magnetic resonance imaging):**If the goiter is very large or spreads into your chest, a CT scan or MRI is used to measure the size and spread of the goiter.

Additional tests are then ordered to do the following:

* Measure the size of the thyroid.
* Detect any nodules.
* Assess whether the thyroid may be overactive or underactive.
* Determine the cause of the goiter.

Tests may include:

* **Thyroid function tests.** A blood sample can be used to measure the amount of Thyroid-stimulating Hormone (TSH) produced by the pituitary gland and how much Thyroxine (T-4) and Triiodothyronine (T-3) is produced by the thyroid. These tests can show whether the goiter is associated with an increase or decrease in thyroid function.
* **Antibody test.** Depending on the results of the thyroid function test, your health care provider may order a blood test to detect an antibody linked to an autoimmune disorder, such as Hashimoto's disease or Graves' disease.
* **Ultrasonography.** Ultrasonography uses sound waves to create a computerized image of tissues in your neck. The technician uses a wand-like device (transducer) over your neck to do the test. This imaging technique can reveal the size of your thyroid gland and detect nodules.
* **Radioactive iodine uptake.** If your health care provider orders this test, you are given a small amount of radioactive iodine. Using a special scanning device, a technician can measure the amount and rate at which your thyroid takes it in. This test may be combined with a radioactive iodine scan to show a visual image of the uptake pattern. The results may help determine function and cause of the goiter.
* **Biopsy.** During a fine-needle aspiration biopsy, ultrasound is used to guide a very small needle into your thyroid to obtain a tissue or fluid sample from nodules. The samples are tested for the presence of cancerous cells.

A goiter is often discovered during a routine physical exam. By touching your neck, your health care provider may detect an enlargement of the thyroid, an individual nodule or multiple nodules. Sometimes a goiter is found when you are undergoing an imaging test for another condition.

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**TREATMENT OPTIONS**

Goiter treatment depends on the size of the goiter, your signs and symptoms, and the underlying cause. If your goiter is small and your thyroid function is healthy, your health care provider may suggest a wait-and-see approach with regular checkups.

### **Medications**

Medications for goiters may include one of the following:

* **For increasing hormone production.** An underactive thyroid is treated with a thyroid hormone replacement. The drug levothyroxine (Levoxyl, Thyquidity, others) replaces thyroxine (T-4) and results in the pituitary gland releasing less thyroid-stimulating hormone (TSH). The drug liothyronine (Cytomel) may be prescribed as a triiodothyronine (T-3) replacement. These treatments may decrease the size of the goiter.
* **For reducing hormone production.** An overactive thyroid may be treated with an antithyroid drug that disrupts hormone production. The most commonly used drug, methimazole (Tapazole), may also reduce the size of the goiter.
* **For blocking hormone activities.** Your health care provider may prescribe a drug called a beta blocker for managing symptoms of hyperthyroidism. These drugs — including atenolol (Tenormin), metoprolol (Lopressor) and others — can disrupt the excess thyroid hormones and lower symptoms.
* **For managing pain.** If inflammation of the thyroid results in pain, it's usually treated with aspirin, naproxen sodium (Aleve), ibuprofen (Advil, Motrin IB, others) or related pain relievers. Severe pain may be treated with a steroid.

### **Surgery**

You may need surgery to remove all or part of your thyroid gland (total or partial thyroidectomy) may be used to treat goiter with the following complications:

* Difficulty breathing or swallowing.
* Thyroid nodules that cause hyperthyroidism.
* Thyroid cancer.

You may need to take thyroid hormone replacement, depending on the amount of thyroid removed.

### **Radioactive iodine treatment**

### Radioactive iodine is a treatment for an overactive thyroid gland. The dose of radioactive iodine is taken orally. The thyroid takes up the radioactive iodine, which destroys cells in the thyroid. The treatment lowers or eliminates hormone production and may decrease the size of the goiter.

### **Management and Treatment**

### A simple goiter may happen for only a short time and may go away on its own without treatment.

### Many goiters, such as multinodular goiter, are associated with normal levels of thyroid hormone. These goiters usually don’t require any specific treatment after your healthcare provider has diagnosed it. However, you may be at risk of developing hypothyroidism or hyperthyroidism in the future.

### If you have an enlarged thyroid gland, it’s still important to see your healthcare provider, since goiters have several possible causes — some of which require treatment.

### *How is goiter treated?*

### Treatment for goiter depends on how large your thyroid has grown, symptoms and what caused it. Treatments include:

### No treatment / “watchful waiting”: If the goiter is small and isn’t bothering you, your healthcare provider may decide that it doesn’t need to be treated. However, they’ll carefully monitor your thyroid for any changes.

### Medications: Levothyroxine (Levothroid®, Synthroid®) is a thyroid hormone replacement therapy. Your provider will likely prescribe it if the cause of the goiter is an underactive thyroid (hypothyroidism). Other medications are prescribed if the cause of the goiter is an overactive thyroid (hyperthyroidism). These drugs include methimazole (Tapazole®) and propylthiouracil. Your provider might prescribe aspirin or a corticosteroid medication if the goiter is caused by inflammation.

### Radioactive iodine therapy: This treatment, used in cases of an overactive thyroid gland, involves taking radioactive iodine orally. The iodine goes to your thyroid gland and kills thyroid cells, which shrinks the gland. After radioactive iodine treatment, you’ll likely need to take thyroid hormone replacement therapy for the rest of your life.

### Surgery: Your provider may recommend surgery to remove all or part of your thyroid gland (thyroidectomy). You may need surgery if the goiter is large and causes problems with breathing and swallowing. Surgery is also sometimes used to remove nodules. Surgery must be done if cancer is present. Depending on the amount of thyroid gland removed, you may need to take thyroid hormone replacement therapy for the rest of your life.

As with surgery, you may need to take thyroid hormone replacement to maintain the appropriate levels of hormones.

**SELF CARE**

Your body gets iodine from your food. The recommended daily allowance is 150 micrograms. A teaspoon of iodized salt has about 250 micrograms of iodine.

Foods that contain iodine include:

* Saltwater fish and shellfish.
* Seaweed.
* Dairy products.
* Soy products.

Most people in the United States get enough iodine in a healthy diet. Too much iodine in the diet, however, can cause thyroid dysfunction.

**PREVENTION TIPS**

**How can I prevent goiter?**

A goiter caused by iodine deficiency (simple goiter) is generally the only type of goiter you can prevent. Consuming a diet that includes fish, dairy and a healthy amount of iodized table salt prevents these types of goiters. Iodine supplements and other supplements are generally not recommended for other types and may do more harm than good.

Use iodized salt in your food. Consume iodine-rich seafood, including seaweed, shrimp, and shellfish. Avoid overexposure to radiation at work or while receiving radiation therapy. A sufficient daily intake of iodine is needed to prevent goiter.

The recommended daily intake (RDI) of iodine is 90 µg/day for children aged 2 to 5 years, 120 µg/day for children aged 6 to 9 years, and 150 µg/day for children from 10 years of age, adolescents, and adults. In pregnancy, the RDI is 250 µg/day and for lactating women, an extra 50 µg/day is recommended to provide sufficient iodine in breast milk. Avoiding goitrogens and radiation exposure are other ways one could prevent goiter.

**POSSIBLE COMPLICATION**

A goiter itself usually doesn't cause complications. The appearance may be troublesome or embarrassing for some people. A large goiter may obstruct the airway and voice box.

Changes in the production of thyroid hormones that may be associated with goiters have the potential for causing complications in multiple body systems.

Consequences of goiter with hypothyroidism, hyperthyroidism, further goiter enlargement, retrosternal extension, nodule formation and thyroid cancer detection are mentioned above and can be regarded as goiter associated presentations or clinical entities and do not count as complications. Potential complications of simple goiter include:

* Compression of the trachea with tracheomalacia
* Iodo-Basedow phenomenon, which is the development of hyperthyroidism if exposed to iodine intake
* Intra-nodular hemorrhage or necrosis

**OUTLOOK / PROGNOSIS**

**What is the prognosis (outlook) for goiter?**

The prognosis (outlook) for goiter depends on its type and what caused it.

Simple goiter has a good prognosis. If your thyroid continues to enlarge, it may compress the surrounding structures and may cause difficulty in breathing and swallowing and hoarseness.

If the goiter is a sign of another thyroid disease, like Graves’ disease or Hashimoto’s disease, the prognosis depends on the underlying cause of your thyroid enlargement.

Benign goiters have a good prognosis. However, all goiters should be monitored by examination and biopsy for possible malignant transformation, which may be signaled by a sudden change in size, pain, or consistency. Fortunately, the risk of this is low. In patients exposed to low levels of radiation the risk rises.eMedicine Logo

**WHEN TO SEE A DOCTOR / RED FLAG**

Regardless of the cause, it’s important to see your healthcare provider regularly (at least annually) if you’ve been diagnosed with goiter so they can monitor it.

If you develop new symptoms, talk to your healthcare provider.

## 

## **EPIDEMIOLOGY**

**Who does goiter affect?**

Anyone can have a goiter, but it’s about four times more likely to develop in females compared to males. Your risk of developing goiter also increases as you age. They’re more common after age 40.

People who have any of the following conditions may also be more likely to develop goiter:

* Obesity.
* Insulin resistance.
* Metabolic syndrome.

You’re also at greater risk for developing goiter if your head and neck have been exposed to radiation for medical treatments and/or if you have a family history of thyroid disease.

**How common is goiter?**

Goiters are relatively common. They affect about 5% of people in the United States.

The most common cause of goiters worldwide is iodine deficiency, which affects an estimated 2.2 billion people.

The more severe the iodine deficiency, the more likely someone is to have goiter:

* With mild iodine deficiency, the incidence of goiter is 5% to 20%.
* With a moderate iodine deficiency, the prevalence increases to 20% to 30%.
* With severe iodine deficiency, the incidence increases to greater than 30%.

### **Frequency**

***United States***

Autopsy studies suggest a frequency of greater than 50% for thyroid nodules; with high-resolution ultrasonography, the value approaches 40% of patients with nonthyroidal illness. In the Framingham study, ultrasonography revealed that 3% of men older than 60 years had thyroid nodules, while 36% of women aged 49-58 years had thyroid nodules.In the United States, most goiters are due to autoimmune thyroiditis (i.e., Hashimoto disease).

***International***

Worldwide, the most common cause of goiter is iodine deficiency. It is estimated that goiters affect as many as 200 million of the 800 million people who have a diet deficient in iodine. In the Wickham study from the United Kingdom, 16% of the population had a goiter.

In a German study, 635 people underwent ultrasonographic thyroid screening, as well as basal TSH measurement, during a preventive-health checkup.Thyroid nodules were detected in 432 (68%) of the persons screened; in a previous German study, ultrasonographic screening of more than 90,000 people detected thyroid nodules in 33% of the normal population. The authors of the latter report attributed this difference to the fact that patients in their study were screened using 13 MHz ultrasonographic scanners, which were more sensitive than the 7.5 MHz scanners used in the previous study. According to the investigators, their results indicated that the question of routine iodine supplementation requires renewed attention.

The most common cause of goiters worldwide is iodine deficiency that affects an estimated 2.2 billion people

**DIFFERENTIAL DIAGNOSIS**

* Anaplastic Thyroid Carcinoma
* Branchial Cleft Cyst
* Carotid Artery Aneurysm
* Lymphatic Malformation (Cystic Hygroma)
* Fibroma
* Granulomatous Disease of the Thyroid
* Infectious Thyroiditis
* Lipomas
* Lymphadenopathy
* Medullary Thyroid Carcinoma
* Papillary Thyroid Carcinoma
* Parathyroid Adenoma
* Parathyroid Cyst
* Pseudo goiter
* Sarcoma
* Subacute Thyroiditis
* Thyroglossal Duct Cyst
* Thyroid Abscess
* Thyroid Lymphoma
* Thyroid Nodule
* *Anaplastic Thyroid Carcinoma:* A rare, aggressive, and highly malignant thyroid cancer characterized by rapid growth, local invasion, and poor prognosis.
* *Branchial Cleft Cyst:* A congenital epithelial cyst arising from incomplete obliteration of branchial clefts, typically presenting as a painless lateral neck mass.
* *Carotid Artery Aneurysm:* An abnormal dilation of the carotid artery in the neck, which can present as a pulsatile mass and carries risk of rupture or embolism.
* *Lymphatic Malformation (Cystic Hygroma):* A benign congenital malformation of lymphatic vessels causing multiloculated cystic masses, usually in the neck region.
* *Fibroma:* A benign tumor composed of fibrous or connective tissue, which can occur in the neck or thyroid region.
* *Granulomatous Disease of the Thyroid:* Inflammatory conditions such as subacute thyroiditis characterized by granuloma formation and thyroid pain.
* *Infectious Thyroiditis:* Infection of the thyroid gland causing pain, swelling, fever, and sometimes abscess formation.
* *Lipomas:* Benign tumors of adipose tissue that can appear as soft, mobile masses in the neck.
* *Lymphadenopathy:* Enlargement of lymph nodes in the neck due to infection, inflammation, or malignancy.
* *Medullary Thyroid Carcinoma:* A malignant tumor arising from parafollicular C cells of the thyroid, often associated with calcitonin secretion and MEN 2 syndromes.
* *Papillary Thyroid Carcinoma:* The most common thyroid cancer, usually slow-growing with excellent prognosis, characterized by papillary structures on histology.
* *Parathyroid Adenoma:* A benign tumor of the parathyroid gland causing primary hyperparathyroidism and hypercalcemia.
* *Parathyroid Cyst:* A rare cystic lesion of the parathyroid gland, usually benign and asymptomatic.
* *Pseudo goiter:* Apparent enlargement of the thyroid region due to extrinsic masses or anatomical variants, not true thyroid enlargement.
* *Sarcoma:* A rare malignant tumor of mesenchymal origin that can occur in the thyroid or neck soft tissues.
* *Subacute Thyroiditis:* A self-limited inflammatory thyroid disorder causing painful thyroid enlargement, often following viral infection.
* *Thyroglossal Duct Cyst:* A congenital midline neck cyst arising from remnants of the thyroglossal duct, typically presenting as a painless, movable mass.
* *Thyroid Abscess:* A localized collection of pus within the thyroid gland due to bacterial infection, often causing pain, swelling, and systemic symptoms.
* *Thyroid Lymphoma:* A rare malignancy of lymphoid tissue within the thyroid, often arising in the setting of chronic lymphocytic thyroiditis.
* *Thyroid Nodule:* A discrete lesion within the thyroid gland that can be benign (colloid, cystic, adenoma) or malignant, often detected by palpation or imaging

**RECENT GUIDELINES OR UPDATES**

A sufficient daily intake of iodine is needed to prevent goiter. The recommended daily intake (RDI) of iodine is 90 µg/day for children aged 2 to 5 years, 120 µg/day for children aged 6 to 9 years, and 150 µg/day for children from 10 years of age, adolescents, and adults. In pregnancy, the RDI is 250 µg/day and for lactating women, an extra 50 µg/day is recommended to provide sufficient iodine in breast milk.

Avoiding goitrogens and radiation exposure are other ways one could prevent goiter.

The patient with goiter can be managed by a family physician, internist, endocrinologist, ENT specialist, general or endocrine surgeon. If there is an indication for surgery, it should ideally be performed by experienced high-thyroid-volume surgeons.

**Histologic Findings**

Simple nontoxic goiters show hyperplasia, colloid accumulation, and nodularity. Nodular hyperplasia is commonly seen in multinodular goiter. Cytologic findings include benign appearing follicular cells, abundant colloid, macrophages, and, sometimes, Hürthle cells. Inflammatory disorders of the thyroid, such as chronic lymphocytic (Hashimoto) thyroiditis, contain a mixed population of lymphocytes mixed with benign appearing follicular cells. Malignant nodules may be follicular in origin, ie, papillary (most common), follicular, Hürthle cell, or anaplastic. They also may be from parafollicular cells, medullary carcinoma or lymphoma, or other categories.

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**POLYCYSTIC OVARY SYNDROME**

*ALTERNATIVE NAMES:* Polycystic ovary syndrome (PCOS) has had several alternative names throughout its history. Some of the alternative names include Hyperandrogenic anovulation (HA), “Stein-Leventhal syndrome”, and “polycystic ovarian syndrome”. Additionally, it has been referred to as “Polycystic ovary disease (PCOD)”.

The name "Stein-Leventhal syndrome" was derived from the first individuals to describe the syndrome's features.

However, the name "PCOS" has been suggested to be a distraction and an impediment to progress, and there have been recommendations to assign a name that reflects the complex interactions that characterize the syndrome.

**DEFINITION / DESCRIPTION**

Polycystic ovary syndrome (PCOS) is a hormonal imbalance that occurs when your ovaries (the organ that produces and releases eggs) create excess hormones. If you have PCOS, your ovaries produce unusually high levels of hormones called androgens. This causes your reproductive hormones to become imbalanced. As a result, people with PCOS often have irregular menstrual cycles, missed periods and unpredictable ovulation. Small follicle cysts (fluid-filled sacs with immature eggs) may be visible on your ovaries on ultrasound due to lack of ovulation (anovulation). However, despite the name "polycystic," you don’t need to have cysts on your ovaries to have PCOS. The ovarian cysts aren’t dangerous or painful.

PCOS is one of the most common causes of female infertility. It can also increase your risk of other health conditions. Your healthcare provider can treat PCOS based on your symptoms and if you wish to become pregnant.

In summary, Polycystic ovary syndrome (PCOS) is a hormonal condition that affects your ovaries, the female reproductive organs that make eggs. It affects about 1 in every 10 women (and people assigned female at birth) who are of childbearing age. It's one of the most common causes of infertility.

It can:

* Stop your periods or make them hard to predict
* Cause acne and unwanted body and facial hair
* Raise your risk for other health problems, including diabetes and high blood pressure

Some people with PCOS have cysts (small sacs of fluid) on their ovaries. That’s why it’s called “polycystic.” But the name is a bit misleading because many people with the condition don’t have cysts. In fact, many don’t have symptoms at all. That's one reason why up to 70% of those with PCOS don’t know they have it.

#### **What age does PCOS start?**

Females can get PCOS any time after puberty. Most people are diagnosed in their 20s or 30s when they’re trying to get pregnant. You may have a higher chance of getting PCOS if you have obesity or if other people in your biological family have PCOS.

The condition starts after [puberty](https://www.webmd.com/teens/facts-about-puberty-girls), but may not be diagnosed until you’re trying to get pregnant.

It never goes away, but symptoms usually get better after menopause. In the meantime, several treatments can relieve the symptoms or help you get pregnant.

*PCOS vs. PCOD*

Polycystic ovary disease (PCOD) is another, older name for PCOS. PCOS has also been called Stein-Leventhal syndrome.

*Endometriosis vs. PCOS*

When you have [endometriosis](https://www.webmd.com/women/endometriosis/endometriosis-causes-symptoms-treatment), the type of tissue that lines your uterus grows in places it shouldn't, such as your vagina or ovaries. Each month, this tissue can break down and bleed. Like PCOS, endometriosis can cause cysts in your ovaries and may lead to infertility. Its main symptoms are cramps and pain in the belly area. Unlike PCOS, it doesn't cause symptoms such as acne or excess body hair.

**Types of PCOS**

Some scientists propose dividing PCOS into types based on symptoms and hormone levels:

* Non-hyperandrogenic PCOS, or type D: You have problems with ovulation (which can lead to [irregular periods](https://www.webmd.com/women/why-is-my-period-so-random) or loss of periods) and cysts on your ovaries. But your levels of androgens (male hormones) are normal.
* Ovulatory PCOS (type C): You have increased levels of androgens along with cysts on your ovaries.
* Non-PCO PCOS (type B): You have high levels of androgens as well as problems with ovulation.
* Full-blown PCOS (type A): You have high levels of androgens, problems with ovulation, as well as cysts on your ovaries.

Informally, you might hear people describe it using other terms that refer to its causes or symptoms:

* Insulin-resistant PCOS. Often, those who have PCOS also have [insulin resistance](https://www.webmd.com/diabetes/insulin-resistance-syndrome), which is when your body makes the hormone insulin but can't use it correctly. Insulin resistance increases your risk for type 2 diabetes.
* Inflammatory PCOS. Inflammation results when your immune system tries to fight off a threat. Research has linked PCOS to low levels of inflammation throughout the body. This could cause or worsen symptoms. Conditions such as insulin resistance and [obesity](https://www.webmd.com/obesity/what-obesity-is) contribute to inflammation.
* Hidden-cause PCOS. Some websites use this term to refer to PCOS for which the cause isn't known. But this is true of PCOS in general. Scientists don't know what causes the condition, though they believe that both your genes and environmental factors play a role.
* Pill-induced PCOS or post-pill PCOS. The pill and other hormonal [birth control](https://www.webmd.com/sex/birth-control/birth-control-side-effects-risks) methods don't cause PCOS. But when you stop using this type of birth control, you could temporarily have irregular periods or other symptoms that look like those of PCOS. Hormonal birth control can also mask the symptoms of PCOS. So, you might not be diagnosed with it until you go off birth control. Doctors sometimes prescribe hormonal birth control to treat PCOS symptoms.

*PCOS and Hormones*

Your body makes many types of hormones. Hormones are chemical messengers that help control many body functions. Some affect your menstrual cycle and are tied to your ability to have a baby. When you have PCOS, your reproductive hormones are out of balance. Several hormones play a role in PCOS.

*PCOS insulin resistance*

Insulin is a hormone that manages your [blood sugar levels](https://www.webmd.com/diabetes/how-sugar-affects-diabetes). Scientists estimate that 30%-80% of those with PCOS have insulin resistance. When your body doesn't react to insulin as it should, you can end up with too much insulin in your body. Some researchers think this excess insulin plays a role in causing your body to overproduce androgens.

Other hormones involved in the syndrome include:

* Androgens. They’re often called male hormones, but everyone has them. When you have PCOS, your ovaries make more androgens than usual. This can keep your ovaries from releasing eggs on their monthly schedule and cause irregular periods. Extra androgens are responsible for many [PCOS symptoms](https://www.webmd.com/women/symptoms-of-pcos), including acne, hair loss, and unwanted hair growth.
* Follicle-stimulating hormone. This hormone helps prepare your body for ovulation and helps control your menstrual cycle.
* Luteinizing hormone. This also helps regulate your monthly cycle, triggering your ovaries to release eggs.
* Progesterone. With PCOS, your body may not have enough of this hormone. So you might miss periods for a long time or have trouble predicting when they’ll come.
* Estrogen. When you have PCOS, your levels of estrogen may be too high in relation to your progesterone levels.

**CAUSES OF PCOS**

The exact cause of PCOS is unknown. There’s evidence that genetics play a role. Several other factors, most importantly obesity, also play a role in causing PCOS:

* Higher levels of male hormones called androgens: High androgen levels prevent your ovaries from releasing eggs, which causes irregular menstrual cycles. Irregular ovulation can also cause small, fluid-filled sacs to develop on your ovaries. High androgen also causes acne and excess hair growth in females.
* Insulin resistance: An increase in insulin levels causes your ovaries to make and release male hormones (androgens). Increased male hormones suppress ovulation and contribute to other symptoms of PCOS. Insulin helps your body process glucose (sugar) and use it for energy. Insulin resistance means your body doesn’t process insulin correctly, leading to high glucose levels in your blood. Not all individuals with insulin resistance have elevated glucose or diabetes, but insulin resistance can lead to diabetes. Being overweight or obesity can also contribute to insulin resistance. An elevated insulin level, even if your blood glucose is normal, can indicate insulin resistance.
* Low-grade inflammation: People with PCOS tend to have chronic low-grade inflammation. Your healthcare provider can perform blood tests that measure levels of C-reactive protein (CRP) and white blood cells, which can indicate the level of inflammation in your body.

### **Can PCOS cause a miscarriage?**

Having PCOS may increase your risk for certain pregnancy complications, although most people with PCOS are able to successfully carry a pregnancy. Other complications of PCOS related to pregnancy include increased risk of:

* Gestational diabetes, preeclampsia and high blood pressure.
* Preterm birth (birth before 37 weeks of pregnancy) or C-section delivery due to obesity, diabetes or high blood pressure.

**RISK FACTORS**

You may be more likely to have PCOS if your mother or sister has it. You may also be more likely to have it if you have insulin resistance or are obese.

Risk factors for PCOS include:

* A family history of menstrual problems or disorders (including PCOS)
* Type 2 diabetes
* Being overweight or obese
* Fast weight gain

Transgender men (also known as female-to-male transsexual people, or FTMs) are prone to PCOS. Hormone therapy may or may not be a reason for that, as so many other factors come into play. Some studies have shown that while hormone therapy can cause changes to the ovaries of transgender men, it doesn’t necessarily cause PCOS.

## **SIGNS / SYMPTOMS**

### **Signs of polycystic ovary syndrome (PCOS)**

The most common signs and symptoms of PCOS include:

* Irregular periods: Abnormal menstruation involves missing periods or not having a period at all. It may also involve heavy bleeding during periods.
* Abnormal hair growth: You may grow excess facial hair or experience heavy hair growth on your arms, chest and abdomen (hirsutism). This affects up to 70% of people with PCOS.
* Acne: PCOS can cause acne, especially on your back, chest and face. This acne may continue past your teenage years and may be difficult to treat.
* Obesity: Between 40% and 80% of people with PCOS have obesity and have trouble maintaining a weight that’s healthy for them.
* Darkening of the skin: You may get patches of dark skin, especially in the folds of your neck, armpits, groin (between the legs) and under your breasts. This is known as acanthosis nigricans.
* Cysts: Many people with PCOS have ovaries that appear larger or with many follicles (egg sac cysts) on ultrasound.
* Skin tags: Skin tags are little flaps of extra skin. They’re often found in your armpits or on your neck.
* Thinning hair: People with PCOS may lose patches of hair on their head or start to become bald.
* Infertility: PCOS is the most common cause of female infertility. Not ovulating regularly or frequently can result in not being able to conceive.

#### **Can I have PCOS but not have any symptoms?**

Yes, it’s possible to have PCOS and not have any symptoms. Many people don’t even realize they have the condition until they have trouble getting pregnant or are gaining weight for unknown reasons. It’s also possible to have mild PCOS, where the symptoms aren’t severe enough for you to notice.

## **DIAGNOSIS METHODS**

There's no single test to specifically diagnose polycystic ovary syndrome (PCOS). Your health care provider is likely to start with a discussion of your symptoms, medications and any other medical conditions. Your provider also may ask about your menstrual periods and any weight changes. A physical exam includes checking for signs of excess hair growth, insulin resistance and acne.

Your health care provider might then recommend:

* **Pelvic exam.** During a pelvic exam, your provider can check your reproductive organs for masses, growths or other changes.
* **Blood tests.** Blood tests can measure hormone levels. This testing can exclude possible causes of menstrual problems or androgen excess that mimic PCOS. You might have other blood testing, such as fasting cholesterol and triglyceride levels. A glucose tolerance test can measure your body's response to sugar (glucose).
* **Ultrasound.** An ultrasound can check the appearance of your ovaries and the thickness of the lining of your uterus. A wandlike device (transducer) is placed in your vagina. The transducer emits sound waves that are translated into images on a computer screen.

If you have a diagnosis of PCOS, your provider might recommend more tests for complications. These tests can include:

* Regular checks of blood pressure, glucose tolerance, and cholesterol and triglyceride levels
* Screening for depression and anxiety
* Screening for obstructive sleep apnea

### **How is polycystic ovary syndrome (PCOS) diagnosed?**

In most cases, your healthcare provider can diagnose PCOS after an examination and discussing your symptoms. They may order blood tests or perform an ultrasound to help with the diagnosis.

Your healthcare provider will:

* Talk to you about your symptoms and medical history.
* Ask about your biological family’s medical history.
* Take your weight and blood pressure.
* Perform a physical exam, looking specifically for excess facial hair, hair loss, acne, discolored skin and skin tags.
* Perform a pelvic exam to look for other causes of abnormal bleeding.
* Order blood tests to check hormone levels and glucose levels.
* Perform a pelvic ultrasound to look at your ovaries, check the thickness of your uterine lining and look for other causes of abnormal bleeding.

### **What are the three symptoms to diagnose PCOS?**

Typically, healthcare providers diagnose PCOS if you have at least two of the three symptoms:

* Irregular or missed periods. Some people with PCOS have very heavy bleeding when they do have a period.
* Signs of excess androgens such as acne or excessive hair growth. Or a blood test confirming high androgen levels.
* Enlarged ovaries or polycystic appearance of ovaries on ultrasound. Many people don’t develop cysts.

## **Management and Treatment**

Your healthcare provider will determine treatment based on your symptoms, medical history and other health conditions, and if you want to get pregnant. Treatments can include medications, lifestyle changes or a combination of both.

#### **If you don’t plan to become pregnant, treatments include:**

* Hormonal birth control: Options include birth control pills, patches, shots, a vaginal ring or an intrauterine device (IUD). Hormonal birth control helps to regulate your menstrual cycle; some forms will also improve acne and help with excess hair growth.
* Insulin-sensitizing medicine: Metformin is a drug used to treat diabetes. It works by helping your body process insulin. Once insulin is under control, some people with PCOS see improvements in their menstrual cycles.
* Medications to block androgens: Some medications can block the effect of androgens. This helps control acne or hair growth. Talk to your healthcare provider about whether such treatment is right for you.
* Lifestyle changes: Eating a nutritious diet and maintaining a body weight that’s healthy for you can have a positive effect on insulin levels.

#### **If you want to become pregnant now or in the future, treatment for PCOS includes:**

* Drugs to induce ovulation (releasing an egg): A successful pregnancy begins with ovulation. Certain drugs have been proven to induce ovulation in people with PCOS. The medications clomiphene and letrozole are taken orally, while gonadotropins are given by injection.
* Surgery: A surgical procedure can help restore ovulation by removing tissue in your ovaries that produces androgen hormones. With newer medications available, surgeons rarely perform this procedure.
* In vitro fertilization (IVF): This is an option for people with PCOS when medication doesn’t help with ovulation. Your provider fertilizes your egg with your partner’s sperm in a lab before transferring it to your uterus.

### **Does PCOS ever go away?**

While there isn’t a cure for PCOS, your healthcare provider can help you manage your symptoms. The effects of PCOS may change over time so that you become less aware of the condition. However, there isn’t a treatment that permanently cures it.

#### **Can you be in menopause and have PCOS?**

The hormone changes you experience during menopause often resolve the symptoms of PCOS. It doesn’t matter how old you are — if your symptoms affect your quality of life, talk to your healthcare provider.

### **Can I get pregnant if I have PCOS?**

Yes, you can get pregnant if you have PCOS. PCOS can make it hard to conceive while also increasing your risk for certain pregnancy complications, but many people with PCOS do get pregnant on their own. Your healthcare provider will work with you to develop a treatment plan to help you ovulate. Your treatment plan could include medication or assisted reproductive technologies like in vitro fertilization (IVF).

Talk to your healthcare provider to make sure you understand your treatment plan and how you can increase your chances of a healthy pregnancy.

PCOS treatment focuses on managing the things that are concerning you. This could include infertility, hirsutism, acne or obesity. Specific treatment might involve lifestyle changes or medication.

### **Lifestyle changes**

Your health care provider may recommend weight loss through a low-calorie diet combined with moderate exercise activities. Even a modest reduction in your weight — for example, losing 5% of your body weight — might improve your condition. Losing weight may increase the effectiveness of medications your provider recommends for PCOS, and it can help with infertility. Your health care provider and a registered dietitian can work with you to determine the best weight-loss plan.

### **Medications**

To regulate your periods, your health care provider might recommend:

* **Combination birth control pills.** Pills that contain both estrogen and progestin decrease androgen production and regulate estrogen. Regulating your hormones can lower your risk of endometrial cancer and correct irregular bleeding, excess hair growth and acne.
* **Progestin therapy.** Taking progestin for 10 to 14 days every 1 to 2 months can regulate your periods and protect against endometrial cancer. This progestin therapy doesn't improve androgen levels and won't prevent pregnancy. The progestin-only mini pill or progestin-containing intrauterine device is a better choice if you also wish to avoid pregnancy.

To help you ovulate so that you can become pregnant, your health care provider might recommend:

* **Clomiphene.** This oral anti-estrogen medication is taken during the first part of your menstrual cycle.
* **Letrozole (Femara).** This breast cancer treatment can work to stimulate the ovaries.
* **Metformin.** This medicine for type 2 diabetes that you take by mouth improves insulin resistance and lowers insulin levels. If you don't become pregnant using clomiphene, your provider might recommend adding metformin to help you ovulate. If you have prediabetes, metformin can slow the progression to type 2 diabetes and help with weight loss.
* **Gonadotropins.** These hormone medications are given by injection.

If needed, talk with your health care provider about procedures that may help you become pregnant. For example, in vitro fertilization may be an option.

To reduce excessive hair growth or improve acne, your health care provider might recommend:

* **Birth control pills.** These pills decrease androgen production that can cause excessive hair growth and acne.
* **Spironolactone (Aldactone).** This medication blocks the effects of androgen on the skin, including excessive hair growth and acne. Spironolactone can cause birth defects, so effective birth control is needed while taking this medication. This medication isn't recommended if you're pregnant or planning to become pregnant.
* **Eflornithine (Vaniqa).** This cream can slow facial hair growth.
* **Hair removal.** Electrolysis and laser hair removal are two options for removing hair. Electrolysis uses a tiny needle inserted into each hair follicle. The needle sends out a pulse of electric current. The current damages and then destroys the follicle. Laser hair removal is a medical procedure that uses a concentrated beam of light to remove unwanted hair. You might need multiple treatments of electrolysis or laser hair removal. Shaving, plucking or using creams that dissolve unwanted hair may be other options. But these are temporary, and hair may thicken when it grows back.
* **Acne treatments.** Medications, including pills and topical creams or gels, may help improve acne. Talk to your health care provider about options.

## **Lifestyle and home remedies**

*To help ease the effects of PCOS, try to:*

* **Stay at a healthy weight.** Weight loss can lower insulin and androgen levels. It also may restore ovulation. Ask your health care provider about a weight-control program, if you need one. Meet with a registered dietitian for help in reaching weight-loss goals.
* **Limit carbohydrates.** High-carbohydrate diets might make insulin levels go higher. Ask your provider if a low-carbohydrate diet could help if you have PCOS. Choose complex carbohydrates, which raise your blood sugar levels more slowly. Complex carbohydrates are found in fruits, vegetables, whole grains and cooked dry beans and peas.
* **Be active.** Exercise helps lower blood sugar levels. If you have PCOS, increasing your daily activity and getting regular exercise may treat or even prevent insulin resistance. Being active may also help you keep your weight under control and avoid developing diabetes.

**Diet and Lifestyle Changes for PCOS and Fertility**

A healthy lifestyle that includes weight control, regular exercise, and blood sugar control can help improve your PCOS symptoms and your fertility.

*Managing weight*

Not everyone who has PCOS is overweight, but many are. Gaining a lot of weight can affect your hormones. If you’re obese or [overweight](https://www.webmd.com/diet/obesity/video/obesity-risks), losing weight may help get your hormones back to normal levels. Losing just 10% of your body weight may help your menstrual cycle become more predictable.

Your doctor may recommend choosing foods lower in calories and fat and controlling portion sizes. But losing weight isn't easy. A nutritionist or dietitian may be able to help. Also, some people find that keeping a journal or using an app to track meals and snacks can make things easier.

*PCOS diet*

To manage your blood sugar, your doctor may suggest focusing on foods that are lower in sugar and certain [carbohydrates](https://www.webmd.com/diet/what-to-know-about-carbs) (carbs). Some carbs are good for you, such as those in high-fiber vegetables and fruits. But it's best to limit refined carbs, such as those found in white flour, white rice, white potatoes, sugar, and highly processed foods. These foods have a high glycemic index, which means they make your blood sugar rise quickly.

Other healthy foods, such as poultry and other lean meats, fish, and whole grains, can help with your blood sugar levels, too. Try to have regular meals, as sticking to a schedule helps your body maintain consistent insulin levels.

*Exercising*

Regular exercise burns calories and increases muscle mass. This can help decrease insulin resistance, which can lower your androgen levels and help with symptoms. Exercise can also boost your mood and self-esteem.

*Getting enough sleep*

Lack of sleep can play a role in hormone imbalances, insulin resistance, and weight gain. Set the stage for restful sleep by:

* Going to sleep and waking up at about the same time each day
* Avoiding screens close to bedtime
* Making sure your bedroom is dark, cool, and quiet

If you often have trouble getting at least 7 hours of sleep a night, talk to your doctor.

*Reducing stress*

A condition such as PCOS can be stressful. In turn, stress might make PCOS symptoms worse. Your body makes cortisol (the so-called stress hormone) from progesterone and other hormones. This can upset the balance of these hormones in your body. Stress can also contribute to weight gain and depression, which are common challenges for people with PCOS. Exercise can help, and so can stress-management techniques such as breathing exercises and mindfulness meditation.

*Limiting caffeine*

While moderate levels of caffeine (up to about 4 cups of coffee a day) are fine, more than that might affect your sleep and maybe even your hormonal balance. Ask your doctor whether you should cut back on caffeine.

*Avoiding endocrine disruptors*

Chemicals called endocrine disruptors are thought to cause hormone imbalances and might even be linked to PCOS. Some common ones are bisphenols (including BPA), parabens, phthalates, and triclosan. They’re found in plastics, cosmetics, industrial chemicals, and pesticides. They can also contaminate food, water, soil, and air. It's difficult to avoid these common chemicals. But some possible ways to reduce your exposure include:

* Avoid products that contain fragrance
* Store food in glass or stainless-steel containers instead of plastic ones
* Avoid food from cans lined with BPA
* Wash your hands often, especially before you eat
* Use a vacuum with a HEPA filter

**Alternative Medicine for PCOS**

While no alternative treatments have been proven to help with PCOS symptoms, a few studies have found evidence that some might have benefits.

*Herbs and supplements*

Herbal medicines might help with PCOS symptoms:

* Chaste tree berry
* Black cohosh
* Cinnamon
* *Tribulus terrestris*, a plant used in Eastern medicine
* Licorice plant
* Licorice plant combined with Chinese peony

The findings were strongest for chaste tree berry and black cohosh. But the researchers noted that we need more and better research into these possible benefits.

11 herbs and supplements to see whether they might help with PCOS symptoms or complications.

It found possible benefits for:

* Inositol, a type of sugar found in many different plant foods
* Omega-3 fish oil supplements

However, the researchers warned that the scientific evidence for these is weak.

The review found little evidence of benefits for:

* Vitamin D
* Vitamin D plus calcium
* Cinnamon
* [Chromium](https://www.webmd.com/diet/supplement-guide-chromium)
* Selenium
* Vitamin B complex
* Black cohosh
* Chamomile tea
* Green tea

A few other studies have found that berberine, a compound found in plants such as goldenseal, may help improve fertility and insulin resistance in people with PCOS. But we need more and better research into this.

Keep in mind that the FDA doesn't regulate dietary supplements for effectiveness or safety. Always talk to your doctor before starting a new supplement. Ask about their potential side effects, interactions with medications you take, and the latest research about their effectiveness.

*Spearmint tea for PCOS*

Some studies have found that regularly drinking tea made from spearmint leaves could help balance hormone levels in those with PCOS. It may also reduce the growth of excess facial and body hair. The tea is caffeine-free, so you might try drinking 2-3 cups a day to see if it helps with your symptoms. But talk to your doctor first, especially if you're pregnant, trying to get pregnant, or have other health conditions.

*Acupuncture for PCOS*

Acupuncture is a type of complementary medicine in which a practitioner inserts thin needles into specific points on your body. Some studies have found it may help regulate hormones and ovulation and reduce insulin resistance in those with PCOS. But other researchers say there's not yet enough good evidence that it works as a treatment for PCOS.

*PCOS and Menopause*

Period-related PCOS symptoms often improve as menopause approaches. Your ovaries no longer work after menopause, so your androgen levels go down. And because you don't have periods anymore, irregular ones aren't a problem.

But your androgen levels might still be higher than normal, so you might still have other symptoms. Further, your odds of developing PCOS complications such as diabetes and [metabolic syndrome](https://www.webmd.com/heart/metabolic-syndrome/metabolic-syndrome-what-is-it) go up as you get older.

**PREVENTION TIPS**

### **Can I prevent PCOS or its effects?**

There’s no proven way to prevent PCOS, but you can take small steps to reduce your symptoms. For example, eating nutritious foods, exercising regularly and managing a healthy weight for your body can help you avoid the effects of PCOS.

Polycystic ovary syndrome (PCOS) is a common hormonal disorder that affects women of reproductive age, and while there is no known way to completely prevent it, certain lifestyle and health management strategies can help reduce the risk or manage its symptoms. Here are some prevention tips and strategies:

* Maintain a Healthy Weight: Being overweight or obese can increase the risk of developing PCOS or worsen its symptoms. Losing even a small amount of weight (around 5% of body weight) can help regulate menstrual cycles, improve insulin sensitivity, and reduce androgen levels.
* Eat a Balanced Diet: A diet rich in whole foods, such as fruits, vegetables, whole grains, lean proteins, and healthy fats, can help manage insulin levels and reduce inflammation. Limiting processed foods, refined sugars, and high-glycemic-index foods is also beneficial.
* Exercise Regularly: Engaging in regular physical activity, such as aerobic exercise, strength training, or high-intensity interval training (HIIT), can improve insulin sensitivity, help with weight management, and reduce the risk of developing PCOS-related complications like type 2 diabetes and cardiovascular disease.
* Manage Stress: Chronic stress can disrupt hormonal balance and contribute to insulin resistance. Practicing stress-reduction techniques such as meditation, yoga, or deep breathing can help maintain hormonal equilibrium.
* Get Regular Checkups: Monitoring your menstrual cycle and overall health can help detect early signs of PCOS. If you experience irregular periods, excessive hair growth, or acne, consult a healthcare provider for evaluation and early intervention.
* Avoid Smoking and Limit Alcohol: Smoking and excessive alcohol consumption can negatively affect hormonal balance and increase the risk of various health issues, including those associated with PCOS.
* Consider Natural Supplements: Some studies suggest that certain supplements, such as inositol, chromium, vitamin D, and omega-3 fatty acids, may help improve insulin sensitivity and hormonal balance in women with PCOS. However, it is important to consult a healthcare provider before starting any supplement regimen.
* Monitor and Manage Insulin Levels: Insulin resistance is a common underlying factor in PCOS. Managing blood sugar levels through diet, exercise, and, if necessary, medication (such as metformin) can help reduce the risk of developing PCOS or its complications.
* Avoid Environmental Toxins: Exposure to endocrine-disrupting chemicals, such as bisphenol A (BPA) and phthalates, may interfere with hormonal function. Reducing exposure to these chemicals by choosing BPA-free products and avoiding plastic containers for food storage can be beneficial.
* Stay Informed and Seek Support: Understanding PCOS and its potential impact on health can empower individuals to make informed decisions about their lifestyle and medical care. Joining support groups or seeking guidance from healthcare professionals can also provide valuable resources and encouragement.

By adopting these prevention strategies, individuals can reduce their risk of developing PCOS or manage its symptoms more effectively. It is important to note that while these tips can be helpful, they should not replace professional medical advice. Always consult a healthcare provider for personalized recommendations.

## **OUTLOOK / PROGNOSIS**

### **Does PCOS put me at risk for other health conditions?**

Research shows PCOS may raise your risk for several health conditions, including:

* Diabetes.
* High blood pressure.
* Cardiovascular disease.
* Endometrial hyperplasia.
* Endometrial cancer.
* Sleep disorders such as sleep apnea.
* Depression and anxiety.

Talk to your healthcare provider to make sure you understand your risk for developing these conditions.

## **Living With**

One of the best ways to cope with PCOS is to maintain a healthy body weight, eat nutritious foods and exercise regularly. These changes to your lifestyle can affect hormone levels, in turn regulating your menstrual cycle and easing your symptoms.

If excess hair growth or acne is hurting your confidence, cosmetic treatments or working with a dermatologist might be helpful.

Finally, if you’re trying to conceive and have PCOS, know that you’re not alone. Nearly 1 in 10 people have PCOS. Your healthcare provider will work with you to help you get pregnant if that’s what you want.

Some women struggle with the physical symptoms of PCOS, such as weight gain, hair growth, and acne. Cosmetic treatments, such as electrolysis and laser hair removal, may help you feel better about your appearance. Talk with your healthcare provider about the best ways to treat the symptoms that bother you.

**POSSIBLE COMPLICATIONS**

Polycystic ovary syndrome (PCOS) can lead to several possible complications, including type 2 diabetes, obesity, obstructive sleep apnea, heart disease, mood disorders, and endometrial cancer.

Women with PCOS also have a higher risk of pregnancy complications such as high blood pressure, pre-eclampsia, gestational diabetes, and miscarriage, especially if they are obese.

Additionally, PCOS is associated with an increased risk of metabolic syndrome, which includes central obesity, insulin resistance, and other related symptoms.

The condition can also contribute to long-term health issues such as cardiovascular disease and type 2 diabetes.

Furthermore, women with PCOS are more likely to experience depression compared to those without the condition

Complications of PCOS can include:

* Infertility
* Gestational diabetes or pregnancy-induced high blood pressure
* Miscarriage or premature birth
* Nonalcoholic steatohepatitis — a severe liver inflammation caused by fat buildup in the liver
* Metabolic syndrome — a cluster of conditions including high blood pressure, high blood sugar, and unhealthy cholesterol or triglyceride levels that significantly increase your risk of heart and blood vessel (cardiovascular) disease
* Type 2 diabetes or prediabetes
* Sleep apnea
* Depression, anxiety and eating disorders
* Cancer of the uterine lining (endometrial cancer)

Obesity commonly occurs with PCOS and can worsen complications of the disorder.

**Possible complications of PCOS**

Women with PCOS are more likely to develop certain serious health problems. These include type 2 diabetes, high blood pressure, problems with the heart and blood vessels, and uterine cancer. Women with PCOS often have problems with their ability to get pregnant (fertility).

**What Are the Complications of PCOS?**

When you have PCOS, you have higher odds of having several other health problems, such as:

* Trouble getting pregnant. Hormonal imbalances can interfere with ovulation. If no healthy egg is available to be fertilized by a sperm, you can’t get pregnant. However, you may still be able to get [pregnant](https://www.webmd.com/baby/getting-started-on-getting-pregnant) despite having PCOS. For that, you might need to take medicine and work with a fertility specialist.
* Pregnancy complications. Most people with PCOS can have a healthy pregnancy. But the condition raises your risk for diabetes (gestational diabetes) and high blood pressure (preeclampsia) during pregnancy. It also increases the risk of preterm delivery, a cesarean section delivery, and miscarriage.
* Insulin issues and diabetes. When you have insulin resistance, the cells in your muscles, organs, and other tissues don’t absorb blood sugar very well. So you end up with excess sugar in your bloodstream. Insulin resistance doesn't usually cause symptoms until blood sugar levels get so high that you have diabetes. More than half of those with PCOS will get type 2 diabetes by the time they're 40.
* Metabolic syndrome. This group of symptoms raises your risk of cardiovascular disease. The symptoms include high triglyceride and low HDL (“good”) cholesterol levels, [high blood pressure](https://www.webmd.com/hypertension-high-blood-pressure/blood-pressure-causes), and high blood sugar levels.

Other possible complications include:

* Depression
* Anxiety
* Bleeding from the uterus and a higher risk of uterine and endometrial cancers
* Sleep problems, including sleep apnea
* Inflammation of the liver

**Infertility**

Screening for ovulatory status in all patients. Even a patient with eumenorrheic menstrual cycles may have anovulation, which can be measured by mid-luteal serum progesterone. Excluding other causes of infertility is also recommended.

**Obstetric Complications**

Women with PCOS should be counselled on the adverse impact of excess weight on clinical pregnancy, miscarriage, and live birth rates following infertility treatment

**Endometrial Cancer**

Multiple studies have shown an increased risk of endometrial cancer in patients with PCOS. Numerous risk factors are shared between both pathologies. The Endocrine Society suggests against going for a routine ultrasound (US) endometrial thickness screening in asymptomatic patients. However, women should be counseled to report unexpected or abnormal uterine bleeding.

**Metabolic and Cardiovascular Diseases**

Screening for obesity must be conducted for PCOS women and adolescents by calculating BMI and waist circumference. Blood pressure measurement, diabetes, and lipid screening should be performed at diagnosis, and then, follow-up levels should be checked at a frequency based on results. Insulin resistance has been associated highly with PCOS. Around 33% to 66% of patients with PCOS have an abnormal degree of insulin resistance.

Endocrine Society guidelines recommend using an oral glucose tolerance test (OGTT), with fasting and 2-hour glucose after a 75 g OGTT, to screen for IGT and type-2 diabetes mellitus. OGTT is preferred over HbA1c due to its decreased sensitivity in PCOS patients. Rescreening should be conducted every 3 to 4 years due to more frequent risk factors than the general population. Additionally, obese and overweight patients should be screened for symptoms of OSA and referred for sleep studies when this test is positive.

**Metabolic Dysfunction-Associated Steatotic Liver Disease**

Women with PCOS have 3 times the increased risk of MASLD, formerly known as nonalcoholic fatty liver disease NAFLD; it has been associated with androgen excess and low sex hormone-binding globulin. Routine measurement of LFT is not recommended unless the patient is overweight or obese, given a low sensitivity and specificity MASLD diagnosis. In these patients, a change in management with newer antidiabetic medications like GLP-1 agonists can decrease the risk of the development of NAFLD.

**Depression**

Evidence for the increased rate of depression symptoms was found for PCOS women compared to non-BMI-matched controls. Major depression, recurrent depression, and suicide attempts were also higher in PCOS women. Screening and identifying depression and anxiety disorders should be conducted. Appropriate treatment should be given.

### **WHEN TO SEE A DOCTOR / RED FLAG**

### See your health care provider if you're worried about your periods, if you're having trouble getting pregnant, or if you have signs of excess androgen. These might include new hair growth on your face and body, acne and male-pattern baldness.

### **When should I see my healthcare provider?**

Contact a healthcare provider if you suspect you have PCOS. Some signs that may point to PCOS include:

* An irregular menstrual cycle. Menstrual cycles are
* often long (longer than 40 days between periods).
* Excess hair growth, acne or other signs of excess androgen hormones.
* Difficulty getting pregnant.
* prolonged bleeding

## **DIFFERENTIAL DIAGNOSIS**

## **Diagnostic Considerations**

Although no agreed-upon diagnostic criteria currently exist for adolescent polycystic ovarian syndrome (PCOS), hyperandrogenemia is essential for the diagnosis in this age group.

All conditions that mimic PCOS should be ruled out before a diagnosis of PCOS is confirmed. Consider the following in the differential diagnosis of PCOS:

* Ovarian hyperthecosis
* Congenital adrenal hyperplasia (late-onset)
* Drugs (e.g., danazol, androgenic progestins)
* Hypothyroidism
* Patients with menstrual disturbances and signs of hyperandrogenism
* Idiopathic hirsutism
* Familial hirsutism
* Masculinizing tumors of the adrenal gland or ovary (rapid onset of signs of virilization)
* Cushing syndrome (low K+, striae, central obesity, high cortisol; high androgens in adrenal carcinoma)
* Hyperprolactinemia
* Exogenous anabolic steroid use
* Stromal hyperthecosis (valproic acid)

Although obesity itself is not considered part of the differential diagnosis, obesity is associated with insulin resistance or any condition that is associated with severe insulin resistance (e.g., insulin receptor opathies), which may clinically manifest in the same way as PCOS. Obesity may unmask features of PCOS in women who are genetically predisposed to this syndrome.

## ***Differential Diagnosis***

* 3-Beta-Hydroxysteroid Dehydrogenase Deficiency
* Acromegaly
* Adrenocortical (Adrenal Cortical) Carcinoma Imaging
* Amenorrhea
* Congenital Adrenal Hyperplasia
* Gigantism and Acromegaly
* Hyperprolactinemia
* Hyperthyroidism and Thyrotoxicosis
* Hypothyroidism
* Iatrogenic Cushing Syndrome
* Ovarian Tumors

### **PCOS and endometriosis**

PCOS and endometriosis are different conditions, but both can cause ovarian cysts and infertility. Endometriosis is a condition where the lining of your uterus (endometrium) grows in other places like your ovaries, vagina or fallopian tubes. It typically causes pelvic pain or severe menstrual cramps. People with PCOS have irregular periods, unpredictable ovulation and other physical side effects due to excess male hormones.

## **EPIDEMIOLOGY**

PCOS is very common — up to 15% of females of reproductive age have PCOS.

In the United States, polycystic ovarian syndrome (PCOS) is one of the most common endocrine disorders of reproductive-age women, with a prevalence of 4-12%.Up to 10% of women are diagnosed with PCOS during gynecologic visits.In some European studies, the prevalence of PCOS has been reported to be 6.5-8%.

A great deal of ethnic variability in hirsutism is observed. For example, Asian (East and Southeast Asia) women have less hirsutism than white women given the same serum androgen values. In a study that assessed hirsutism in southern Chinese women, investigators found a prevalence of 10.5%.In hirsute women, there was a significant increase in the incidence of acne, menstrual irregularities, polycystic ovaries, and acanthosis nigricans.

PCOS affects premenopausal women, and the age of onset is most often premenarchal (before bone age reaches 16 y). However, clinical recognition of the syndrome may be delayed by failure of the patient to become concerned by irregular menses, hirsutism, or other symptoms or by the overlap of PCOS findings with normal physiologic maturation during the 2 years after menarche. In lean women with a genetic predisposition to PCOS, the syndrome may be unmasked when they subsequently gain weight.

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### **Androgen insensitivity syndrome**

**DEFINITION AND DESCRIPTION**

Androgen insensitivity syndrome (AIS) occurs when someone is genetically male but is insensitive to androgens (male sex hormones). This means the person has male sex chromosomes (one X and one Y chromosome) but may have female genitals.

AIS is a disorder of sex differentiation. It was previously called testicular feminization syndrome. It affects male fetuses as they develop in the uterus, as well as sexual development during puberty. AIS prevents male genitals from developing as they should. It almost always results in infertility during adulthood.

### **Types of androgen insensitivity syndrome**

There are three types of AIS:

* Complete androgen insensitivity syndrome (CAIS): A person’s external genital appears female. But they don’t have female sex organs (no ovaries, fallopian tubes or uterus). People with CAIS are often raised as girls.
* Partial androgen insensitivity syndrome (PAIS): A person’s external genitals may appear partially (not fully) developed male or female or may not be clearly one or the other. People with PAIS are often raised as boys, but not always.
* Mild androgen insensitivity syndrome (MAIS): A person’s genitals appear male, but they’re usually infertile. Some experts consider MAIS a type of PAIS.

### **Who gets androgen insensitivity syndrome?**

Males who inherit an abnormal gene, called the androgen receptor (AR) gene, from their mothers have a 1 in 4 chance of developing AIS. Females can also inherit and carry the gene, but they won’t develop AIS.

Androgen insensitivity syndrome is rare. About 1 in 99,000 male infants are born with partial androgen insensitivity syndrome and 2 to 5 per 100,000 are born with complete androgen insensitivity syndrome.

## **Symptoms and Causes**

AIS is the result of an abnormal X-linked gene, meaning it’s a gene on the X chromosome and the mother passes it to her child. The gene can’t produce androgen receptors. These are cells that allow your body to respond to androgens, such as testosterone.

### **What are the symptoms of androgen insensitivity syndrome?**

The most common symptom across all forms of AIS is infertility. People with CAIS won’t be able to get pregnant or make their partners pregnant. They have genitals that appear female, but they don’t have female reproductive organs. It’s very rare for people with PAIS or MAIS to make their partners pregnant. Even if they have a very small penis, sperm production is usually low or non-existent.

Other signs and symptoms of CAIS include:

* Abnormally tall stature for a female during puberty.
* Amenorrhea (no menstrual periods).
* Little or no pubic hair or underarm hair during puberty.
* Narrow or shallow vagina.
* Undescended testicles (testicles that are still in your abdominal cavity).

Other signs and symptoms of PAIS can include:

* Bifid scrotum (scrotum splits in two).
* Clitoromegaly (large clitoris).
* Gynecomastia (enlarged male breast tissue).
* Hypospadias (the urethra’s hole is on the underside of your penis instead of the tip).
* Labial adhesions (lips of skin around your vagina seal shut).
* Micropenis (abnormally small penis).
* Partially undescended testicles.

Other signs and symptoms of MAIS include:

* Gynecomastia.
* Micropenis.
* Sparse body hair.

## **Diagnosis and Tests**

A healthcare provider can often diagnose PAIS right after birth by looking at a baby’s genitals. But CAIS or MAIS might not be evident until the age of 11 or 12 when puberty begins. This is the time when a healthcare provider might notice issues. A child with CAIS may not be having menstrual periods or have any pubic hair. A child with MAIS might continue having a very small penis or develop breast tissue. Puberty is also when undescended testicles can herniate, or bulge through an opening in the abdominal wall. Sometimes, healthcare providers discover undescended testicles if your child has surgery for an inguinal hernia.

### **What tests help diagnose androgen insensitivity syndrome?**

Your healthcare provider will need to do tests to confirm a diagnosis:

* Blood tests check hormone levels, sex chromosomes and genetic abnormalities.
* Imaging exams, such as ultrasound, can confirm the absence of female reproductive organs.

If you have a family history of AIS, you may choose to have genetic testing if you’re considering having children. These tests can tell you if you’re a carrier of the abnormal gene.

## **Management and Treatment**

Treatment for AIS depends on sex, which is recorded for an infant at birth. Most treatments take place after puberty. This gives your child’s body time to go through developmental changes. It also allows your child to play a more active role in their treatment decisions.

But some health experts think certain treatments, such as removal of the testicles, should happen before puberty. They think other treatments can happen after the completion of puberty. This reduces the risk of gonadoblastomas, which are tumors that can form in undescended testicles.

Children raised as males may choose to have:

* Surgery to repair their male genitals, such as hypospadias repair or orchiopexy (surgery to move undescended testicles to the scrotum).
* Breast reduction surgery to remove excess breast tissue.
* Hernia repair to close open or weakened tissue in their abdominal wall.
* Hormone therapy with testosterone.

Children raised as females may choose to have:

* Surgery to remove male genitals or extra clitoral tissue.
* Non surgical vaginal dilation to make their vagina deeper.
* Hormone therapy with estrogen.

## **Outlook / Prognosis**

People with AIS can lead full, healthy lives. Most people respond well to treatments like hormone therapy and surgery. But AIS usually results in infertility, which can be difficult for many people. It can also have profound psychological effects on children and young adults. Your risk of testicular tumors also increases by about 30% without a gonadectomy (removal of gonads).

## **Prevention**

There’s no way to prevent AIS. If you have a family history of the disease and worry about passing the abnormal gene to your child, genetic testing can help you find out if you’re a carrier.

## **Living With**

Caring for your child’s psychological health is a huge part of managing AIS. A strong support system of healthcare providers, friends and family members who understand their condition is important. Support groups can also help your child share their experiences with others who are going through similar challenges. It’s important to talk with your child about their AIS around the time of puberty. That’s when they’ll notice a lack of pubertal progression.

## **Epidemiology**

The best available data suggest an androgen insensitivity syndrome incidence of approximately 1 case per 20,400 liveborn males. This statistic is based on analysis of a Danish patient registry that included only hospitalized cases; thus, the true incidence of androgen insensitivity syndrome may be higher.Complete androgen insensitivity syndrome appears more common than partial androgen insensitivity syndrome, although exact figures are unavailable. In the international disorders of sex development registry, of 649 accessible cases, 170 cases had suspected androgen insensitivity syndrome. Of these 170 cases, 19 (11%) had reported anomalies and 9 of these had confirmed androgen receptor mutations.

All patients with androgen insensitivity syndrome are chromosomally and gonadally male. However, separating the concepts of sex and gender is crucial with these patients. The term sex is usually based on physical attributes, whereas the concept of gender is based on an individual's self-concept and self-identification, as well as the role an individual assumes in society.

Most patients with complete androgen insensitivity syndrome have a female gender. This may be due, in part, to the patient's role assignment and upbringing before the diagnosis or to the patient's choice of female "sex/gender" at diagnosis. The significance of the androgen effect's absence is increasingly recognized for its influence on the maturing brain (and other systems) in terms of developing adult gender identity.

## Diagnostic considerations

Other conditions to consider in the workup of suspected androgen insensitivity syndrome include the following:

* 17,20-lyase deficiency
* 17-beta-hydroxysteroid dehydrogenase deficiency type 3
* Frasier syndrome
* Mutations in SRY, NR5A1, WT1
* Mutations in the luteinizing hormone receptor
* p450 oxidoreductase deficiency

## **Differential Diagnoses**

* 17-Hydroxylase Deficiency Syndrome
* 3-Beta-Hydroxysteroid Dehydrogenase Deficiency
* 5-Alpha-Reductase Deficiency
* Congenital Adrenal Hyperplasia
* Denys-Drash Syndrome
* Klinefelter Syndrome
* Mayer-Rokitansky-Kuster-Hauser Syndrome
* Smith-Lemli-Opitz Syndrome

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# **MENSTRUAL IRREGULARITIES**

*ALTERNATIVE NAMES:* Irregular menstruation is also known as “amenorrhea”, which refers to the absence of normal periods. Other terms used to describe menstrual irregularities include “oligomenorrxhea”, which is infrequent menstruation with intervals of greater than 35 days, and “polymenorrhea”, which is characterized by more frequent menstrual periods than the normal 21–35-day cycle. Additionally, “metrorrhagia” is a type of abnormal menstruation that involves bleeding at irregular intervals and with variable amounts.

**DEFINITION / DESCRIPTION**

Menstrual irregularities can have a variety of causes, including pregnancy, hormonal imbalances, infections, diseases, trauma, and certain medications.

**Irregular periods**

Most women have menstrual periods that last four to seven days. Your period usually occurs every 28 days, but normal menstrual cycles can range from 21 days to 35 days. In fact, the average cycle length is 29 days. Many things cause irregular periods (or irregular menstruation) such as changes in hormone levels, stress, certain health conditions, medications and more.

**Examples of irregular periods**

Your period is still considered “regular” even if it varies slightly from cycle to cycle. Examples of irregular menstruation include:

* Periods that occur fewer than 21 days or more than 35 days apart.
* Missing three or more periods in a row.
* Menstrual flow (bleeding) that’s much heavier or lighter than usual.
* Periods that last longer than seven days.
* Length of time between cycles varies by more than nine days. For example, one cycle is 28 days, the next is 37 days and the next is 29 days.
* Periods that are accompanied by severe pain, cramping, nausea or vomiting.
* Bleeding or spotting that happens between periods, after menopause or after sexual intercourse.
* Soaking through one or more tampons or sanitary pads in an hour.

Your menstrual cycle may not always be predictable — and that may be OK. It’s normal to have slight variations in cycle length or have a menstrual period that seems slightly heavier or lighter in flow than your previous period. Menstrual irregularities are fairly common, and you don’t have to be able to predict your cycle to the exact day for it to be considered “normal.”

**Conditions related to irregular menstruation**

* **Amenorrhea**: A condition where your periods have stopped completely. The absence of a period for 90 days or more is considered abnormal unless you’re pregnant, breastfeeding or going through menopause (which generally occurs between ages 45 and 55). If you haven’t started menstruating by age 15 or 16 or within three years of your breasts developing, you may also have amenorrhea.
* **Oligomenorrhea**: A condition where your periods occur infrequently. You may go more than 35 days between periods or have six to eight periods a year.
* **Dysmenorrhea**: A medical term for painful periods and severe menstrual cramps. Some discomfort during your cycle is normal.
* **Abnormal uterine bleeding**: Abnormal uterine bleeding is bleeding between monthly periods, prolonged bleeding or an extremely heavy period.

**Different Types of Menstrual Disorders**

There are several types of menstrual disorders that women may experience. Each type presents unique symptoms and requires specific management strategies. The key menstrual disorders list includes:

* Amenorrhea: Absence of menstruation.
* Dysmenorrhea: Painful menstrual cramps.
* Menorrhagia: Excessive or prolonged menstrual bleeding.
* Oligomenorrhea: Infrequent menstrual periods.
* Polymenorrhea: Frequent menstrual periods

**CAUSES OF IRREGULAR PERIODS (GENERALLY LIGHT)**

Causes of menstrual irregularities include:

* Perimenopause (generally in the late 40s and early 50s)
* Primary ovarian insufficiency (POI)
* Eating disorders (anorexia nervosa or bulimia)
* Excessive exercise
* Thyroid dysfunction (too much or too little thyroid hormone)
* Elevated levels of the hormone prolactin, which is made by the pituitary gland to help the body produce milk
* Uncontrolled diabetes
* Cushing's syndrome (elevated levels of the hormone cortisol, used in the body's response to stress)
* Late-onset congenital adrenal hyperplasia (problem with the adrenal gland)
* Hormonal birth control (birth control pills, injections, or implants)
* Hormone-containing intrauterine devices (IUDs)
* Scarring within the uterine cavity (Asherman's syndrome)
* Medications, such as those to treat epilepsy or mental health problems

## *Common causes of heavy or prolonged menstrual bleeding include:*

* Adolescence (during which cycles may not be associated with ovulation)
* Polycystic ovary syndrome (PCOS) (bleeding irregular but heavy)
* Uterine fibroids (benign growths of uterine muscle)
* Endometrial polyps (benign overgrowth of the lining of the uterus)
* Adenomyosis (the presence of uterine lining in the wall of the uterus)
* Non-Hormonal IUDs
* Bleeding disorders, such as leukemia, platelet disorders, clotting factor deficiencies, or (less common) von Willebrand disease
* Pregnancy complications (miscarriage)

## *Common causes of dysmenorrhea (menstrual pain) include:* Endometriosis (uterine lining grows outside the uterus)

## Uterine abnormalities (fibroids or adenomyosis)

## IUDs

## Pelvic scarring due to sexually transmitted infections, such as chlamydia or gonorrhea

## Heavy menstrual flow

## **MEDICAL CONDITIONS THAT MAY CAUSE MENSTRUAL IRREGULARITIES**

## *Premenstrual Syndrome (PMS)*

## Symptoms include irritability, fatigue, cramps, chest pain, headache, back pain, acne, diarrhea, bloating, insomnia, anxiety, depression, stress, food cravings, and emotional mood swings. The symptoms of PMS can be different each month and different for each woman. Although PMS is uncomfortable, it is not a cause for concern. Symptoms usually disappear as soon as you menstruate.

## *Severe Periods*

## In this condition, the bleeding is heavier than usual. You may also experience longer-than-average periods of 5-7 days. Heavy cycles are triggered mainly by hormonal imbalances, especially estrogen and progesterone. Changes in food or exercise, menstrual infections, hypothyroidism, fibroids, puberty, and cervical inflammation are among the other triggers.

## *Painful Periods*

## Some physical aches and cramps occur frequently during the onset of your period. However, some women experience severe pain during their period. Pain during this time is typically the consequence of an underlying medical issue, such as pelvic inflammatory disorders, fibroids, or endometriosis.

## *Lack of Menstruation*

## Sometimes, women do not menstruate. Amenorrhea is the term for this condition. There are primary and secondary forms of amenorrhea.

## Primary Amenorrhea: In cases where a 16-year-old girl does not get her first period, it is known as primary amenorrhea. This may be due to a problem with the pituitary gland, a congenital disability (Birth Defect) in the reproductive system, or postponement of puberty.

## Secondary Amenorrhea: If you miss your regular periods for six months or longer, this is known as secondary amenorrhea. The causes of secondary amenorrhea vary in adults and adolescents.

## In adolescent girls, it can be caused by sudden weight gain or loss, anorexia, suspension of birth control, ovarian cysts, pregnancy, or an overactive thyroid gland. In adults, it can be caused by pregnancy, premature ovarian failure, pelvic inflammatory disease, menopause, or interruption of birth control.

There are many causes of irregular periods, ranging from stress to more serious underlying medical conditions.

**Medical conditions and irregular periods**

Certain health conditions are associated with missed menstrual periods. They include:

* **Endometriosis**: Endometriosis occurs when endometrial tissue grows outside of your uterus. The tissue often attaches itself to your ovaries or fallopian tubes. Endometriosis may cause abnormal bleeding, cramps or severe pain before and during your period.
* **Pelvic inflammatory disease**: Pelvic inflammatory disease (PID) is a bacterial infection that affects the female reproductive system. It’s typically caused by an untreated sexually transmitted infection (STI). Bacteria enter your vagina and spread to your uterus and upper genital tract. Symptoms of PID include a heavy vaginal discharge with an unpleasant odor, irregular periods and pelvic pain.
* **Polycystic ovary syndrome**: In polycystic ovary syndrome (PCOS), your ovaries make large amounts of androgens, which are a type of hormone. This hormone prevents or delays ovulation, causing irregular periods. People with PCOS may stop menstruating completely.
* **Primary ovarian insufficiency**: This condition occurs in women under age 40 whose ovaries don’t function as they should, causing missed or irregular periods. It can occur during treatment for cancer with chemotherapy and radiation or if you have certain autoimmune conditions.
* **Thyroid or pituitary gland disorders**: Hypothyroidism (underactive thyroid), hyperthyroidism (overactive thyroid) and other thyroid or pituitary gland disorders affect your hormones. This causes your period to be irregular.
* **Bleeding disorders**: You may experience heavy menstrual bleeding if you develop a bleeding or blood clotting disorder.
* **Uterine cancer or ovarian cancer:**Certain cancers can affect a person’s menstrual period. Changes may include bleeding that’s heavier than usual or missed periods.

**Lifestyle factors and irregular periods**

Disruptions or changes in your daily routine can have an impact on your menstrual cycle. Some examples of lifestyle factors include:

* Stress.
* Gaining or losing a significant amount of weight.
* Exercise routines that result in very low body fat (long-distance runners, dancers or gymnasts).
* Viruses or other illnesses.

**Other causes of abnormal menstruation**

Certain medications, complications of pregnancy or breastfeeding may also cause your period to be irregular. Other causes include:

* **Birth control pills**: Most birth control pills contain a combination of hormones. The pills prevent pregnancy by keeping your ovaries from releasing eggs. Going on or off birth control pills can affect menstruation. You may have irregular or missed periods for up to six months after discontinuing birth control pills.
* **Medications**, like steroids or anticoagulant drugs (blood thinners).
* **Miscarriage or an ectopic pregnancy** (the fertilized egg implants outside your uterus).
* **Surgery, scarring or blockages** in your uterus, ovaries or fallopian tubes.

## **SYMPTOMS OF MENSTRUAL DISORDERS**

## Early identification of menstrual disorders can help manage symptoms effectively. Common symptoms of menstrual disorders symptoms include:

## Irregular Periods: Periods that are inconsistent in length or timing.

## Heavy Bleeding: Excessive bleeding that can lead to anemia.

## Painful Periods: Severe cramping or pelvic pain.

## Absent Periods: Missed periods for several cycles.

## Spotting: Light bleeding or spotting between periods.

**DIAGNOSIS METHODS**

**Irregular periods diagnosed**

If you sense changes in your menstrual cycle, begin keeping records of when your periods begin and end. Note symptoms, the amount of flow or if you experience cramping, bleeding between periods or passing large clots. These are all helpful to share with your healthcare provider.

To diagnose irregular periods, your provider will ask you about your menstrual cycle and medical history. They’ll perform a physical examination, including a pelvic exam. They might also order certain tests, including:

* **Pelvic ultrasound**: An ultrasound can detect irregular bleeding due to uterine fibroids, polyps or an ovarian cyst.
* **Endometrial biopsy**: Your provider removes a sample of tissue from the lining of your uterus. It can help diagnose endometriosis, hormonal imbalances or precancerous cells.
* **Hysteroscopy**: A procedure that allows your provider to look inside your uterus in order to diagnose and treat certain causes of abnormal bleeding.

**Management and Treatment**

*How are irregular periods treated?*

The treatment for irregular periods depends on the underlying cause.

**Medication for irregular periods**

Medications are often the first treatment for irregular periods. If medication doesn’t help, your provider may recommend surgery. Possible medications include:

* Hormonal birth control: Irregular or heavy bleeding caused by PCOS, uterine fibroids, endometriosis or other medical conditions may be managed with hormonal birth control. They also help by regulating your cycle, making it more predictable. These can be combination hormonal birth control pills that consist of estrogen and progestin, or progestin-only birth control. Both types come in different forms like pills, a vaginal ring, injection or an IUD (intrauterine device).
* Tranexamic acid: A medication prescribed to treat heavy menstrual bleeding. You take one pill at the start of your period to control your bleeding.
* Pain relievers: You may find relief from mild to moderate pain or cramps by taking an over-the-counter pain reliever, such as ibuprofen or acetaminophen.
* Hormone therapy: Hormone therapy may be helpful if your irregular period is due to perimenopause. It can also help with other menopausal symptoms like vaginal dryness and hot flashes. There are risks associated with hormone therapy, so be sure to discuss these with your healthcare provider.
* Antibiotics: You may be given antibiotics if the cause of irregular bleeding is from an infection.
* Gonadotropin-releasing hormone agonists: These medications shrink the size of uterine fibroids and control heavy bleeding, but temporarily stop your menstrual period.

**Surgery for irregular periods**

There are surgical treatment options depending on your condition, age and whether you want to get pregnant in the future. Surgical treatments for irregular periods include:

* Endometrial ablation: Endometrial ablation is a procedure that uses heat, cold or different types of energy to destroy the tissue that lines your uterus so you bleed less during your period. You must have a form of birth control to have this procedure. If you still wish to get pregnant in the future, you shouldn’t have this procedure.
* Myomectomy: A procedure to remove uterine fibroids, a cause of irregular bleeding.
* Uterine artery embolization: A procedure that cuts off blood supply to your uterus in order to stop uterine fibroids.
* Hysterectomy: In severe cases, surgery may be necessary to remove excess endometrial tissue growing in your pelvis or abdomen. A hysterectomy might be required as a last resort if your uterus has been severely damaged.

**PREVENTION TIPS**

**How can I lower my risk of having an irregular period?**

Here are some recommendations for self-care:

* Try to maintain a healthy lifestyle by exercising moderately and eating nutritious foods. If you want to lose weight, do it gradually instead of turning to diets that drastically limit your calorie and food intake.
* Make sure you get enough rest.
* Practice stress reduction and relaxation techniques.
* Cut back on prolonged or intense exercise routines.
* Use birth control pills or other contraceptive methods as directed.
* Change your tampons or sanitary pads every four to six hours to avoid toxic shock syndrome and prevent infections.
* See your gynecologist and primary care provider for regular check-ups.

**What can I do to prevent irregularities?**

Sometimes, birth control pills can help make an irregular menstrual cycle more regular. Birth control devices that contain progestin can make periods less heavy and ease cramping. Treatment for any problems that may cause these irregularities, such as an eating disorder, also might help. However, some menstrual irregularities can't be prevented.

**POSSIBLE COMPLICATIONS**

Menstrual irregularities can lead to various complications, including **infertility, anemia, and an increased risk of certain health conditions**. For instance, irregular menstrual cycles can indicate underlying issues such as hormonal imbalances or ovulatory disorders, which may affect a woman's ability to conceive.

Additionally, heavy menstrual bleeding associated with irregularities can lead to anemia due to excessive blood loss.

Menstrual irregularities have also been linked to an increased risk of chronic diseases such as metabolic syndrome, coronary heart disease, type 2 diabetes mellitus, and rheumatoid arthritis.

Moreover, women with irregular menstrual cycles may face a higher risk of adverse obstetric and neonatal outcomes, including preeclampsia, antepartum hemorrhage, gestational hypertension, preterm birth, low birth weight, and perinatal death.

In some cases, menstrual irregularities may be a sign of more serious conditions such as uterine or ovarian cancer, which can cause unusual bleeding patterns.

Furthermore, irregular periods can impact a woman's quality of life, contributing to psychological and mental health issues such as depression and anxiety.

It is important to address menstrual irregularities promptly to prevent these potential complications. If you experience persistent or severe menstrual irregularities, it is advisable to consult a healthcare professional for proper evaluation and treatment.

**OUTLOOK / PROGNOSIS**

Menstrual irregularities can have varying prognoses depending on the underlying cause and the effectiveness of treatment. Many women experience improvement with appropriate management and lifestyle changes.

The prognosis for menstrual irregularities varies depending on the underlying cause and the effectiveness of treatment. Regular monitoring and follow-up with healthcare providers are important for managing symptoms and addressing any underlying health issues.

Menstrual irregularities can impact a woman’s quality of life and may be indicative of underlying health conditions. Understanding the types, causes, and management strategies for menstrual irregularities is essential for maintaining reproductive health.

Through a combination of lifestyle changes, medical treatments, and ongoing care, women can effectively manage menstrual irregularities and support overall well-being.

## **WHEN TO SEE A DOCTOR / RED FLAG**

## See a doctor if you experience:

## Irregular or missed periods for several cycles.

## Severe pain that affects your daily activities.

## Heavy bleeding or periods lasting more than 7 days.

## Spotting or unusual bleeding between periods.

## Emotional issues like depression, mood swings, or anxiety around your period.

## Missed periods for more than 3 months without a clear reason.

## Getting checked early can help manage symptoms and improve your health. Don't hesitate to contact your healthcare provider if you have concerns.

**Additional Common Questions**

**Is it normal to miss a period for two months?**

Skipping one or two periods isn’t ideal, but it’s not too concerning. Take a look at any changes in your life recently. Things like stress, a new workout routine, losing or gaining weight, or changing birth control can all impact your cycle. Call your healthcare provider if you miss your period for three or more months in a row or if you experience other unusual symptoms during your next period.

**How much delay in periods is normal?**

Slight delays in your period are typically OK. Some people are able to predict their period to the exact day, while others can’t. Contact your provider if you notice a sudden change in the time between cycles or the duration (days) of your period, especially if it’s significant. This doesn’t always indicate a problem, but it’s a good idea to get it checked out.

**When are irregular periods more common?**

Irregular periods are more common when you first begin menstruating (around age 9 to 14) or during perimenopause (around age 50 or just before menopause).

**Should I be worried if my period is irregular?**

Irregular periods may be nothing to worry about because some variation in menstruation is normal. What’s normal for you may be different from what’s normal for your closest friends. However, certain symptoms could be a sign of a bigger problem.

Contact your gynecologist if you’re concerned about your menstrual cycle or if you’re trying to get pregnant and have unpredictable periods (this can make getting pregnant difficult). They’ll be able to tell you what’s normal and if treatment is needed.

**RECENT GUIDELINES OR UPDATES**

**Menstrual cycle: What's normal, what's not**

*Your menstrual cycle can say a lot about your health. Understand how to track your menstrual cycle and what to do about irregularities.*

Do you know when your last menstrual period began or how long it lasted? If not, it might be time to start paying attention.

Keeping track of your menstrual cycles can help you understand what's typical for you. You also can record your ovulation and find important changes — such as a missed period or menstrual bleeding that isn't typical. While irregularities in your period usually aren't serious, sometimes they are caused by other health problems.

**Menstrual cycle**

The menstrual cycle is the monthly series of changes the body goes through to prepare for pregnancy. Each month, one of the ovaries releases an egg. This is called ovulation. Hormonal changes at this time get the uterus ready for pregnancy. If the released egg isn't fertilized during ovulation, the lining of the uterus sheds through the vagina. This is a menstrual period.

**What's typical?**

The menstrual cycle is counted from the first day of one period to the first day of the next. The cycle isn't the same for everyone. Menstrual bleeding might happen every 21 to 35 days and last 2 to 7 days. For the first few years after menstruation begins, long cycles are common. However, menstrual cycles tend to shorten and become more regular as people age.

Your menstrual cycle might be regular — about the same length every month — or somewhat irregular. Your period might be light or heavy, painful or pain-free, long or short, and still be considered typical. Within a broad range, "typical" is what's typical for you.

Certain kinds of birth control, such as extended-cycle birth control pills and intrauterine devices (IUDs), will change a menstrual cycle. Talk to your health care provider about what to expect.

When you get close to the time when your menstrual cycles will end, called menopause, your cycle might become irregular again. However, the risk of cancer of the uterus gets higher as you age. Talk with your health care provider about any irregular bleeding around menopause.

**How can I track my menstrual cycle?**

To find out what's typical for you, start keeping a record of your menstrual cycle on a calendar. Begin by tracking your start date every month for several months in a row to identify the regularity of your periods.

If you're worried about your periods, also track the following every month:

* **End date.** How long does your period typically last? Is it longer or shorter than usual?
* **Flow.** Record the heaviness of your bleeding. Does it seem lighter or heavier than usual? How often do you need to change your tampon or pad? Have you passed any blood clots?
* **Bleeding changes.** Are you bleeding in between periods?
* **Pain.** Describe any pain you have with your period. Does the pain feel worse than usual? It is not unusual to have some cramping or pain with your periods.
* **Other changes.** Have you noticed any changes in your mood or behavior? Did anything new happen around the time you noticed changes in your periods?

**What causes menstrual cycle irregularities?**

Menstrual cycle irregularities can have many different causes, including:

* **Pregnancy or breast-feeding.** A missed period can be an early symptom of pregnancy. Breast-feeding typically delays the return of your period after pregnancy.
* **Eating disorders, extreme weight loss or too much exercising.** Eating disorders — such as anorexia nervosa — extreme weight loss and higher physical activity can interrupt your period.
* **Polycystic ovary syndrome (PCOS).** People with this common disorder may have irregular periods. They also can have enlarged ovaries that contain small collections of fluid — called follicles — located in each ovary. These follicles can be seen during an ultrasound exam. People who have PCOS often have more follicles in the ovaries than other people.
* **Premature ovarian failure.** Premature ovarian failure refers to the loss of typical ovarian function before age 40. People who have this condition, also known as primary ovarian insufficiency, might have irregular or occasional periods for years.
* **Pelvic inflammatory disease (PID).** This infection of the reproductive organs can cause irregular menstrual bleeding.
* **Uterine fibroids.** Uterine fibroids are growths in the uterus that are not cancer. They can cause heavy and prolonged menstrual periods.

In addition, talk with your health care provider if:

* Your periods suddenly stop for more than 90 days — and you're not pregnant.
* Your periods become irregular after having been regular.
* You bleed for more than seven days.
* You bleed more heavily than usual or soak through more than one pad or tampon every hour or two.
* Your periods are less than 21 days or more than 35 days apart.
* You bleed between periods.
* You develop severe pain during your period.
* You suddenly get a fever and feel sick after using tampons.

Remember, keeping track of your period can help you find out what's typical for you and what isn't. If you have questions or concerns about your menstrual cycle, talk to your health care provider.

*Diagnostic Considerations*

The key diagnostic issue in dysmenorrhea is differentiating primary dysmenorrhea from secondary dysmenorrhea.

In addition to the conditions listed in the differential diagnosis, other problems to be considered include the following:

* Peritonitis
* Pregnancy or pregnancy loss
* Uterine neoplasm, benign or malignant
* Iatrogenic causes

## 

## **DIFFERENTIAL DIAGNOSIS**

* Adenomyosis
* Appendicitis
* Urinary Tract Infection (UTI) and Cystitis (Bladder Infection) in Females
* Ectopic Pregnancy
* Endometriosis
* Inflammatory Bowel Disease
* Irritable Bowel Syndrome (IBS)
* Ovarian Cancer
* Ovarian Cysts
* Pelvic Inflammatory Disease

## 

## **EPIDEMIOLOGY**

### *United States statistics*

Dysmenorrhea may affect more than 50% of menstruating women, and its reported prevalence has been highly variable (e.g., 45-95%). A survey of 113 patients in a family practice setting showed a prevalence of 29-44%,but figures as high as 90% in women aged 18-45 years have been reported.The use of oral contraceptives (OCs) and nonsteroidal anti-inflammatory drugs (NSAIDs), both of which are effective in ameliorating symptoms of primary dysmenorrhea, may hinder accurate assessment of prevalence.

Primary dysmenorrhea peaks in late adolescence and the early 20s.The incidence falls with increasing age and with increasing parity. In many studies,though not all the reported prevalence and severity of dysmenorrhea in parous women are substantially lower. An epidemiologic study found no significant differences in prevalence and severity of dysmenorrhea between nulligravid women and those in whom pregnancy had been terminated by either spontaneous or induced abortion.

In an epidemiologic study of an adolescent population (age range, 12-17 years), Klein and Litt reported that dysmenorrhea had a prevalence of 59.7%.Of patients reporting pain, 12% described it as severe, 37% as moderate, and 49% as mild. Dysmenorrhea caused 14% of patients to miss school frequently.

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**GIGANTISM AND ACROMEGALY**

ALTERNATIVE NAMES: Alternative names for acromegaly include “**Maries disease”, “acromegaloidism”, and “acromegalia”**. Other terms that have been used include “hypersoma” and “somatomegaly”.

**DEFINITION / DESCRIPTION**

Acromegaly is a rare condition in adults that causes some bones, organs and other tissue to grow bigger. A small gland in the brain called the pituitary gland drives these changes by making too much growth hormone. This usually happens due to a tumor of the pituitary gland. The tumor isn't cancer.

When the body has too much growth hormone, bones get bigger. In childhood, this leads to increased height as part of a condition called gigantism. In adults with acromegaly, a change in height doesn't happen. Instead, bones in the hands, feet and face become bigger.

These changes happen slowly over many years. So, people with acromegaly and their loved ones may take a long time to notice the symptoms. And healthcare professionals may have a hard time finding and treating the condition early on.

Without treatment, acromegaly can lead to other serious and sometimes life-threatening health conditions called complications. But treatments such as surgery, medicine and radiation can lower the risk of complications. Treatment also can improve many acromegaly symptoms.

**CAUSES**

The most common cause of acromegaly is a tumor in the pituitary gland. The tumor is called an adenoma. It isn't cancer. But it makes too much growth hormone over a long amount of time.

Too much growth hormone causes many symptoms of acromegaly. Some of the symptoms, such as headaches and impaired vision, are due to the tumor pressing on nearby brain tissues.

Rarely, tumors in other parts of the body cause acromegaly. These include tumors of the lung or pancreas. Sometimes these tumors release growth hormones. Or they make a hormone called growth hormone-releasing hormone. This signals the pituitary gland to make more growth hormone.

The pituitary gland is located at the base of the brain, behind the bridge of the nose. It makes growth hormone and other hormones. Growth hormone plays an important role in controlling physical growth.

The pituitary gland releases growth hormone into the bloodstream. This triggers the liver to make a hormone called insulin-like growth factor-1, also called IGF-1. IGF-1 is really what causes bones and other tissues to grow. Too much growth hormone leads to too much IGF-1. And that can cause acromegaly symptoms and complications.

**RISK FACTORS**

People who have a rare genetic condition called multiple endocrine neoplasia, type 1 have a higher risk of acromegaly. This condition also is called MEN 1.

In MEN 1, the parathyroid glands, pancreas and pituitary gland may grow tumors and release extra hormones. Extra parathyroid hormone can cause thin bones and kidney stones. A pancreas tumor may make the hormone insulin and cause low blood sugar. If the pituitary tumor makes extra growth hormone, acromegaly results. Very rarely, acromegaly can run in families.

**SIGNS / SYMPTOMS**

Acromegaly symptoms can change the way some body parts look. Changes can include:

* Thick ears and lips.
* A broad nose.
* Enlarged hands and feet.
* A jutting brow or jaw.
* Gaps between teeth.
* An enlarged tongue.
* An expanded rib cage that may cause the chest to have a round shape.

Skin changes can include:

* Acne.
* Harmless skin growths are called skin tags.
* Coarse, oily and thickened skin.
* Swelling in the tissue under the skin.

Most often, people with acromegaly don't have every possible body change. And because the changes come on slowly, they may take years to notice. But over time, rings may no longer fit fingers like they used to. Or shoe size may get bigger. Sometimes, people notice the changes only by comparing old photos with newer ones.

Other acromegaly symptoms can include:

* Vision troubles, including loss of side vision.
* More sweating and body odor than is typical.
* Extreme tiredness.
* Headaches.
* Joint pain.
* Deeper voice.

## 

## **DIAGNOSIS METHODS AND TESTS**

Diagnosis involves the steps that your healthcare professional takes to find out if you have acromegaly. Your healthcare professional asks about your health history and does a physical exam. You also may need the following tests:

* **IGF-1 measurement.** This blood test measures the level of IGF-1 in your blood. A high IGF-1 level can mean that the level of growth hormone also is high. This can be a clue for acromegaly.
* **Growth hormone suppression test.** This blood test measures your growth hormone level before and after you drink a type of sugar water called glucose. In people who don't have acromegaly, the glucose drink typically causes the growth hormone level to fall. But if you have acromegaly, your growth hormone level tends to stay high.
* **Imaging tests.** Magnetic resonance imaging (MRI) can help pinpoint the location and size of a tumor in your pituitary gland. If no pituitary tumors are seen, you may need more imaging tests to look for other types of tumors. Your healthcare professional also may recommend X-rays of the hands and feet. These can help check for bone growth.

**TREATMENT OPTIONS**

Acromegaly treatment aims to improve symptoms and treat or prevent complications. The goal is to lower growth hormone and IGF-1 back to their proper levels and keep them there.

To help lower your growth hormone (GH) and IGF-1 levels, treatment options often include:

* Surgery to remove the tumor that's causing symptoms. Most often, this is the first treatment for acromegaly that's caused by a pituitary gland tumor.
* Medicine to help lower hormone levels. This is usually an option if surgery doesn't bring down growth hormone to the right level.
* Radiation to shrink the size of the tumor. Often, this is a treatment choice if surgery isn't an option. It's also an option if surgery can't remove the whole tumor or if medicine doesn't help enough.

Some people need a mix of these treatments. Your treatment plan depends on factors such as:

* The location and size of your tumor.
* How serious your symptoms are.
* Your age and overall health.

It's common for some changes in physical features to improve with treatment. For example, swelling of soft tissue often goes down. And the skin often becomes less oily and coarse. But enlarged bones don't return to the size that they used to be.

If you also have other health conditions due to acromegaly, you may need other treatments to manage them.

### **Surgery or other procedures**

Surgeons can remove most pituitary tumors using a method called transsphenoidal surgery. A surgeon works through the nose to remove the tumor from the pituitary gland. If the tumor causing symptoms isn't located on the pituitary gland, the surgeon recommends another type of surgery to remove the tumor.

Removing the tumor often returns growth hormone to the right level, especially if the tumor is small. If the tumor was putting pressure on the tissues around the pituitary gland, removing the tumor also helps relieve headaches and vision changes.

Sometimes, surgeons can't remove the whole tumor. When this happens, the level of growth hormone may still be too high after surgery. Another surgery, medicines or radiation treatments may be needed.

### **Medicines**

Medicine can help lower hormone levels or block the hormones' effects. Your healthcare professional may recommend one or more of the following:

* **Medicines called somatostatin analogues that cause the body to make less growth hormone.** In the body, a brain hormone called somatostatin limits the production of growth hormone. The medicines octreotide (Mycapssa, Sandostatin) and lanreotide (Somatuline Depot) are lab-made versions of somatostatin. Taking one of these medicines signals the pituitary gland to make less growth hormone. That also helps lower IGF-1. These medicines also might make a pituitary tumor smaller. You take the medicines by mouth or receive a monthly shot.
* **Medicines called dopamine agonists that lower hormone levels.** The medicines cabergoline and bromocriptine (Cycloset, Parlodel) may help lower levels of GH and IGF-1 in some people. These medicines also may help make a tumor smaller. You take dopamine agonists by mouth, and the doses often are high. That can raise the risk of side effects. Side effects can include upset stomach, vomiting, stuffy nose, tiredness, dizziness, sleep problems and mood changes.
* **Medicine called a growth hormone antagonist that blocks the action of growth hormone.** The medicine pegvisomant (Somavert) blocks the effect of growth hormone on the body's tissues and results in lower IGF-1 levels. Pegvisomant doesn't lower the level of growth hormone or shrink tumor size. It may affect the liver, so your healthcare professional monitors your liver health with blood tests while you're on pegvisomant. The medicine is given as a daily shot and may be used along with other medicines.

### **Therapies**

Radiation therapy destroys any leftover tumor cells after surgery to remove the tumor. It also slowly lowers the level of growth hormone. It may take months or years for radiation to improve acromegaly symptoms in ways that you notice.

Radiation often lowers levels of other pituitary hormones too — not just growth hormone. If you get radiation, you'll likely need regular follow-up healthcare visits. These visits let your healthcare professional check your hormone levels and make sure that your pituitary gland is working right. Follow-up care may last for the rest of your life.

Types of radiation therapy include:

* **Stereotactic radiosurgery.** Stereotactic radiosurgery uses 3D imaging to deliver a beam of high dose of radiation to the tumor cells. This treatment also limits the amount of radiation to the healthy tissue that surrounds the tumor. Most often, stereotactic radiosurgery is given in a single dose. This type of radiation may bring growth hormone back to the right level within 5 to 10 years. The most common technique that healthcare professionals use to give this type of radiation is called Gamma Knife. It doesn't involve the use of a knife.
* **Proton beam radiation.** This type of radiation uses tiny particles called protons that point to the tumor. It may cause less damage to the pituitary gland and the tissue that surrounds it than does conventional radiosurgery.
* **Conventional radiation therapy.** This type of radiation involves receiving small doses of radiation over 4 to 6 weeks. The risk of damage to the pituitary gland is higher than it is with proton beam radiation and stereotactic radiosurgery. You may not see the full effect of conventional radiation therapy for 10 or more years after treatment.

**OUTLOOK / PROGNOSIS**

The prognosis depends on the stage at which the diagnosis is made, as well as the response of hormone levels to treatment, either surgical or non-surgical.

### **POSSIBLE COMPLICATIONS**

### Without treatment, acromegaly can lead to other health conditions called complications. These complications can include the following.

### Conditions of the heart and blood vessels such as:

### High blood pressure.

### Higher risk of narrow arteries, which may lead to a heart attack or stroke.

### A disease of the heart muscle called cardiomyopathy.

### Cancer and conditions that can lead to cancer:

### Higher risk of some cancers.

### Growths called polyps on the lining of the colon. Without treatment, these growths can lead to colon cancer.

### Sexual and reproductive health conditions such as:

### Missed periods or irregular vaginal bleeding.

### Trouble getting or keeping an erection, also called erectile dysfunction.

### Less sexual desire.

### Other serious conditions including:

### The most common type of arthritis, called osteoarthritis.

### Type 2 diabetes.

### An irregular growth of the thyroid gland, called a goiter.

### A condition called sleep apnea in which breathing stops and starts many times during sleep.

### A condition called carpal tunnel syndrome that causes numbness, tingling, and weakness in the hand and arm.

### Spinal cord compression or fractures.

### Vision changes or vision loss.

### Early treatment of acromegaly can prevent these complications or keep them from becoming worse. Without treatment, acromegaly and its complications can lead to early death.

**Cardiovascular Complications**

* Hypertension is seen in about 40% of patients with acromegaly and is usually mild. Anti-hypertensive treatment is similar to non-acromegalic patients. Good control of blood pressure is very important irrespective of the modality used for acromegalic treatment.
* Cardiomyopathy is seen in most patients with acromegaly. An echocardiogram and electrocardiogram (ECG) should be done at baseline and repeated yearly. Treatment of acromegaly improves cardiomyopathy; however, this depends on the patient's age, disease duration, and hypertension. In addition to the echocardiogram and ECG, patients with gigantism will need Doppler of the peripheral arteries and veins.

**Obstructive Sleep Apnea (OSA)**

The prevalence of sleep apnea is 70% of all patients with acromegaly. Prognathism, enlarged tongue, and soft tissue accumulation in the upper airways predispose to OSA. Clinical assessment (Epworth score) and, if needed, polysomnography should be done at baseline and repeated every year. Surgical correction of prognathism may help, and referral to the maxillofacial surgeon should be considered.

**Arthropathy**

Around 75% of patients with acromegaly are affected by arthropathy. Both small and large joints are affected. Bony expansion and soft tissue swelling can lead to nerve entrapment. Early diagnosis and aggressive treatment of acromegaly are essential to prevent arthropathy, as these changes are irreversible.

**Colon Polyps**

Colon length is increased in acromegaly, and so are the mucosal folds. There is an increased prevalence of colonic polyps; however, the risk of colon cancer may or may not be increased. Patients should get a colonoscopy at baseline and every five years.

The incidence of both benign and malignant tumors in patients with acromegaly has increased lately, like kidney and ureteral cancers, but not the mortality from cancers.

**Hypopituitarism** can occur as a result of surgery or radiation. An annual assessment of pituitary hormones is recommended, and replacement hormones are needed.

**Vertebral fractures** have been reported more frequently in patients with acromegaly. In a recent study, there seems to be a correlation between a hypogonadal state and bone loss in this population.

### **WHEN TO SEE A DOCTOR / RED FLAG**

Get a healthcare checkup if you think you have symptoms of acromegaly. The condition usually develops slowly. Even family members may take a long time to notice the physical changes that happen. But it's important for a healthcare professional to find the condition as early as possible. Treatment can help prevent serious health conditions that can happen along with acromegaly.

**EPIDEMIOLOGY**

The prevalence of acromegaly is 78 cases per million population, and the incidence is ten new cases per year per million population.There is no gender preponderance with equal incidence in males and females. The average age of presentation is 44 years, with younger patients tending to have more aggressive disease. About 33% of the cases of acromegaly have co-existent hyperprolactinemia.

**DIFFERENTIAL DIAGNOSIS**

Acromegaloidism: This is a condition where the patients have acromegaloid facial features or tall stature; however, laboratory assessments of GH and IGF-1 are normal. Imaging of the pituitary in these cases is unremarkable.

Soto's syndrome: This is a congenital overgrowth syndrome characterized by tall stature, acromegaloid facies, intellectual disabilities, macrocephaly, and advanced bone age. Other clinical features include neonatal hypotonia, congenital heart defects, strabismus, scoliosis, and a predisposition to cancer. Soto syndrome is due to the haploinsufficiency of the NSD1 gene on chromosome 5. Laboratory assessment of IGF-1 and GH levels is normal. Genetic studies are needed to differentiate it from acromegaly.

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**GIGANTISM**

*ALTERNATIVE NAMES:* Gigantism is also known as “**gigantism”, “hypersoma”, and “somatomegaly”**.

Gigantism is very rare and should be suspected when the patient's height is 3 standard deviations above normal mean height or 2 standard deviations above the adjusted mean parental height. Since gigantism is associated with various syndromes like neurofibromatosis, Carney complex, and McCune Albright syndrome, evaluation for neurofibromas with cafe au lait spots, optic gliomas, and skin lentigines should be done.

With gigantism, excessive growth hormone production starts before the bone growth plates close. The growth plate is the area near the ends of a child’s long bones from which bone growth occurs.

Each long bone has a growth plate at each end that closes with solid bone replacing it once a child has finished growing.

Excess growth hormone causes long bones to grow significantly, resulting in children becoming taller and larger than children of the same age.

**Does gigantism turn into acromegaly?**

Gigantism does not turn into acromegaly. That’s because each disorder is defined by the age when it begins.

If a person overproduces growth hormones during childhood, they’ll have gigantism. As an adult, they will still have gigantism, because their condition developed when they were a child.

Gigantism will not turn into acromegaly, because acromegaly is a condition that specifically develops in adulthood.

**CAUSES**

**Other gigantism causes**

In some cases, gigantism might be related to other conditions, like:

* Carney complex
* McCune-Albright syndrome
* multiple endocrine neoplasia type 1 or 4
* neurofibromatosis
* GPR101 gene mutation

**RISK FACTORS**

Gigantism is a rare condition characterized by excessive growth due to high levels of growth hormone (GH) during childhood.

While the exact risk factors for gigantism are not fully understood, several factors have been identified that may contribute to its development. One of the primary causes of gigantism is a benign pituitary tumor, specifically a somatotroph adenoma, which leads to the overproduction of GH.

These tumors can be either microadenomas (less than 1 cm) or macroadenomas (greater than 1 cm).

Genetic factors also play a role in the development of gigantism. Mutations in certain genes, such as the AIP gene, have been associated with the formation of pituitary tumors that cause gigantism.

Additionally, gigantism can be linked to other rare genetic disorders, including Carney complex, McCune-Albright syndrome, and multiple endocrine neoplasia type 1 or 4. These conditions involve abnormalities in the endocrine system and can lead to the development of pituitary tumors.

Another potential risk factor is the presence of a genetic mutation known as GPR101, which has been overexpressed in some cases of sporadic or inherited gigantism that manifests during childhood or adolescence. This gene is located on the X chromosome and may contribute to the overproduction of GH.

In some cases, gigantism may be associated with other conditions such as neurofibromatosis, a group of genetic disorders that affect the skin and nervous system, leading to the formation of tumors, including GH-secreting tumors.7 Familial isolated pituitary adenomas (FIPA) is another inherited condition that can lead to the development of pituitary adenomas, which may secrete GH and cause gigantism.

It is important to note that while these factors may increase the risk of developing gigantism, the condition is still relatively rare, and the exact mechanisms underlying its development are not fully understood. Early diagnosis and treatment are crucial to managing the condition and preventing complications.

**SIGNS / SYMPTOMS**

*Symptoms of gigantism may include:*

* excessive growth in height, muscles, and organs
* enlarged hands and feet with thick fingers and toes
* thickening of facial features
* prominent forehead and jaw
* delayed puberty
* irregular menstrual periods
* difficulty with side vision or double vision
* increased sweating
* weakness

Sometimes, gigantism links with other conditions, such as:

* Carney complex
* McCune-Albright syndrome
* multiple endocrine neoplasia type 1 or type 4
* neurofibromatosis
* GPR101 gene mutation

A child with gigantism will be much larger and taller than other children of the same age. Other symptoms include:

* large hands and feet
* thick toes and fingers
* very soft hands
* enlarged jaw and forehead
* significant underbite
* enlarged tongue, nose, and lips
* deepening voice in boys
* oily skin
* excessive sweating
* skin tags
* joint pain
* headache
* difficulty sleeping
* irregular menstrual periods

**DIAGNOSIS METHODS**

Doctors diagnose gigantism and acromegaly using similar tests. They first ask about a person’s medical history and conduct a physical examination. They may then order the following tests:

IGF-1 test: A person must fast overnight for an IGF-1 test. A healthcare professional then takes a blood sample to check the levels of IGF-1 in the blood. Levels of IGF-1 typically parallel those of growth hormone. High levels of IGF-1 suggest a person may have gigantism or acromegaly.

Oral glucose tolerance test: A doctor orders this test to confirm a diagnosis. A person drinks a sugary liquid, and then a healthcare professional tests their blood every 30 minutes for 2 hours

to measure growth hormone levels. Typically, the sugar in the drink causes growth hormone levels to decrease. However, if the levels do not go down substantially, it confirms a diagnosis of gigantism or acromegaly.

MRI scan: Healthcare professionals use MRI scans to locate the tumor on the pituitary gland and determine its size. If they cannot find a tumor, they order other imaging tests to identify non pituitary tumors that may be elevating growth hormone levels.

For children with gigantism, a doctor may order additional tests to check the condition is not affecting other parts of their body. These tests may include:

* echocardiogram
* sleep study
* X-rays

**TREATMENT OPTIONS AND MANAGEMENT**

Treatment goals for gigantism and acromegaly include:

* controlling the size of the tumor
* regulating growth hormone and IGF-1 levels
* improving symptoms
* treating the effects of growth hormones on other body systems

A doctor will develop an individual plan of treatment that considers factors such as a person’s age, tumor size, symptom severity, and growth hormone and IGF-1 levels. A doctor may recommend

**Surgery**

Transsphenoidal surgery can remove pituitary tumors. Transsphenoidal surgery is a method that surgeons use to enter the nose to remove a pituitary tumor.

If the tumor causing elevated growth hormone levels is not on the pituitary gland, surgeons use other types of surgery.

Removing the tumor lowers growth hormone levels and improves symptoms.

**Medications**

A doctor may recommend one medication or combination of drugs to help normalize growth hormones. These may include the following:

Somatostatin analogs (SSAs): These drugs signal the pituitary gland to produce less growth hormone. They may also decrease the pituitary tumor size.

Dopamine-receptor agonists: These medications also curb growth hormone secretion but do not work as well as SSAs.

Growth hormone-receptor antagonists: This medication helps reduce IGF-1 levels and alleviates symptoms but does not reduce the tumor size or growth hormone levels.

**Radiation therapy**

Doctors may recommend radiation therapy if surgery is not possible or when surgery cannot remove all the tumor tissue. Radiation therapy uses high energy X-rays to kill tumor cells and slowly lowers growth hormone levels.

Radiation therapy reduces growth hormone and IGF-1 levels over an extended period, so it can take many years for it to have an effect on symptoms.

**POSSIBLE COMPLICATIONS**

**Complications of gigantism**

Gigantism may lead to:

* high blood pressure
* diabetes
* heart disease
* heart failure due to an enlarged heart
* thyroid cancer
* hypothyroidism
* colon polyps
* hypopituitarism, or the low secretion of pituitary hormones
* delayed puberty

**Complications of acromegaly**

The complications of acromegaly are similar to those of gigantism. The condition may increase your risk of:

* high blood pressure
* diabetes
* sleep apnea
* heart disease
* hypopituitarism
* arthritis
* uterine fibroids
* colon polyps
* vision issues
* compressed spinal cord

**Complications of gigantism**

Long-term complications that some people with gigantism might experience due to excessive height and the overall effects of excess growth hormone include:

* Mobility issues due to muscle weakness.
* Osteoarthritis.
* Peripheral neuropathy.
* Sleep apnea.
* Enlarged heart (cardiomegaly) and heart valve issues.
* Metabolic complications such as Type 2 diabetes.

Issues participating in everyday tasks such as buying clothes and traveling due to a very tall height can also diminish the quality of life of people with untreated gigantism.

**OUTLOOK / PROGNOSIS**

**Living with acromegaly and gigantism**

If you have gigantism or acromegaly, it’s important to visit your doctor regularly. They can help manage your growth hormone levels by providing the most appropriate treatments.

If you’ve had surgery, your growth hormone levels will be measured after 12 weeks. Surgery can successfully treat up 50 to 80 percent of cases, according to the UCLA Pituitary and Skull Base Tumor Program, depending on the size of your tumor. The success rate is higher for smaller tumors.

You may also need regular testing to manage complications. This includes tests like:

* sleep apnea test
* echocardiogram
* colonoscopy
* X-ray
* bone mineral density test

Regardless of your treatment plan, your doctor will continue to monitor your growth hormone levels and pituitary gland function.

**PROGNOSIS**

Because of the small number of people with gigantism, mortality and morbidity rates for this disease during childhood are unknown.

In acromegaly, a severe disease that is often diagnosed late, morbidity and mortality rates are high, particularly as a result of associated cardiovascular, cerebrovascular, and respiratory disorders and malignancies.

Because IGF-I is a general growth factor, somatic hypertrophy in acromegaly occurs across all organ systems. Associated complications include the following:

* Acromegalic heart
* Increased muscle and soft tissue mass
* Increased kidney size
* Articular overgrowth of synovial tissue and hypertrophic arthropathy
* Joint symptoms, back pain, and kyphosis - Common presenting features
* Thick skin
* Hyperhidrosis (often malodorous)
* Carpal tunnel syndrome and other entrapment syndromes
* Macroglossia - May result in sleep apnea
* Cerebral aneurysm and increased risk of cerebrovascular accident - Less common

The prevalence of gastritis, duodenitis, peptic ulcer, and intestinal metaplasia may be enhanced in acromegaly as compared with a normal, healthy population.

Early diagnosis of acromegaly, however, results in early transsphenoidal pituitary microsurgery, and currently, patients are more likely to be cured than in the past.

Reversal of excessive GH produces the following:

* Decreased soft tissue swelling
* Diminished sweating
* Restoration of normal glucose tolerance

No studies have established, however, that the treatment of acromegaly leads

**Prognosis (outlook) for gigantism**

The prognosis (outlook) for children and adolescents diagnosed with gigantism depends on several factors, including:

* How early or late they’re diagnosed.
* How effective treatment is at managing growth hormone levels.
* If they develop complications related to gigantism.

In general, people who are older at diagnosis tend to have more complications than people who are diagnosed at a younger age, probably due to longer exposure to excess growth hormone and insulin-like growth factor 1.

Because of this, it’s essential to talk to your child’s healthcare provider as soon as possible if you’re noticing abnormal or unexpected changes in their growth and/or physical features.

**What is the life expectancy of someone with gigantism?**

Early diagnosis and treatment of gigantism are crucial to prevent excessive height and associated complications and improve life expectancy.

If gigantism is left untreated, it’s associated with significant complications and an increased death rate of around twice the normal average.

**PREVENTION TIPS**

**Can gigantism be prevented?**

Unfortunately, there’s nothing you can do to prevent gigantism, though early diagnosis is crucial. Prompt treatment can help prevent or slow the changes that cause your child to grow very tall.

**WHEN TO SEE A DOCTOR / RED FLAG**

**Living With**

If your child has been diagnosed with gigantism, they’ll need to see their healthcare provider and/or endocrinologist regularly to monitor treatment and to make sure their hormone levels are in an optimum range.

**DIFFERENTIAL DIAGNOSIS**

**Diagnostic Considerations**

Differentials in gigantism include the following:

* Familial tall stature
* Exogenous obesity
* Cerebral gigantism (Sotos syndrome) - From *NSD1* gene mutation or other causes
* Weaver syndrome
* Estrogen receptor mutation

**Carney complex**

Carney complex is a familial multiple neoplasia and lentiginosis syndrome. Growth hormone (GH) ̶ producing pituitary tumors have been described in individuals with the disorder. Acromegaly may be diagnosed at an earlier age in Carney complex patients, of whom an estimated 10% manifest acromegaly.

Carney complex can exist in the following forms:

* Carney complex (NAME syndrome [nevi, atrial myxoma, myxoid neurofibroma, ephelides])
* Carney complex (LAMB syndrome [lentigines, atrial myxoma, mucocutaneous myxomas, blue nevi])

Manifestations and primary findings in Carney complex include cardio cutaneous syndrome, which is characterized by the following:

* Pigmented skin lesions and atrial myxomas
* Lentigines (mucocutaneous)
* Atrial myxomas (may be fatal)
* Mucocutaneous myxomas
* Blue nevi
* Congenital melanocytic nevi
* Schwannomas

Endocrine abnormalities of Carney complex include the following:

* Acromegaly
* Endocrine overactivity
* Cushing syndrome
* Sexual precocity in boys
* Thyroid hyperplasia
* Primary pigmented nodular adrenocortical disease
* Testicular tumors
* Uterine myxomas

**McCune-Albright syndrome**

McCune-Albright syndrome is manifested

**EPIDEMIOLOGY**

The prevalence of acromegaly is 78 cases per million population, and the incidence is ten new cases per year per million population. There is no gender preponderance with equal incidence in males and females. The average age of presentation is 44 years, with younger patients tending to have more aggressive disease. About 33% of the cases of acromegaly have co-existent hyperprolactinemia

*Acromegaloidism:* This is a condition where the patients have acromegaloid facial features or tall stature; however, laboratory assessments of GH and IGF-1 are normal. Imaging of the pituitary in these cases is unremarkable.

*Soto's syndrome:* This is a congenital overgrowth syndrome characterized by tall stature, acromegaloid facies, intellectual disabilities, macrocephaly, and advanced bone age. Other clinical features include neonatal hypotonia, congenital heart defects, strabismus, scoliosis, and a predisposition to cancer. Soto syndrome is due to the haploinsufficiency of the NSD1 gene on chromosome 5. Laboratory assessment of IGF-1 and GH levels is normal. Genetic studies are needed to differentiate it from acromegaly.

Gigantism is extremely rare; the incidence being estimated at 8 per million person-years.Although still rare, acromegaly is more common than gigantism, with a prevalence of 36-69 cases per million and an incidence of 3-4 cases per million per year.

Gigantism may begin at any age before epiphyseal fusion. X-linked Acro gigantism (X-LAG) caused by microduplications on chromosome Xq26.3, encompassing the gene *GPR101*, is a severe infant-onset gigantism syndrome with onset as early as 2-3 months of age (median, 12 months).Other genetic causes of gigantism include familial isolated pituitary adenoma (FIPA) caused by aryl hydrocarbon receptor interacting protein (*AIP*) gene mutations, multiple endocrine neoplasia type 1 (MEN1), McCune-Albright syndrome (MAS), and Carney complex with onset during prepubescent.

The mean age for onset of acromegaly is in the third decade of life; the delay from the insidious onset of symptoms to diagnosis is 5-15 years, with a mean delay of 8.7 years. The mean age at diagnosis for acromegaly is 40 years in males and 45 years in females.

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### **MULTIPLE ENDOCRINE NEOPLASIA**

*ALTERNATIVE NAMES:* Multiple endocrine neoplasia (MEN) is also referred to by several alternative names. These include "**multiple endocrine adenomatosis**" and "multiple endocrine adenomas,"

**DEFINITION / DESCRIPTION**

Multiple endocrine neoplasia (MEN) is a rare genetic condition characterized by multiple tumors and/or cancer that affect specific endocrine system glands and tissues.

**There are two main types of the condition:**

* Multiple endocrine neoplasia (MEN) type 1: This is a genetic condition in which multiple tumors affect different aspects of your endocrine system.
* Multiple endocrine neoplasia type 2 (MEN2): This is a genetic polyglandular (multiple glands) cancer syndrome. People with MEN2 will develop medullary thyroid cancer (carcinoma) and have an increased risk of developing other tumors that affect other glands in the endocrine system.

Other names for multiple endocrine neoplasia type 1 include:

* MEN-1.
* MEN-1 syndrome.
* Multiple endocrine adenomatosis.
* Wermer's syndrome.

Other names for multiple endocrine neoplasia type 2 include:

* MEN-2.
* MEN2 syndrome.
* Sipple syndrome.

### **Endocrine system**

Your endocrine system is a network of several glands and organs that create and secrete (release) hormones.

Hormones are chemicals that coordinate different functions in your body by carrying messages through your blood to your organs, skin, muscles and other tissues. These signals tell your body what to do and when to do it.

The following organs and glands make up your endocrine system and produce and release hormones:

* Hypothalamus: This gland is located on the undersurface of your brain and controls aspects of your endocrine system.
* Pituitary gland: This little gland, which is attached to your hypothalamus, makes hormones that control several other glands, such as your thyroid gland, adrenal glands, ovaries and testicles.
* Thyroid: Your thyroid is a butterfly-shaped gland in the front of your neck. It’s partially responsible for your metabolism (how your body uses energy from the food you eat).
* Parathyroid glands: These four tiny glands, which are usually located next to your thyroid gland, control the level of calcium and phosphorus in your body.
* Adrenal glands: You have two adrenal glands, one on top of each kidney. They control your metabolism, blood pressure, sexual development and response to stress.
* Pineal gland: This gland manages your sleep cycle by releasing melatonin.
* Pancreas: Your pancreas produces insulin, which is crucial to metabolism and controlling blood sugar levels. It’s also part of your digestive system.
* Ovaries: The ovaries release sex hormones called estrogen, progesterone and testosterone.
* Testes: The testes (testicles) make sperm and release the hormone testosterone.

### **What parts of the endocrine system are affected by multiple endocrine neoplasia type 1?**

People with MEN type 1 develop tumors in multiple glands of their endocrine system. The most common affected areas include:

* Parathyroid glands (most common).
* Gastroenteropancreatic tract (a tumor can form in your pancreas or in other parts of the gastrointestinal tract, including your stomach and duodenum).
* Pituitary gland.

Most tumors associated with MEN type 1 are benign (noncancerous), but some tumors can be cancerous (malignant) and can spread to other areas of your body (metastasize).

Endocrine glands that are affected by tumors usually release excessive amounts of hormones into your bloodstream, which can result in a variety of symptoms and health issues.

Since MEN type 1 was discovered, healthcare providers have identified more than 20 different endocrine and non-endocrine tumors in individuals with MEN type 1. Other less common types of tumors that can form due to MEN type 1 include:

* Neuroendocrine tumors of your thymus (a lymphoid organ in your chest) and bronchi (the air passages in your lungs).
* Adrenocortical tumors (form in the outer layer of your adrenal glands).
* Lipomas (fatty tumors located just below your skin).
* Visceral leiomyomas (smooth muscle tumors).
* Truncal and facial collagenomas (excess collagen in the trunk of your body and face).
* Facial angiofibromas (a group of lesions that form on your face).
* Breast cancer.
* Meningioma (a primary central nervous system tumor, meaning it begins in your brain or spinal cord).
* Ependymomas (a type of tumor that can form in your brain or spinal cord).

### **What parts of the endocrine system are affected by multiple endocrine neoplasia type 2?**

All people with MEN type 2 will develop medullary thyroid cancer (carcinoma), known as MTC. Medullary thyroid cancer represents approximately 1% to 2% of thyroid cancers in the United States. MTC is different from other types of thyroid cancers because it originates from a certain type of cell called C cells of the thyroid gland. These cells do not make thyroid hormone, like other cells in your thyroid do. C cells make a hormone called calcitonin, which lowers blood calcium levels.

MTC can spread (metastasize) to lymph nodes and other organs. The primary treatment for MTC is surgery in which a surgeon removes your thyroid (thyroidectomy).

People with MEN type 2 also develop one or both of the following two conditions:

* Pheochromocytoma: This is a rare tumor that forms in the middle of one or both of your adrenal glands (adrenal medulla). The tumor is made of a certain type of cell called chromaffin cells, which produce and release certain hormones. Most pheochromocytomas are benign (not cancer). Approximately 10% to 15% of pheochromocytomas may be malignant (cancer) and metastasize.
* Hyperparathyroidism (overactive parathyroid gland): Hyperparathyroidism happens when your parathyroid gland(s) release too much parathyroid hormone (PTH), which causes calcium levels in your blood to rise. This is usually caused by a benign parathyroid tumor (adenoma) or when two or more of your parathyroid glands become enlarged, a condition called hyperplasia.

### **Who does multiple endocrine neoplasia (MEN) affect?**

Multiple endocrine neoplasia (MEN) affects males and females equally.

The onset of MEN type 1 varies widely. It has been diagnosed in children as young as 8 and in adults as old as 80.

## **SIGNS / SYMPTOMS**

### **Symptoms of multiple endocrine neoplasia type 1**

The symptoms of MEN type 1 vary depending on which glands are affected by the overgrowth of tissue (hyperplasia) or a tumor. Although most MEN type 1 tumors are benign (noncancerous), tissue overgrowth or tumors can cause the affected glands to produce and release more hormones than your body needs. Higher-than-normal hormone levels are the main reason people who have MEN type 1 experience certain symptoms.

Since people with MEN type 1 can develop several different tumors, symptoms can vary widely from person to person — even within members of the same family and identical twins. In addition, people with MEN type 1 can develop tumors and symptoms at different ages, and symptoms can range from none (asymptomatic) or mild to severe and life-threatening.

It’s important to note that not everyone with MEN type 1 will have the same symptoms. Below are symptoms related to the following types of tumors and conditions associated with MEN type 1:

* Hyperparathyroidism.
* Gastrinomas.
* Insulinomas.
* Prolactinomas.

This is not a complete list of symptoms, since a person with MEN type 1 can develop any number of several different types of tumors, which each have different side effects and symptoms.

#### **Symptoms related to parathyroid gland hyperplasia and tumors**

The parathyroid glands are the most commonly affected endocrine glands in MEN type 1. Over 90% of people with MEN type 1 develop hyperparathyroidism (overactive parathyroid) by age 50.

Symptoms of mild hyperparathyroidism include:

* Joint pain.
* Muscle weakness.
* Fatigue.
* Depression.
* Trouble concentrating.
* Loss of appetite.

Symptoms of severe hyperparathyroidism include:

* Nausea and vomiting.
* Confusion and forgetfulness.
* Increased thirst and frequent urination.
* Constipation.
* Bone pain.

#### **Symptoms related to pancreas and duodenum tumors (gastrinomas)**

Approximately 40% of adults with MEN type 1 develop multiple gastrinomas, which are benign tumors that release a hormone called gastrin. People with MEN type 1 usually have gastrinomas located in the first portion of their duodenum (the first part of the small intestine that connects to the stomach), and sometimes in their pancreas.

Gastrinomas cause higher-than-normal levels of gastrin, which causes your stomach to release too much acid. Symptoms of gastrinomas include:

* Abdominal pain.
* Diarrhea.
* Acid reflux (esophageal reflux).
* Peptic ulcers.

The second most common tumor that affects the gastroenteropancreatic tract in people with MEN type 1 is insulinoma, a benign tumor that secretes insulin. It occurs in approximately 10% of cases. Insulinoma can cause low blood sugar (hypoglycemia), which can cause the following symptoms:

* Confusion.
* Shakiness.
* Sweating.
* Hunger.
* Anxiety.
* Heart palpitations.
* Temporary vision changes.

#### **Symptoms related to pituitary gland tumors**

Approximately 25% of people with MEN type 1 develop benign tumors in their pituitary gland. Your pituitary gland is often called the “master gland” because it creates and releases several important hormones, such as growth hormone, prolactin and thyroid-stimulating hormone.

Prolactinomas, benign tumors that secrete prolactin, are the most common pituitary gland tumors associated with MEN type 1. They are the third most common tumors associated with MEN type 1 after parathyroid tumors and gastrinomas.

Among women, symptoms of prolactinomas include:

* Changes in menstruation unrelated to menopause, such as irregular periods (menstruation) or no periods (amenorrhea).
* Infertility.
* Milky discharge from the nipples when not pregnant or breastfeeding is called galactorrhea.
* Loss of interest in sex.

Among men, common symptoms of a prolactinoma include:

* Loss of interest in sex associated with low levels of testosterone.
* Erectile dysfunction (ED).
* Infertility.

If the prolactinoma is large, it may also cause the following symptoms:

* Headaches.
* Nausea and/or vomiting.
* Vision changes, such as double vision or decreased peripheral vision.

### **Symptoms of multiple endocrine neoplasia type 2**

The symptoms of MEN type 2 vary depending on which glands are affected and can vary widely from person to person — even within members of the same family. Symptoms are usually caused by medullary thyroid cancer (MTC) and higher-than-normal hormone levels caused by certain tumors.

It’s important to note that not everyone with MEN type 2 will have the same symptoms. Below are symptoms related to the following types of tumors and conditions associated with MEN type 2:

* Medullary thyroid cancer (MTC).
* Pheochromocytomas.
* Hyperparathyroidism.

This is not a complete list of symptoms, since a person with MEN type 2 can develop other tumors.

#### **Symptoms related to medullary thyroid cancer (MTC)**

All people with MEN type 2 develop medullary thyroid cancer. Symptoms of medullary thyroid cancer include:

* A lump in the front of your neck.
* Pain in the front of your neck.
* Changes to your voice, such as hoarseness.
* Coughing.
* Trouble swallowing.
* Shortness of breath.

#### **Symptoms related to pheochromocytomas**

Approximately 50% of people with MEN type 2 will develop a pheochromocytoma, a usually benign tumor in your adrenal gland(s).

Symptoms of pheochromocytoma happen when the tumor releases too much adrenaline or noradrenaline into your blood. However, some pheochromocytoma tumors don’t make these hormones and don’t cause symptoms (are asymptomatic). Common symptoms of pheochromocytoma, which often occur as spells include:

* High blood pressure (hypertension).
* Headache.
* Excessive sweating for no known reason.
* A pounding, fast or irregular heartbeat.
* Feeling shaky.

#### **Symptoms related to hyperparathyroidism**

Symptoms of hyperparathyroidism include:

* Joint pain.
* Muscle weakness.
* Fatigue.
* Depression.
* Trouble concentrating.
* Loss of appetite.
* Nausea and vomiting.
* Increased thirst and frequent urination.
* Constipation.
* Bone pain.

**CAUSES**

**Causes multiple endocrine neoplasia (MEN)**

Both types of multiple endocrine neoplasia are caused by gene mutations (changes), and both types can either be inherited (passed from biological parent to child) or occur randomly at the embryo level (when you were developing in the uterus). If a biological parent has MEN, their child has a 50% chance of having the condition.

MEN type 1 is caused by mutations of the *MEN1* gene. The *MEN1* gene is a tumor suppressor gene, meaning it helps prevent tumors from forming by controlling cell division and instructing cells when to die (a normal process). When tumor suppressor genes, such as *MEN1* malfunction, certain cells may continue to grow and reproduce, causing tumors to form.

MEN type 2 is caused by mutations of the *RET* gene, which is a gene that plays a role in the development of cancer. When working as it should, the *RET* gene helps control cell division and regulation of cell death. Mutations of the *RET* gene lead to uncontrolled growth of cells, causing tumors to form in certain organs and glands.

## **DIAGNOSIS METHODS AND TESTS**

### **Multiple endocrine neoplasia type 1 diagnosed**

A person is diagnosed with MEN type 1 if they have at least two of the three endocrine tumors associated with the condition (parathyroid tumor, pituitary tumor and/or a tumor in the gastroenteropancreatic tract) or if they have one of the associated tumors and a family history of MEN type 1.

#### **What tests are used to diagnose MEN type 1?**

Before a healthcare provider can diagnose MEN type 1, they need to diagnose one or more different types of tumors in the individual. A variety of blood tests can detect elevated levels of certain hormones, which can be a sign of certain tumors. For example, higher-than-normal levels of parathyroid hormone (PTH) in addition to hypercalcemia (excess calcium in your blood) can indicate the presence of a parathyroid tumor.

Healthcare providers then use imaging tests, such as CT (computed tomography) scans or MRI (magnetic resonance imaging) scans, to help find and diagnose tumors.

Providers can also confirm a MEN type 1 diagnosis through genetic testing of the *MEN1* gene.

### **Multiple endocrine neoplasia type 2 diagnosed**

A person is diagnosed with MEN type 2 if they have medullary thyroid cancer (MTC) and pheochromocytoma and/or parathyroid enlargement (hyperplasia) or tumor (adenoma).

#### **What tests are used to diagnose MEN type 2?**

Before a healthcare provider can diagnose MEN type 2, they need to diagnose medullary thyroid cancer (MTC) and other types of tumors in the individual.

A variety of blood tests can detect elevated levels of certain hormones, which can be a sign of MTC and other tumors. For example:

* Higher-than-normal levels of calcitonin can indicate MTC.
* Higher-than-normal levels of parathyroid hormone (PTH) can indicate a parathyroid tumor (adenoma) or hyperplasia.
* Higher-than-normal levels of catecholamines (a group of hormones produced by your adrenal glands) may indicate pheochromocytoma.

Healthcare providers then use imaging tests, such as CT (computed tomography) scans or MRI (magnetic resonance imaging) scans, to help find and diagnose tumors associated with MEN type 2.

Providers can also confirm a MEN type 2 diagnosis through genetic testing of the *RET* gene.

## **MANAGEMENT AND TREATMENT OPTIONS**

### **How is multiple endocrine neoplasia (MEN) treated?**

The treatment of multiple endocrine neoplasia (MEN) depends entirely on what endocrine glands and organs are affected and usually requires a team of healthcare providers, including:

* Endocrinologists.
* Surgeons.
* Oncologists (cancer specialists).
* Pediatricians, if applicable.

Treatment may include:

* Medications to treat symptoms and to counteract the effects of excess hormones.
* Surgery to remove tumors or entire affected glands, such as the thyroid.
* Replacement hormones if an endocrine gland is surgically removed.
* Cancer treatment, such as chemotherapy and radiation therapy, cancer has metastasized (spread to other areas of your body).

Each case of MEN is unique and each requires specific treatment. Don’t be afraid to ask your healthcare provider about treatment options that’ll work best for you.

### **Is there a cure for multiple endocrine neoplasia (MEN)?**

There is currently no cure for multiple endocrine neoplasia, but it is manageable. Healthcare providers treat the changes in each gland as they happen with surgery or with medications.

## **PREVENTION TIPS**

### **Can I prevent multiple endocrine neoplasia (MEN)?**

Unfortunately, you cannot prevent developing multiple endocrine neoplasia since it’s a genetic mutation. The gene mutations that cause MEN are either inherited from a biological parent or happen randomly for no known reason at the embryo level (when you were developing in the uterus).

If one of your first-degree relatives (biological parents and siblings) has been diagnosed with MEN, talk to your healthcare provider about genetic testing that can screen for MEN. If you do have MEN, genetic testing could help detect the tumors in their early phases.

**POSSIBLE COMPLICATIONS**

Multiple endocrine neoplasia (MEN) can lead to various complications depending on the type and the specific glands affected. For MEN type 1, complications may include **hyperparathyroidism, which disrupts the normal balance of calcium in the blood, leading to kidney stones, thinning of bones, nausea, vomiting, high blood pressure, weakness, and fatigue**. Additionally, tumors in other endocrine glands, such as the adrenal glands, can cause issues, and carcinoid tumors may develop in the stomach, thymus, and lungs.

For MEN type 2, complications often involve **medullary thyroid carcinoma**, which can be life-threatening if not treated. Pheochromocytomas, which are adrenal gland tumors, can cause dangerously high blood pressure. Other complications may include the development of neuromas in the mucous membranes, spinal abnormalities, and skeletal issues.

Complications can also vary based on the type, size, and location of the tumor, and they can differ from person to person, even among family members who have the disorder.

## **OUTLOOK / PROGNOSIS**

### **Prognosis (outlook) for multiple endocrine neoplasia (MEN)?**

The prognosis (outlook) for MEN depends on several factors, including:

* How early MEN is diagnosed.
* Which endocrine glands are affected?
* If the tumors are benign or cancerous.
* The type of treatment used.
* If a cancerous tumor has spread to other parts of your body (metastasized).

If you have been diagnosed with MEN, your healthcare provider will be able to give you a better idea of what you can expect for your treatment and prognosis.

## **WHEN TO SEE A DOCTOR / RED FLAG**

If you have been diagnosed with multiple endocrine neoplasia, you will need to see your healthcare provider regularly to monitor your condition and to see if treatment is working.

If one of your first-degree relatives (biological parents or siblings) has been diagnosed with MEN, talk to your healthcare provider about genetic testing that can screen for MEN.

**EPIDEMIOLOGY**

The prevalence of all MEN2 worldwide is 1 in 35,000, while in the United States, it is 1 in 30,000 to 50,000. The epidemiology of MEN2B is unknown. The prevalence of MEN2B is estimated to be between 1 in 600,000 to 1 in 4 million.

Multiple endocrine neoplasia type 1 affects about 1 in 30,000 people; multiple endocrine neoplasia type 2 affects an estimated 1 in 35,000 people. Among the subtypes of type 2, type 2A is the most common form, followed by FMTC. Type 2B is relatively uncommon, accounting for about 5 percent of all cases of type 2. The prevalence of multiple endocrine neoplasia type 4 is unknown, although the condition appears to be rare.

**DIFFERENTIAL DIAGNOSIS**

* Familial hyperparathyroidism
* Familial hypocalciuric hypercalcemia
* Multiple endocrine neoplasia type 1
* Sturge-Weber syndrome
* Tuberous sclerosis
* Von Hippel-Lindau syndrome
* Von Recklinghausen disease

*Familial Hyperparathyroidism:* An inherited disorder characterized by overactivity of one or more parathyroid glands, leading to excessive secretion of parathyroid hormone, hypercalcemia, and symptoms such as kidney stones, bone loss, fatigue, and gastrointestinal issues

*Familial Hypocalciuric Hypercalcemia:* A benign inherited condition causing lifelong mild hypercalcemia with low urinary calcium excretion, typically asymptomatic and caused by mutations affecting calcium-sensing receptors, distinct from hyperparathyroidism.

*Multiple Endocrine Neoplasia Type 1 (MEN1):* A hereditary syndrome characterized by tumors in multiple endocrine glands, primarily the parathyroids, pancreatic islets, and pituitary gland, leading to hormone overproduction and associated clinical syndromes.

*Sturge-Weber Syndrome:* A rare congenital neurocutaneous disorder characterized by facial port-wine stain (nevus flammeus), leptomeningeal angiomas causing seizures and neurological deficits, and ocular abnormalities such as glaucoma.

*Tuberous Sclerosis:* A genetic disorder causing benign tumors (hamartomas) in multiple organs including the brain, skin, kidneys, and heart, often associated with seizures, developmental delay, and characteristic skin lesions.

*Von Hippel-Lindau Syndrome:* An inherited disorder characterized by the development of multiple tumors and cysts in various organs, including hemangioblastomas of the brain and retina, renal cell carcinoma, and pheochromocytomas.

Von Recklinghausen Disease (Neurofibromatosis Type 1): A genetic disorder marked by multiple café-au-lait spots, neurofibromas, Lisch nodules in the iris, and increased risk of tumors of the nervous system.

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**ADDISON DISEASE**

ALTERNATIVE NAMES: Addison disease is also known as “primary adrenocortical insufficiency”, “chronic adrenocortical insufficiency”, “primary hypocortisolism”, “primary hypocorticism”, “primary adrenal insufficiency”, “chronic adrenal insufficiency”, “primary hypocorticalism”, “primary hypoadrenocorticism”, and “primary hypoadrenalism”.

**DEFINITION / DESCRIPTION**

Addison's disease is a rare condition that happens when the body doesn't make enough of some hormones. Another name for Addison's disease is primary adrenal insufficiency. With Addison's disease, the adrenal glands make too little of the hormone cortisol. Often, they also make too little of another hormone called aldosterone.

Damage to the adrenal glands causes Addison's disease. Symptoms can start slowly. Early symptoms may include extreme tiredness, salt cravings and weight loss.

Addison's disease can affect anyone. Without treatment, it can be life-threatening. Treatment involves taking lab-made hormones to replace those that are missing.

Addison’s disease is a chronic condition in which your adrenal glands don’t produce enough of the hormone’s cortisol and aldosterone.

Your adrenal glands, also known as suprarenal glands, are small, triangle-shaped glands that are located on top of each of your two kidneys. They’re a part of your endocrine system.

Cortisol is a hormone that helps your body respond to stress, including the stress of illness, injury or surgery. It also helps maintain your blood pressure, heart function, immune system and blood glucose (sugar) levels. Cortisol is essential for life.

Aldosterone is a hormone that affects the balance of sodium (salt) and potassium in your blood. This in turn controls the amount of fluid your kidneys remove as urine (pee), which affects blood volume and blood pressure.

Addison’s disease is also called primary adrenal insufficiency. A related disorder, secondary adrenal insufficiency, happens when your pituitary gland doesn’t release enough adrenocorticotropic hormone (ACTH), which activates your adrenal glands to produce cortisol.

**Addison's disease and Cushing's syndrome**

Addison’s disease happens when your body doesn’t have enough cortisol (and aldosterone), whereas Cushing’s syndrome happens when your body has too much cortisol (hypercortisolism).

Addison’s disease can affect people of all age groups, but it’s most common in people 30 to 50 years old.

People who have autoimmune polyendocrine syndrome, a rare, inherited condition in which your immune system mistakenly attacks many of your tissues and organs, are much more likely to have Addison’s disease. Your mucous membranes, adrenal glands and parathyroid glands are commonly affected by this syndrome, though it can affect other types of tissues and organs.

People who have the following autoimmune disease are also at higher risk of developing the autoimmune (most common) form of Addison's disease:

* Type I diabetes.
* Pernicious anemia.
* Graves' disease.
* Chronic thyroiditis.
* Dermatitis herpetiformis.
* Vitiligo.
* Myasthenia gravis.

Addison’s disease is rare. In the United States, it affects 1 in 100,000 people.

**CAUSES**

**What causes Addison’s disease?**

The most common cause of Addison’s disease is an autoimmune response, which occurs when your immune system attacks healthy tissues for an unknown reason. With Addison’s disease, your immune system attacks the outer portion of your adrenal glands (the adrenal cortex), where they make cortisol and aldosterone. Symptoms don’t usually develop until 90% of the adrenal cortex has been damaged, which can take several months to years.

Approximately 75% of cases of Addison’s disease are due to an autoimmune attack. Autoimmune Addison’s disease may happen by itself or as part of a rare, inherited syndrome, specifically autoimmune polyendocrine syndromes I (APS type-1) and II (Schmidt syndrome).

In the past, tuberculosis was a major cause of Addison’s disease. It remains a prominent cause of the condition in developing countries.

Other less common causes of Addison’s disease include:

* Repeated infections, including HIV/AIDS-related infections and fungal infections.
* When cancer cells from another part of your body invade your adrenal glands.
* Bleeding (hemorrhaging) into your adrenal glands.
* Surgical removal of your adrenal glands.
* Amyloidosis (a condition in which amyloid proteins build up in vital organs, causing damage).
* Fungal infection

A lack of the hormone ACTH leads to secondary adrenal insufficiency. That can happen if you must take certain steroids for a long time due to a health problem. For example, people with asthma or rheumatoid arthritis may need to take prednisone. Other causes include:

* Pituitary gland tumors
* Loss of blood flow to the pituitary
* Pituitary gland is removed or you have radiation treatment of the pituitary gland
* Parts of the hypothalamus are removed

Addison's disease also is known as **primary adrenal insufficiency**. A related condition is called secondary adrenal insufficiency. These conditions have different causes.

Addison's disease, also called ***primary adrenal insufficiency***

This condition happens when the outer layer of the adrenal glands becomes damaged and can't make enough hormones. Most often, the damage is due to a disease in which the immune system attacks healthy tissues and organs by mistake. This is called an autoimmune disease. People with Addison's disease are more likely than are other people to have another autoimmune disease as well.

*Other causes of Addison's disease can include:*

* A serious infection called tuberculosis that mainly affects the lungs and also can destroy the adrenal glands.
* Other infections of the adrenal glands.
* Spread of cancer to the adrenal glands.
* Bleeding into the adrenal glands.
* A group of genetic conditions present at birth that affect the adrenal glands. This is called congenital adrenal hyperplasia.
* Medicines that block the body's ability to make glucocorticoid, such as ketoconazole (Ketozole), mitotane (Lysodren) and etomidate (Amidate). Or medicines that block the action of glucocorticoid in the body, such as mifepristone (Mifeprex, Korlym).
* Treatment for cancer with medicines called checkpoint inhibitors.

***Secondary adrenal insufficiency***

This type of adrenal insufficiency has many symptoms in common with Addison's disease. But it's more common than Addison's disease. Secondary adrenal insufficiency happens when the pituitary gland near the brain doesn't prompt the adrenal glands to make cortisol.

Typically, the pituitary gland makes a hormone called adrenocorticotropic hormone (ACTH). ACTH in turn causes the outer layer of the adrenal glands to make its hormones, including glucocorticoids and androgens. But with secondary adrenal insufficiency, too little ACTH causes the adrenal glands to make too little of these hormones.

Most symptoms of secondary adrenal insufficiency are like those of Addison's disease. But people with secondary adrenal insufficiency don't develop darkened skin. And they're less likely to have serious dehydration or low blood pressure. They're more likely to have low blood sugar.

Factors that can cause the pituitary gland to make too little ACTH include:

* Pituitary tumors that aren't cancer.
* Surgery or radiation therapy of the pituitary gland.
* Brain injury.

A short-term cause of secondary adrenal insufficiency can happen in people who suddenly stop taking medicines called corticosteroids. These medicines treat conditions such as asthma and arthritis. But stopping the medicine suddenly rather than tapering off can lead to secondary adrenal insufficiency.

**SIGNS / SYMPTOMS**

Addison's disease symptoms usually happen slowly, often over months. The disease may happen so slowly that people who have it might ignore the symptoms at first. Physical stress such as an illness or injury can make symptoms get worse fast.

You may have mild symptoms when you are under physical stress. Each person’s symptoms will vary. Symptoms may include:

* Weakness
* Fatigue
* Dizziness
* Dark skin (primary adrenal insufficiency only)
* Bluish-black color around the nipples, mouth, rectum, scrotum, or vagina (primary adrenal insufficiency only)
* Weight loss
* Fluid loss (dehydration)
* Lack of appetite
* Muscle aches
* Upset stomach (nausea)
* Vomiting
* Diarrhea
* Low blood pressure
* Low sugar levels
* In women, irregular or no menstrual periods

If not treated, adrenal insufficiency may lead to:

* Severe belly (abdominal) pain
* Extreme weakness
* Low blood pressure
* Kidney failure
* Shock

These symptoms may look like other health problems. Always see your healthcare provider for a diagnosis.

Early symptoms of Addison's disease can affect you in various ways. Some early symptoms can cause discomfort or loss of energy, including:

* Extreme tiredness, also called fatigue.
* Dizziness or fainting when standing after sitting or lying down. This is due to a type of low blood pressure called postural hypotension.
* Sweating due to low blood sugar, also called hypoglycemia.
* Upset stomach, diarrhea or vomiting.
* Pain in the stomach area, also called the abdomen.
* Muscle cramps, weakness, widespread pain or joint pain.

Other early symptoms can cause changes in how you look, such as:

* Body hair loss.
* Areas of darkened skin, especially on scars and moles. These changes may be harder to see on Black or brown skin.
* Weight loss due to less hunger.

Early Addison's disease symptoms also can affect emotions, mental health and desires. These symptoms include:

* Depression.
* Irritable mood.
* Lower sex drive in women.
* Salt craving.

**Emergency symptoms due to adrenal crisis**

Sometimes the symptoms of Addison's disease become worse fast. If this happens, it's an emergency known as an adrenal crisis. You also may hear it called an Addisonian crisis or acute adrenal failure. Call your local emergency number if you have Addison's disease with any the following symptoms:

* Serious weakness.
* Sudden, terrible pain in the lower back, stomach area or legs.
* Severe upset stomach, vomiting or diarrhea.
* Extreme loss of body water, also called dehydration.
* Fever.
* Confusion or much less awareness of the surroundings.
* Loss of consciousness.
* Low blood pressure and fainting.

Without fast treatment, an adrenal crisis can lead to death.

Damage to the adrenal glands causes Addison's disease. These glands sit just above the kidneys. The adrenal glands are part of the system of glands and organs that makes hormones, also called the endocrine system. The adrenal glands make hormones that affect almost every organ and tissue in the body.

The adrenal glands are made up of two layers. The inner layer, called the medulla, makes hormones such as adrenaline. Those hormones control the body's response to stress. The outer layer, called the cortex, makes a group of hormones called corticosteroids. Corticosteroids include:

* *Glucocorticoids.* These hormones include cortisol, and they affect the body's ability to turn food into energy. They also play a role in the immune system and help the body respond to stress.
* *Mineralocorticoids.* These hormones include aldosterone. They balance the body's sodium and potassium to keep blood pressure in a healthy range.
* *Androgens.* In all people, the adrenal glands make small amounts of these sex hormones. They cause male sexual development. And they affect muscle mass, body hair, sex drive, and a sense of well-being in all people.

**Symptoms of Addison’s disease**

With Addison’s disease, the damage to your adrenal glands usually happens slowly over time, so symptoms occur gradually. Symptoms vary from person to person.

Symptoms of Addison’s disease include:

* Steadily worsening fatigue (most common symptom).
* Patches of dark skin (hyperpigmentation), especially around scars and skin creases and on your gums.
* Abdominal pain.
* Nausea and vomiting.
* Diarrhea.
* Loss of appetite and unintentional weight loss.
* Muscle pain, muscle spasms and/or joint pain.
* Dehydration.
* Low blood pressure, which can cause lightheadedness or dizziness upon standing.
* Changes in mood and behavior, such as irritability, depression and poor concentration.
* A craving for salty food.
* Low blood sugar (hypoglycemia).

Women with Addison’s disease may also have abnormal menstruation (periods), lose body hair and have a decreased sexual drive.

In some cases — such as after an injury or severe illness or time of intense stress — symptoms can come on quickly and cause a life-threatening event called an addisonian crisis or acute adrenal failure.

An addisonian crisis is a medical emergency. If it’s not treated, it can lead to shock and death. Symptoms of an addisonian crisis include:

* Extreme weakness.
* Sudden, severe pain in your lower back, belly or legs.
* Feeling restless, confused, afraid or other mental changes.
* Severe vomiting and diarrhea, potentially leading to dehydration.
* Low blood pressure.
* Loss of consciousness.

Get to the nearest hospital as soon as possible if you’re having these symptoms.

**RISK FACTORS**

Most people who get Addison's disease don't have any factors that put them at higher risk of developing the condition. But the following may raise the risk of adrenal insufficiency:

* A history of having a disease or surgery that affects the pituitary gland or the adrenal glands.
* Certain genetic changes that affect the pituitary or adrenal glands. These include gene changes that cause the inherited disease congenital adrenal hyperplasia.
* Other autoimmune endocrine conditions, such as hypothyroidism or type 1 diabetes.
* Traumatic brain injury

**POSSIBLE COMPLICATIONS**

Addison's disease can lead to other health conditions called complications. These include adrenal crisis, also called Addisonian crisis. If you have Addison's disease and haven't started treatment, you may develop this life-threatening complication.

Stress on the body such as injury, infection or illness can trigger adrenal crisis. Typically, the adrenal glands make two or three times the usual amount of cortisol in response to physical stress. But with adrenal insufficiency, the adrenal glands don't make enough cortisol to meet this need. And that can lead to adrenal crises.

Adrenal crisis results in low blood pressure, low blood levels of sugar and high blood levels of potassium. This complication needs treatment right away.

*What are the complications of adrenal insufficiency?*

You may have sudden severe symptoms. This is called acute adrenal insufficiency, or Addisonian crisis. This can occur when your body is stressed. That can happen for many reasons, such as an illness, fever, surgery, or dehydration. You may also have a crisis if you stop taking your steroids or lower the amount of your steroids suddenly. The symptoms of an Addisonian crisis include the symptoms of adrenal insufficiency or Addison’s disease. But if an Addisonian crisis is not treated, it can lead to:

* Shock
* Seizures
* Coma

**Living with adrenal insufficiency**

Take your medicine exactly as prescribed. You should also carry a medical alert card or tag at all times. This can make sure you get proper treatment if there is an emergency. When traveling, always carry an emergency kit with a shot of cortisol.

**PREVENTION TIPS**

Addison's disease can't be prevented. But you can take steps to lower the risk of adrenal crisis:

* Talk with your healthcare professional if you always feel tired or weak or are losing weight without trying. Ask if you should get tested for adrenal insufficiency.
* If you have Addison's disease, ask your healthcare professional what to do when you're sick. You'll likely need to learn how to adjust the amount of medicine that you take. You also may need to take the medicine as a shot.
* If you become very sick, go to an emergency room. This is crucial if you're vomiting and you can't take your medicine.

Some people with Addison's disease worry about serious side effects from corticosteroid medicines. But people with Addison's disease aren't likely to get the side effects of high-dose corticosteroids used to treat many other diseases. That's because the dose prescribed is much lower and only replaces the amount that's missing.

If you take corticosteroids, follow up with your healthcare professional regularly to make sure your dose is not too high.

**DIAGNOSIS METHODS AND TESTS**

**How is Addison’s disease diagnosed?**

Since symptoms of Addison’s disease usually develop slowly over time and are usually vague and common to many different conditions, it often leads to a delay in the proper diagnosis.

Healthcare providers often “accidentally” discover Addison’s disease when a routine blood test, such as a basic metabolic panel, shows low levels of sodium or high levels of potassium.

Dark patches on your skin are another common symptom that signals healthcare providers to test for Addison’s disease.

If your provider suspects you may have Addison’s disease based on your symptoms, they’ll order more tests to officially diagnose the condition.

**What test will be done to diagnose Addison’s disease?**

Diagnosis involves the steps that your healthcare team takes to find out if you have Addison's disease. Your healthcare professional talks with you about your medical history and your symptoms. You might have some of the following tests that check for Addison's disease or for secondary adrenal insufficiency:

* Blood test. This test can measure blood levels of sodium, potassium, cortisol and adrenocorticotropic hormone (ACTH). A blood test also can measure proteins called antibodies related to Addison's disease caused by an autoimmune disease.
* ACTH stimulation test. ACTH tells the adrenal glands to make cortisol. This test measures the level of cortisol in the blood before and after a shot of lab-made ACTH.
* Insulin-induced hypoglycemia test. This test is done to find out if the pituitary gland is causing secondary adrenal insufficiency. The test involves checking blood sugar and cortisol levels after a shot of insulin.
* Imaging tests. A CT scan of the stomach area checks the size of the adrenal glands and looks for other issues. An MRI of the pituitary gland can spot damage that may cause secondary adrenal insufficiency.

**TREATMENT OPTIONS**

**How is Addison’s disease diagnosed?**

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Addison's disease treatment involves taking medicines to correct the levels of steroid hormones that the body isn't making enough of. Some treatments include corticosteroid medicines taken by mouth such as:

* Hydrocortisone (Cortef), prednisone (Rayos, Prednisone Intensol) or methylprednisolone (Medrol) to replace cortisol. You take these medicines on a schedule. This helps mimic the changes in cortisol levels the body typically goes through over 24 hours.
* Fludrocortisone acetate to replace aldosterone.

You'll likely need plenty of sodium in your diet. This is especially true during heavy exercise and when the weather is hot. It's also true if you have digestive troubles such as diarrhea.

Your healthcare professional may tell you to raise the dose of your medicine for a short time if your body is stressed. Such stress can come from having surgery, an infection or a minor illness. If you're vomiting and can't keep down your medicine, you may need shots of corticosteroids.

Follow these treatment recommendations as well:

* Always carry a medical alert card and bracelet. A steroid emergency card and medical alert bracelet or tag let emergency care professionals know what kind of care you need. Also have a written action plan.
* Keep extra medicine handy. It can be dangerous to miss even one day of medicine. So, keep a small supply at work and take extra medicine with you when you travel.
* Carry a corticosteroid medicine injection kit. The kit contains a needle, a syringe and an injectable form of corticosteroids to use in case of emergency.
* Stay in contact with your healthcare professional. Your healthcare team can monitor your hormone levels. If you have trouble with your medicine, your healthcare professional may need to change the doses or when you take them.
* Have yearly checkups. At least once a year, see your healthcare professional or a doctor who treats hormone conditions. Your healthcare professional may recommend yearly screening tests for autoimmune diseases.

Addisonian crisis is a medical emergency. Treatment typically includes medicines or solutions given through a vein. These include:

* Corticosteroids.
* Saline solution.
* Sugar.

**OUTLOOK / PROGNOSIS**

The prognosis for Addison’s disease is generally good. Although people who have Addison’s disease will need to take medicine for the rest of their lives, they can live normal, healthy lives.

The dosages of these medications, however, need to be closely monitored to prevent over- or under-treatment. Over-treatment with glucocorticoids (hydrocortisone) may result in obesity, Type 2 diabetes and osteoporosis. Over-treatment with fludrocortisone can cause high blood pressure (hypertension).

Up to 50% of people with Addison’s disease develop other autoimmune conditions.

**How do I take care of myself if I have Addison’s disease?**

If you have Addison’s disease, you should carry an identification card and wear a medical alert bracelet or necklace at all times to let medical professionals know you have the condition in emergencies.

Talk to your healthcare provider about what you should do when you become sick or are experiencing intense stress since you’ll likely need to increase your medication dosages.

Ask your provider about keeping a shot of cortisol for emergencies, and be sure someone with you knows how to give you the shot.

**WHEN TO SEE A DOCTOR**

See a healthcare professional if you have common symptoms of Addison's disease, such as:

* Long-lasting fatigue.
* Muscle weakness.
* Loss of appetite.
* Darkened areas of skin.
* Weight loss that doesn't happen on purpose.
* Serious upset stomach, vomiting or stomach pain.
* Lightheadedness or fainting with standing.
* Salt cravings.

Get emergency care right away if you have any symptoms of an adrenal crisis.

**When should I see my healthcare provider about Addison’s disease?**

If you have Addison’s disease, you’ll need to see your healthcare provider (likely an endocrinologist) regularly to make sure your medication dosages are working for you.

Call your provider if you have major stress — such as an injury, illness or the death of a loved one — because you might need an adjustment to your medicine.

Seek medical attention right away if you have any of the symptoms of an addisonian crisis, such as sudden, extreme weakness and intense pain.

***When should I call my healthcare provider?***

Any condition that stresses your body can affect how much medicine you need. Call your healthcare provider if:

* You have any kind of illness, especially a fever, vomiting, or diarrhea
* You become pregnant
* You need surgery

Get medical help right away if you have sudden severe symptoms (Addisonian crisis).

**EPIDEMIOLOGY**

**Frequency**

*United States*

The prevalence of Addison disease is 40-60 cases per 1 million population.

*International*

The occurrence of Addison disease is rare. The reported prevalence in countries where data are available is 39 cases per 1 million population in Great Britain and 60 cases per 1 million population in Denmark. A study by Olafsson and Sigurjonsdottir found the prevalence of primary adrenal insufficiency in Iceland to be 22.1 per 100,000 population.A study by Hong et al found the prevalence of primary adrenal insufficiency in Korea to be 4.17 per 1 million population.

*Mortality/Morbidity*

Morbidity and mortality associated with Addison disease usually are due to failure or delay in making the diagnosis or a failure to institute adequate glucocorticoid and mineralocorticoid replacement.

If not treated promptly, acute Addisonian crisis may result in death. This may be provoked either de novo, such as by adrenal hemorrhage, or in the setting of an acute event superimposed on chronic or inadequately treated adrenocortical insufficiency.

With slow-onset chronic Addison disease, significant low-level, nonspecific, but debilitating, symptomatology may occur.

Even after diagnosis and treatment, the risk of death is more than 2-fold higher in patients with Addison disease. Cardiovascular, malignant, and infectious diseases are responsible for the higher mortality rate.

**DIFFERENTIAL DIAGNOSIS**

* Adrenal Crisis
* Adrenal Hemorrhage
* C-17 Hydroxylase Deficiency
* Eosinophilia
* Histoplasmosis
* Hyperkalemia
* Sarcoidosis
* Tuberculosis (TB)

*REFERENCES:*

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**CONGENITAL ADRENAL HYPERPLASIA (CAH)**

**DEFINITION / DESCRIPTION**

Congenital adrenal hyperplasia (CAH) is the medical name for a group of genetic conditions that affect the adrenal glands. The adrenal glands are a pair of walnut-sized organs above the kidneys. They make important hormones, including:

* Cortisol. This controls the body's response to illness or stress.
* Mineralocorticoids such as aldosterone. These control sodium and potassium levels.
* Androgens such as testosterone. These sex hormones are needed for growth and development in both males and females.

In people with CAH, a gene change results in a lack of one of the enzyme proteins needed to make these hormones.

The two major types of congenital adrenal hyperplasia are:

* Classic CAH. This type is rarer and more serious. It's usually found by tests at birth or in early infancy.
* Nonclassic CAH. This type is milder and more common. It may not be found until childhood or early adulthood.

There is no cure for congenital adrenal hyperplasia. But with proper treatment, most people who have CAH can lead full lives.

**CAUSES**

The most common cause of CAH is the lack of the enzyme protein known as 21-hydroxylase. Sometimes, CAH is called 21-hydroxylase deficiency. The body needs this enzyme to make proper amounts of hormones. Very rarely, a lack of other much rarer enzymes also can cause CAH.

CAH is a genetic condition. That means it's passed from parents to children. It's present at birth. Children with the condition have two parents who both carry the genetic change that causes CAH. Or they have two parents who have CAH themselves. This is known as the autosomal recessive inheritance pattern.

People can carry the CAH gene and not have symptoms of the condition. This is called being a silent carrier. If a silent carrier becomes pregnant, that person can pass the gene to a child. If tests show that you're a silent carrier of the CAH gene and you have a partner of the opposite sex, talk with your healthcare professional. It's likely that your partner will need to get tested for the CAH gene before pregnancy so that you can better understand the risks.

**RISK FACTORS**

Factors that raise the risk of having CAH include:

* Parents who both have CAH.
* Parents who are both carriers of the changed gene that causes CAH.
* Being of Ashkenazi Jewish, Latino, Mediterranean, Yugoslav or Yup'ik descent.

**SIGNS AND SYMPTOMS**

Symptoms of CAH vary. The symptoms depend on which gene is affected. They also depend on how greatly the adrenal glands lack one of the enzymes needed to make hormones. With CAH, the hormones that the body needs to work properly are thrown out of balance. That may lead to too little cortisol, too little aldosterone, too many androgens or a mix of these issues.

***Classic CAH***

Symptoms of classic CAH can include:

* Not enough cortisol. With classic CAH, the body doesn't make enough of the hormone cortisol. This can cause problems keeping blood pressure, blood sugar and energy at healthy levels. It also can cause problems during physical stress such as illness.
* Adrenal crisis. People with classic CAH can be seriously affected by a lack of cortisol, aldosterone or both. This is known as an adrenal crisis. It can be life-threatening.
* External genitals that don't look typical. In female infants, some parts of the genitals on the outside of the body may look different than usual. For instance, the clitoris may be enlarged and resemble a penis. The labia may be partly closed and look like a scrotum. The tube through which urine leaves the body and the vagina may be one opening instead of two separate openings. The uterus, fallopian tubes and ovaries often develop in a typical manner.  
  Male infants with CAH often have genitals that look typical but sometimes are enlarged.
* Too much androgen. An excess of the male sex hormone androgen can lead to short height and early puberty for children. Pubic hair and other signs of puberty may appear at a very early age. Serious acne also may occur.  
  Extra androgen hormones in females may lead to facial hair, more body hair than usual and a deeper voice.
* Altered growth. Children may grow fast. And their bones could be more developed than is typical for their age. Final height may be shorter than average.
* Fertility issues. These can include irregular menstrual periods or not having periods at all. Some women with classic CAH may have trouble becoming pregnant. Fertility issues sometimes can occur in men.

***Non classic CAH***

Often, there are no symptoms of non-classic CAH when a baby is born. Some people with non-classic CAH never have symptoms. The condition is not found on routine infant blood screening tests. If symptoms occur, they usually appear in late childhood or early adulthood.

Females who have non classic CAH may have genitals that look typical at birth. Later in life, they may have:

* Irregular menstrual periods, or none.
* Trouble getting pregnant.
* Features such as facial hair, more body hair than usual and a deeper voice.

Sometimes, non-classic CAH may be confused with a hormonal condition that happens during the reproductive years called polycystic ovary syndrome.

Non classic CAH symptoms in children of either birth sex also can include:

* Symptoms of early puberty, such as growth of pubic hair sooner than usual.
* Serious acne.
* Rapid growth during childhood with bones that are more developed than is typical.
* Shorter than expected final height.

**DIAGNOSIS METHODS AND TESTS**

Healthcare professionals may find congenital adrenal hyperplasia (CAH):

* Before a baby is born.
* Shortly after birth.
* During childhood or later in life.

*Prenatal testing*

Tests used to find CAH before birth in fetuses who are at risk for the condition include:

* Amniocentesis. This procedure involves using a needle to remove a sample of the fluid from the womb. This is called amniotic fluid. Then a lab checks the cells in the fluid.
* Chorionic villus sampling. This test involves removing cells from the organ that provides a fetus with oxygen and nutrients. This organ is called the placenta. A lab checks the sample of placenta cells.

Tests to confirm whether a baby has CAH are done after the baby is born.

*Newborns and infants*

In the United States and many other countries, newborns are routinely tested for 21-hydroxylase deficiency. The screening test is recommended during the first few days of life. This test can find the classic form of CAH. It doesn't identify the non-classical form.

In female infants whose outer genitals look very different than is typical, other tests can be done. The tests check structures inside cells that contain genes, called chromosomes, to identify genetic sex. Also, an ultrasound of the pelvis can find the presence of reproductive organs such as the uterus and ovaries.

*Children and adults*

Tests to find CAH in children and adults include:

* Physical exam. A physical exam usually includes a check of blood pressure and heart rate. Symptoms also are reviewed. If a healthcare professional suspects CAH, blood and urine tests are done.
* Blood and urine tests. These tests look for hormones made by the adrenal glands at levels outside the standard ranges. The tests also check the levels of minerals called electrolytes, such as sodium. These minerals balance the amount of water in the body.
* X-ray. This test might be done to find out if a child's bones are more developed than is typical for the child's age.
* Genetic testing. Genetic testing may be needed to confirm if CAH is the cause of symptoms.

**TREATMENT OPTIONS**

For children, a healthcare professional likely will make a referral to a specialist in childhood hormonal issues. This specialist is called a pediatric endocrinologist. For adults, a referral often is made to an adult endocrinologist. The treatment team also may include other healthcare professionals such as:

* A doctor who finds and treats urinary tract conditions, called a urologist.
* A mental health professional called a psychologist.
* A doctor who finds and treats conditions of the female reproductive system, called a reproductive endocrinologist.
* An expert in genes called a geneticist.

Treatment may include medicines, surgery and mental health support.

**Medications**

The goal of treating CAH with medicines is to lower the number of androgens the body makes and replace hormones the body lacks. People with classic CAH can manage the condition by taking hormone replacement medicines throughout their lives.

People with non classic CAH may not need treatment. Or they may need only small doses of medicines called corticosteroids.

Medicines for CAH are taken every day. During illnesses or times of serious stress, other medicines or higher doses may be needed.

Medicines may include:

* Corticosteroids to replace cortisol.
* Mineralocorticoids replace aldosterone to help keep salt in the body and get rid of extra potassium.
* Salt supplements to help keep salt in the body.

Regular checkups are needed to make sure the medicines work well. These appointments usually include:

* A physical exam. This exam includes checking a child's growth and development. That involves closely tracking changes in height, weight, blood pressure and bone growth. People with CAH need health checkups on a regular basis throughout their lives.
* Checking for side effects. Medicine side effects may include the loss of bone mass and growth that is slower than usual. The risk of those side effects rises if steroid-type replacement medicine doses are high and used long term.
* Blood tests to check hormone levels. It's important to have regular blood tests to make sure that hormone levels are balanced. Children who haven't yet reached puberty need enough cortisone to suppress androgens to grow to a typical height. For females with CAH, androgens are suppressed to minimize symptoms such as a deeper voice or extra body hair.  
  But too much cortisone can cause a condition called Cushing syndrome. Cushing syndrome can lead to symptoms such as a fatty lump between the shoulders and a rounded face. It also can cause high blood pressure, bone loss and type 2 diabetes.

With classic CAH, it's a good idea to wear a medical identification bracelet or necklace that says you have congenital adrenal hyperplasia. It can help a healthcare team provide the right treatment in case of an emergency.

**Reconstructive surgery**

Some female infants with classic CAH have outer genitals that look very different than is typical. The healthcare team may suggest reconstructive surgery as part of treatment. Surgery can help the genitals function better and look more typical.

Surgery may involve making the clitoris smaller and rebuilding the vaginal opening. The surgery typically is done between about 3 and 6 months of age. Females who have reconstructive genital surgery as infants may need more cosmetic surgery later in life.

Some parents choose to wait to decide on genital surgery for their child. They might delay surgery until the child is old enough to understand the risks and make choices about surgery.

A decision about the timing of surgery should be made after a thorough discussion between the family and the healthcare team.

**Mental health support**

Mental health support is key for children and adults with CAH. It can help with the social and emotional parts of the condition. Look for a mental health professional who has experience helping people with CAH.

**Research**

Treatment of CAH during pregnancy with lab-made corticosteroids that cross the placenta to the fetus are controversial and considered experimental. More research is needed to determine the long-term safety and the effect of this treatment on a baby's brain.

**POSSIBLE COMPLICATIONS**

People who have classic CAH are at risk of a life-threatening condition called adrenal crisis. This emergency needs to be treated right away. Adrenal crisis can happen within the first few days after birth. It also can be triggered at any age by an infectious illness or physical stress such as surgery.

With adrenal crisis, very low levels of cortisol in the blood can cause:

* Diarrhea.
* Vomiting.
* Dehydration.
* Confusion.
* Low blood sugar levels.
* Seizures.
* Shock.
* Coma.

Aldosterone also may be low. This leads to dehydration, low sodium and high potassium levels.The non classic form of CAH doesn't cause adrenal crisis.

People who have either classic or non-classic CAH may have irregular menstrual cycles and fertility issues.

**PREVENTION TIPS**

There is no known way to prevent CAH. If you're thinking of starting a family and you're at risk of having a child with CAH, talk with your healthcare professional. You may be told to see a genetic counselor.

**OUTLOOK / PROGNOSIS**

Congenital adrenal hyperplasia (CAH) is a group of genetic disorders that affect the adrenal glands, leading to imbalances in hormone production. The prognosis of CAH varies depending on the type and severity of the condition.

For patients with CAH, especially those with 21-hydroxylase deficiency, the prognosis can be significantly impacted. A study found that patients with CAH had an increased mortality rate compared to controls, with a hazard ratio of 2.3 in males and 3.5 in females.

The causes of death in patients with CAH were adrenal crisis (42%), cardiovascular issues (32%), cancer (16%), and suicide (10%).

The prognosis for individuals with CAH can be improved with appropriate management. Classical CAH, which is more severe, can result in adrenal crisis and death if not detected and treated. However, with early diagnosis and treatment, patients can lead normal lives.

Non-classical CAH is milder and may or may not present symptoms, and patients can also lead normal lives with adequate care and treatment.

Treatment for CAH typically involves hormone replacement therapy, including synthetic cortisol and, in some cases, aldosterone. This helps to manage the hormone imbalances and prevent complications. Patients with CAH should be regularly followed up from childhood to adulthood by multidisciplinary teams to ensure optimal treatment and monitoring.

In summary, the prognosis for CAH depends on the type and severity of the condition, with early diagnosis and treatment playing a crucial role in improving outcomes. While there are risks associated with CAH, particularly in the classical form, with proper management, patients can lead healthy and normal lives.

**WHEN TO SEE A DOCTOR / RED FLAG**

Most often, classic CAH is found at birth through routine newborn screening tests. Or it's found when a baby's outer genitals do not look typical. CAH also may be detected when infants show symptoms of serious illness due to low levels of cortisol, aldosterone or both.

In children who have non classic CAH, symptoms of early puberty may appear. If you have concerns about your child's growth or development, schedule a checkup with your child's healthcare professional.

In older people who have irregular periods, trouble getting pregnant or both, screening for CAH may be appropriate.

If you are planning pregnancy or are pregnant and may be at risk of CAH, ask your healthcare professional about genetic counseling. A genetic counselor can tell you if your genes might affect you or any children you decide to have.

**DIFFERENTIAL DIAGNOSIS**

* 3-Beta-Hydroxysteroid Dehydrogenase Deficiency
* 5-Alpha-Reductase Deficiency
* Adrenal Hypoplasia
* Androgen Insensitivity Syndrome
* Bilateral adrenal hemorrhage
* Congenital Adrenal Hyperplasia
* Defects in testosterone synthesis
* Denys-Drash Syndrome
* Differences (Disorders) of Sex Development (DSDs)
* Fluid, Electrolyte, and Nutrition Management of the Newborn
* Gender Identity
* Hyperkalemia in Emergency Medicine
* Hyponatremia in Emergency Medicine
* Mixed gonadal dysgenesis
* Nutritional Considerations in Failure to Thrive
* Obstructive uropathy
* Pediatric Adrenal Insufficiency (Addison Disease)
* Pediatric Cryptorchidism Surgery
* Infantile Hypertrophic Pyloric Stenosis
* Pediatric Hypokalemia
* Polycystic Ovarian Syndrome
* Pseudohypoparathyroidism
* Kidney Disease and Pregnancy
* Sinonasal Manifestations of Cystic Fibrosis
* Small-Bowel Obstruction Imaging and Diagnosis
* WAGR Syndrome

**RECENT GUIDELINES OR UPDATES**

Congenital adrenal hyperplasia is one of the most prevalent genetic endocrine diseases. A new guideline from the endocrine society offers expert opinion and evidence-based recommendations on the diagnosis and management of this challenging condition.

Steroid 21-hydroxylase deficiency accounts for about 95% of cases of congenital adrenal hyperplasia (CAH). Newborns are currently being screened for the classical forms of this disease throughout the United States and in 12 other countries. As such, it seems important to develop the best practice guidelines for treating not only infants and children, but affected adults as well. This report gives a brief overview of the most recent expert opinion and clinical practice guidelines for CAH as formulated by The Endocrine Society Task Force.

Recent guidelines for congenital adrenal hyperplasia (CAH) emphasize the importance of early diagnosis, appropriate treatment, and long-term management. The Endocrine Society's 2018 clinical practice guideline for CAH due to steroid 21-hydroxylase deficiency highlights the need for newborn screening programs to incorporate screening for CAH, ensuring early detection and timely intervention.

The guideline also recommends that infants with positive screens be referred to pediatric endocrinologists for evaluation and management.

For adolescents with CAH, the guideline suggests starting the transition to adult care several years before leaving pediatric endocrinology to ensure continuous care throughout their lives.

The guidelines also emphasize shared decision-making among patients, their families, and healthcare professionals regarding medical, surgical, and psychological management.

In terms of treatment, the guidelines recommend maintenance therapy with hydrocortisone for growing individuals with classic CAH, while cautioning against the chronic use of more potent or long-acting glucocorticoids due to potential adverse side effects.

Additionally, the guidelines stress the importance of monitoring for signs of glucocorticoid excess and inadequate androgen normalization to optimize treatment outcomes.

The guidelines also address the use of fludrocortisone and sodium chloride supplements in newborns and early infancy, as well as the importance of educating patients and their guardians on adrenal crisis prevention and emergency glucocorticoid use.

Furthermore, the guidelines highlight the need for ongoing research into new therapies and ways to improve the quality of life for individuals with CAH.

**EPIDEMIOLOGY**

*Race*

Congenital adrenal hyperplasia occurs among people of all races. Congenital adrenal hyperplasia secondary to *CYP21A1* mutations and deletions is particularly common among the Yupik Eskimos.

*Sex*

Because all forms of congenital adrenal hyperplasia are autosomal recessive disorders, both sexes are affected with equal frequency. However, because accumulated precursor hormones or associated impaired testosterone synthesis impacts sexual differentiation, the phenotypic consequences of mutations or deletions of a particular gene differ between the sexes.

*Age*

Classic congenital adrenal hyperplasia is generally recognized at birth or in early childhood because of ambiguous genitalia salt wasting, or early virilization. Nonclassic adrenal hyperplasia is generally recognized at or after puberty because of oligomenorrhea or virilizing signs in females.

*United States*

The most common form of congenital adrenal hyperplasia is due to mutations or deletions of *CYP21A,* resulting in 21-hydroxylase deficiency. This deficiency accounts for more than 90% of adrenal hyperplasia cases. Mutations or partial deletions that affect *CYP21A* are common, with estimated frequencies as high as 1 in 3 individuals in selected populations (e.g., Ashkenazi Jews) to 1 in 7 individuals in New York City. The estimated prevalence is 1 case per 60 individuals in the general population.

Classic adrenal hyperplasia has an overall prevalence of 1 case per 16,000 population; however, in selected populations (e.g., the Yupik of Alaska), the prevalence is as high as 1 case in 400 population. Congenital adrenal hyperplasia caused by 11-beta-hydroxylase deficiency accounts for 5-8% of all congenital adrenal hyperplasia cases.

*International*

Congenital adrenal hyperplasia caused by 21-hydroxylase deficiency is found in all populations. 11-beta-hydroxylase deficiency is more common in persons of Moroccan or Iranian-Jewish descent.

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**ADRENAL TUMORS**

*ALTERNATIVE NAMES:* Adrenal tumors are also referred to by several alternative names depending on their type and characteristics. For example, “adrenal incidentalomas” are tumors found *unexpectedly* during imaging tests for unrelated conditions.

**ADRENAL TUMOR(BENIGN)**

*ALTERNATIVE NAMES:* An alternative name for a benign adrenal tumor is an adrenal adenoma.

Adenomas are a type of polyp, and another name for an adenoma is an adenomatous polyp.

**DEFINITION / DESCRIPTION**

Benign adrenal tumors are masses that aren't cancer. They form in the adrenal glands. The adrenal glands are part of the endocrine system. These glands make hormones that send messages to nearly every organ and tissue in the body.

There are two adrenal glands, one above each kidney. Each gland has two types of tissue: the cortex and the medulla. Benign adrenal tumors that grow in the cortex are called adrenal adenomas. Those that grow in the medulla are called pheochromocytomas (fee-o-kroe-moe-sy-TOE-muhs).

Most benign adrenal tumors cause no symptoms and don't need treatment. But sometimes these tumors make high levels of some hormones that can cause problems. Hormones from the cortex control metabolism, blood pressure and certain body features, such as hair growth. Hormones from the medulla control the body's response to stress.

***Adrenal adenoma***

Adrenal adenomas are benign (noncancerous) tumors in your adrenal glands. Your adrenal glands are small, triangular glands located atop both of your kidneys. They secrete hormones that help your body respond to stress. Your adrenal glands also release hormones that regulate your blood sugar, blood pressure and immune system, among other essential functions.

Your adrenal glands have two parts, your adrenal cortex and your adrenal medulla. Your adrenal cortex secretes hormones, including cortisol and aldosterone. The adrenal medulla produces dopamine, epinephrine and norepinephrine. Adrenal adenomas form in your adrenal cortex.

Adrenal adenomas don’t usually cause symptoms or require treatment. Some may lead to the overproduction of one or more normal adrenal hormones.

**What types of adrenal adenomas are there?**

Adrenal adenomas are either functioning or non functioning.

* Functioning (active) adrenal adenomas secrete excess adrenal gland hormones and may cause symptoms that require treatment.
* Nonfunctioning (inactive) adrenal adenomas don’t produce excess adrenal hormones. Most adrenal adenomas are nonfunctioning. They don’t cause symptoms or require treatment.

Neither type of tumor is likely to become cancer, but a nonfunctional adrenal adenoma can become functional.

**Can adrenal adenoma become cancerous?**

Adrenal adenomas can become cancerous, but this is rare. The most common cancerous tumor that forms in your adrenal glands is adrenocortical carcinoma. Like adrenal adenomas, functioning adrenocortical carcinoma tumors secrete excess hormones. They may cause symptoms similar to functioning adrenal adenomas.

Only about 1 in 1 million people develop adrenocortical carcinoma. The majority of adrenal tumors are benign (noncancerous).

**Who do adrenal adenomas affect?**

Anyone can get an adrenal adenoma, although the likelihood increases with age. Approximately 3% to 9% of people have adrenal adenomas. They’re the most common type of adrenal gland tumor.

Functioning adrenal adenomas can cause your adrenal glands to secrete excess amounts of one or more types of hormone. As a result, you may experience symptoms of certain adrenal disorders, including:

* Cushing’s syndrome (hypercortisolism): This condition occurs when your adenoma secretes too much cortisol. Tumors in your pituitary gland most often cause Cushing’s syndrome, but adrenal tumors can also lead to Cushing's syndrome. Symptoms include high blood pressure, weight gain (especially around your middle) and sexual dysfunction. It can increase your likelihood of diabetes.
* Primary aldosteronism (Conn’s syndrome): This condition occurs when your adenoma secretes too much aldosterone. Signs and symptoms include low potassium levels, high blood pressure, headache, fatigue and muscle weakness.
* In rare instances, an adrenal adenoma may secrete excess sex hormones. Too many androgens (for example, testosterone) in females may lead to irregular periods, increased body hair (hirsutism), a deeper voice, etc. Too much estrogen in males may cause decreased sex drive and erectile dysfunction.

**CAUSES**

The cause of benign adrenal tumors often is not known.

*What causes adrenal adenomas?*

Researchers don’t know what causes an adrenal adenoma or other benign adrenal gland tumors to form. Still, certain genetic conditions may increase your risk, including:

* Multiple endocrine neoplasia, type 1 (MEN1).
* Familial adenomatous polyposis (FAP).
* Carney complex.
* Li-Fraumeni syndrome[.](https://my.clevelandclinic.org/health/diseases/22073-li-fraumeni-syndrome#:~:text=A%252520note%252520from%252520Cleveland%252520Clinic,syndrome's%252520impact%252520on%252520your%252520lives.)
* Multiple endocrine neoplasia type 2 (MEN2).
* Neurofibromatosis Type 1.

Obesity and tobacco use may also increase your chances of having adrenal adenoma.

**RISK FACTORS**

The following might raise the risk of developing a benign adrenal tumor:

* A family history of benign adrenal tumors.
* Certain syndromes passed through families, called genetic syndromes, that make benign adrenal tumors more likely.
* A history of having an adrenal tumor surgically removed.

It is important to note that the risk factors for adrenal adenomas often depend on your genes, and you can develop an adrenal adenoma even if no one in your family has a history of adrenal gland tumors.

If you have been diagnosed with a nonfunctioning adrenal adenoma, your healthcare provider may recommend periodic CT scans or hormone testing to monitor the tumor.

**SIGNS / SYMPTOMS**

Symptoms depend on whether the tumor makes hormones, what hormone it makes and how much it makes. But many benign adrenal gland tumors don't cause symptoms because they don't make hormones.

The most common type of benign adrenal tumor, called adenoma, comes from the adrenal cortex. This type of tumor might cause symptoms such as:

* Weight gain.
* Easy bruising.
* High blood pressure, also called hypertension.
* Diabetes.
* Depressed mood.
* Tiredness.
* Muscle weakness or cramping.

A type of benign adrenal tumor from the medulla is called pheochromocytoma. It might cause the following symptoms:

* High blood pressure, also called hypertension.
* Fast heartbeat.
* Sweating.
* Tremors.
* Headache.

**Symptoms of adrenal adenoma**

Functioning adrenal adenomas may produce symptoms related to having excess hormones in your body, especially excess cortisol (Cushing’s syndrome) or excess aldosterone (Primary aldosteronism).

Signs and symptoms may include:

* Headache.
* Muscle weakness or occasional numbness.
* Fatigue and achiness (like backaches).
* High blood pressure (hypertension).
* High blood sugar levels or diabetes.
* Low potassium levels.
* Stretch marks on your abdomen.
* Weight gain, especially in your upper body.
* Mood changes (feeling anxious, panicked or depressed).

Females may experience irregular menstrual cycles and increased masculine characteristics (virilization). Males may experience sexual dysfunction.

**DIAGNOSIS METHODS AND TESTS**

Benign adrenal tumors often are found by chance on imaging that's done for another reason. A healthcare professional then looks at how likely the tumor is to be cancer and whether it's making too much hormone.

***How are adrenal tumors diagnosed?***

Many people don’t realize they have an adrenal adenoma until their healthcare provider discovers an adrenal gland tumor during an imaging procedure for an unrelated medical condition. These tumors are sometimes called “incidentalomas” because they’re found incidentally, or by chance.

Your healthcare provider will first determine whether a tumor is cancerous (for example, adrenocortical carcinoma) or benign (for example, adrenal adenoma). If it’s an adrenal adenoma, they’ll perform tests to determine whether it’s secreting excess hormones.

**What tests are used to diagnose adrenal adenoma?**

Your healthcare provider will perform a physical exam and ask you about your symptoms and medical history. They may perform any of the following tests to learn more about your tumor:

* Blood or urine test: A blood or urine test allows your healthcare provider to check for elevated hormone levels that may be a sign of a functioning tumor. You may need to collect your urine for 24 hours so they can test it for elevated cortisol.
* Imaging: A CT scan is the most commonly used imaging procedure used to diagnose adrenal adenoma. In some instances, your healthcare provider may order an MRI instead. Imaging helps them determine whether a tumor is malignant or benign. For example, larger tumors (more than 4 centimeters) are more likely to be cancerous than smaller tumors.
* Biopsy: Your healthcare provider may perform a fine-needle aspiration if other tests don’t provide enough information about whether a tumor is cancer or an adrenal adenoma. During this procedure, they’ll use a thin hollow needle to remove tissue from the tumor. A lab specialist, called a pathologist, examines the tissue underneath a microscope to check for signs of cancer.

Other tests may include adrenal vein sampling or a metaiodobenzylguanidine (MIBG) scan.

**TESTS**

Along with a physical exam, a healthcare professional runs blood and urine tests to see if the tumor is making too much hormone. The tests also show which hormone the tumor is making.

Imaging tests can give more details about the tumor. They can show whether the tumor is at high risk of being a cancer, which is rare.

Imaging tests might include:

* **CT scan.** This type of scan takes a series of X-ray images from different angles and makes them into cross-sectional images.
* **MRI.** This type of scan uses radio waves and a magnetic field to make detailed images.
* **M-iodobenzylguanidine (MIBG) imaging.** This type of scan uses a radioactive compound that's injected into the body. Some adrenal gland tumors take up the compound. The image can show tiny amounts of the compound that are picked up by a tumor.
* **Positron emission tomography (PET).** This type of scan also can detect radioactive compounds taken up by a tumor.
* **Ga-DOTATATE PET scanning.** This newer imaging test isn't widely offered. Ga-DOTATATE PET scanning is done along with either a CT scan or an MRI. This type of test is good at finding tumors of the endocrine system, such as benign adrenal tumors.

**TREATMENT OPTIONS**

Benign adrenal tumors often don't need treatment. Treatment depends on how likely the tumor is to become cancer. Treatment also might depend on whether the tumor is making hormones, the type of hormone it makes and how much it's making.

Treatment for small benign adrenal tumors that aren't making hormones might involve watching the tumor. There might be repeat imaging tests 3 to 6 months after diagnosis, and then every one or two years. Watching also might involve testing hormones every year for five years.

If the tumor is getting bigger or causing symptoms, the symptoms might be treated with medicines. Medicines also might be used to treat symptoms such as high blood pressure before surgery.

Surgery to remove the adrenal gland, called adrenalectomy, might be used to treat a benign adrenal tumor. The surgery may be done laparoscopically if the tumor is small and not likely to be cancer.

**Management and Treatment**

*What is the treatment for adrenal adenoma?*

Your treatment depends on whether the tumor is non functioning or functioning (secreting excess hormones). If a non functioning tumor is small, your healthcare provider may recommend periodic CT scans to ensure it doesn’t increase in size or become functional. If the tumor grows rapidly or gets bigger (usually nearing 5 centimeters), your healthcare provider may recommend surgery. Large tumors and rapid growth increase the likelihood of a tumor becoming cancerous.

Treatments for functioning tumors almost always involve surgery. Treatments include:

* Adrenalectomy (adrenal gland removal): Your healthcare provider may remove your adrenal gland via laparoscopy if the tumor is benign and small. During a laparoscopy, they make tiny cuts into your abdomen and perform the surgery through the incisions. For a larger tumor or one that may be cancerous, your healthcare provider may perform surgery by making a larger incision in your back. In some instances, your remaining adrenal gland may make enough hormones to keep you healthy. In others, you may need hormone therapy to supplement the lack of hormones.
* Medications: If you’re not a candidate for surgery, your healthcare provider may prescribe medicines that prevent the adenoma from making excessive amounts of hormones. You may also receive medications for several weeks to help stabilize your hormone levels following an adrenalectomy.

**PREVENTION TIPS**

There are no specific prevention tips for adrenal tumors as there are no modifiable risk factors for this condition.

It is hard to catch tumors in the adrenal gland early because there are no routine screening tests used to find them.

Adrenal tumors are often found incidentally on imaging tests for an unrelated health concern. Therefore, maintaining a healthy lifestyle and regular medical check-ups may help in early detection, but there is nothing you can do to prevent this condition.

***Can adrenal gland tumors be prevented?***

Adrenal gland tumors, including adrenal adenoma, can’t be prevented. The risk factors for adrenal adenoma often depend on your genes. Still, you can develop an adrenal adenoma even if no one in your family has a history of adrenal gland tumors.

**Living With**

*How do I take care of myself?*

Follow your healthcare provider’s guidance about how often you should be tested if you’ve been diagnosed with a nonfunctioning adrenal adenoma. Depending on your tumor, your healthcare provider may recommend periodic CT scans or hormone testing.

***What questions should I ask my doctor?***

* What type of adrenal gland tumor do I have?
* Is it benign or cancerous?
* What is the likelihood that my tumor could become cancerous?
* Is it a functioning or non functioning tumor?
* Do I need treatment?
* What treatments would you recommend?
* Will I need hormone therapy as part of my treatment/recovery?

**POSSIBLE COMPLICATIONS**

Benign adrenal tumors can lead to various complications, primarily due to their potential to cause hormonal imbalances. These tumors may secrete excessive amounts of hormones, leading to conditions such as Cushing's syndrome, Conn's syndrome, or pheochromocytoma, each with its own set of symptoms and health risks.

For instance, Cushing's syndrome can result in weight gain, fatigue, reduced fertility, and personality changes, while Conn's syndrome can cause high blood pressure and low potassium levels, potentially leading to severe health issues if left untreated.

Additionally, benign adrenal tumors can sometimes grow large enough to press on nearby organs, causing symptoms such as abdominal pain or affecting the production of adrenal hormones.

Although most benign adrenal tumors are noncancerous and do not spread, they can still pose significant health challenges if they lead to hormonal imbalances or physical compression of surrounding structures. Regular monitoring and appropriate treatment are essential to manage these potential complications.

**OUTLOOK / PROGNOSIS**

Benign adrenal tumors are noncancerous and typically do not spread to other parts of the body.

Most benign adrenal tumors do not cause symptoms and often go undetected unless discovered incidentally during imaging for other conditions. These tumors are sometimes referred to as "incidentalomas".

For non-functional adrenal adenomas, treatment is usually not necessary, and a watch-and-wait approach is often recommended. Regular imaging studies and hormone level tests may be conducted to monitor the tumor's growth and ensure it does not become functional.

If a non-functional tumor grows large enough to cause pain or other symptoms, surgical removal may be considered.

Functional adrenal adenomas, which produce excess hormones, can lead to conditions such as Cushing's syndrome or hyperaldosteronism. These tumors are typically treated with surgery, and symptoms often resolve after the tumor is removed.

In some cases, medication may be used to manage symptoms, especially if surgery is not an option.

Overall, the prognosis for benign adrenal tumors is generally good, as they do not typically progress to cancer and can often be managed effectively with monitoring or treatment.

However, it is important to note that some benign tumors may have the potential to become malignant, although this is rare.

Regular follow-up with a healthcare provider is essential to ensure proper management and early detection of any changes.

***What is the long-term prognosis after treatment for adrenal adenoma?***

Treatment outcomes associated with adrenalectomy are excellent. Removing the affected adrenal gland often relieves the symptoms related to functional adrenal adenomas.

**WHEN TO SEE A DOCTOR / RED FLAG**

If you have been diagnosed with a benign adrenal tumor, it is important to consult a doctor for proper evaluation and management. Most non-functional adrenal tumors do not require treatment and may be monitored over time, but there are certain situations where medical attention is necessary. For example, if the tumor begins to secrete hormones, leading to symptoms such as high blood pressure, weight gain, or abnormal hair growth, it is important to seek medical care.

Additionally, if the tumor grows in size or causes pain, surgical intervention may be recommended.

Functional adrenal tumors, which produce excess hormones, often require surgery to remove the tumor and alleviate symptoms.

It is also important to consult a doctor if you have a family history of genetic conditions that increase the risk of adrenal tumors, such as multiple endocrine neoplasia syndromes.

Regular follow-up with a healthcare provider is essential to monitor the tumor and ensure it does not develop into a more serious condition.

**DIFFERENTIAL DIAGNOSIS**

**The differential diagnoses include the following:**

* Carcinoma
* Metastasis
* Nodular hyperplasia
* Cysts
* Myelolipoma
* Angiomyolipoma
* Hemangioma
* Pheochromocytoma
* Hamartoma
* Granulomatosis

**EPIDEMIOLOGY**

The increasing utilization of computed tomography (CT) imaging has led to a higher frequency of reported cases of adrenal adenomas. The reported prevalence of adrenal incidentaloma varies depending on the criteria used. Based on CT findings, studies have reported that the prevalence of adrenal incidentalomas ranges between 0.35% and 1.9%. However, an autopsy series indicated a slightly higher prevalence of 2.3%.

Adrenal adenomas account for approximately 54% to 75% of adrenal incidentalomas. Although most studies indicate a higher prevalence of adrenal adenomas in females than males, there are a few cases of male predominance, notably in a large Korean study. The mean age for diagnosis is 57, with reported cases spanning a wide range of ages from 16 to 83.

Approximately 15% of adrenal incidentalomas exhibit hypersecretion of hormones. The reported prevalence of hypercortisolism ranges from 1% to 29%, hyperaldosteronism from 1.5% to 3.3%, and pheochromocytoma from 1.5% to 11%.

In rare cases, a patient may present with bilateral adrenal nodules. In such instances, it is essential to consider other potential causes of bilateral adrenal masses, including metastatic disease, congenital adrenal hyperplasia, lymphoma, infections, hemorrhage, and infiltrative conditions affecting the adrenal glands.

**RECENT GUIDELINES OR UPDATES**

Recent guidelines for the management of benign adrenal tumors emphasize a multidisciplinary approach, focusing on distinguishing benign from malignant lesions and determining the need for further investigation or treatment. According to the European Society of Endocrinology (ESE) clinical practice guidelines, adrenal incidentalomas are adrenal masses detected on imaging performed for reasons other than suspected adrenal disease. In most cases, these are benign, with adrenal adenomas being the most common type.

For benign adrenal masses, the guidelines recommend that if the noncontrast CT is consistent with a benign adrenal mass (homogenous appearance and Hounsfield units [HU] ≤ 10), no further imaging is required.

If the CT demonstrates a homogeneous adrenal mass with unenhanced HU between 11 and 20 and a tumor size < 4 cm, and the results of the hormonal work-up do not indicate significant hormone excess, an immediate additional imaging may be suggested to avoid any follow-up imaging.

The guidelines also highlight the importance of excluding pheochromocytoma by measuring plasma free metanephrines or urinary fractionated metanephrines in all patients with adrenal lesions with features not typical for a benign adenoma (e.g., unenhanced HU > 10). Recent studies have shown that the possibility of an adrenal tumor with HU ≤ 10 being a pheochromocytoma is close to zero, making it reasonable to avoid measuring metanephrines in patients with clear CT features of an adrenal adenoma.

For the differentiation of malignant from benign adrenal tumors, the guidelines mention the use of imaging techniques such as CT, MRI, and positron emission tomography with [18F]2-deoxy-D-glucose (FDG-PET/CT). FDG-PET/CT has the advantage of a low risk of false negative results, although it is more expensive and not always easily available.

In addition, the guidelines emphasize the importance of a focused history and physical examination aimed at identifying signs/symptoms of adrenal hormone excess, adrenal malignancy, and/or extra-adrenal malignancy. A low threshold for a multidisciplinary review by endocrinologists, surgeons, and radiologists is recommended when the imaging is not consistent with a benign lesion, there is evidence of hormone hypersecretion, the tumor has grown significantly during follow-up imaging, or adrenal surgery is being considered.

Adrenal incidentalomas are adrenal masses detected on imaging performed for reasons other than suspected adrenal disease. In most cases, adrenal incidentalomas are nonfunctioning adrenocortical adenomas but may also require therapeutic intervention including that for adrenocortical carcinoma, pheochromocytoma, hormone-producing adenoma, or metastases. Here, we provide a revision of the first international, interdisciplinary guidelines on incidentalomas. We followed the Grading of Recommendations Assessment, Development and Evaluation system and updated systematic reviews on 4 predefined clinical questions crucial for the management of incidentalomas: (1) How to assess risk of malignancy?;

(2) How to define and manage mild autonomous cortisol secretion?;

(3) Who should have surgical treatment and how should it be performed?; and (4) What follow-up is indicated if the adrenal incidentaloma is not surgically removed?

***Selected Recommendations:***

(1) Each adrenal mass requires dedicated adrenal imaging. Recent advances now allow discrimination between risk categories: Homogeneous lesions with Hounsfield unit (HU) ≤ 10 on unenhanced CT are benign and do not require any additional imaging independent of size. All other patients should be discussed in a multidisciplinary expert meeting, but only lesions >4 cm that are inhomogeneous or have HU >20 have sufficiently high risk of malignancy that surgery will be the usual management of choice.

(2) Every patient needs a thorough clinical and endocrine work-up to exclude hormone excess including the measurement of plasma or urinary metanephrines and a 1-mg overnight dexamethasone suppression test (applying a cutoff value of serum cortisol ≤50 nmol/L [≤1.8 µg/dL]). Recent studies have provided evidence that most patients without clinical signs of overt Cushing's syndrome but serum cortisol levels post dexamethasone >50 nmol/L (>1.8 µg/dL) harbor increased risk of morbidity and mortality. For this condition, we propose the term “mild autonomous cortisol secretion” (MACS).

(3) All patients with MACS should be screened for potential cortisol-related comorbidities that are potentially attributable to cortisol (eg, hypertension and type 2 diabetes mellitus), to ensure these are appropriately treated.

(4) In patients with MACS who also have relevant comorbidities surgical treatment should be considered in an individualized approach.

(5) The appropriateness of surgical intervention should be guided by the likelihood of malignancy, the presence and degree of hormone excess, age, general health, and patient preference. We provide guidance on which surgical approach should be considered for adrenal masses with radiological findings suspicious of malignancy.

(6) Surgery is not usually indicated in patients with an asymptomatic, nonfunctioning unilateral adrenal mass and obvious benign features on imaging studies. Furthermore, we offer recommendations for the follow-up of nonoperated patients, management of patients with bilateral incidentalomas, for patients with extra-adrenal malignancy and adrenal masses, and for young and elderly patients with adrenal incidentalomas. Finally, we suggest 10 important research questions for the future.

***Guidelines Summary***

*Diagnosis*

Guidelines issued in 2009 by the American Association of Clinical Endocrinologists (AACE) and American Association of Endocrine Surgeons (AAES) for the management of adrenal incidentalomas recommend that evaluation of patients with an adrenal incidentaloma include clinical, biochemical, and radiographic testing for the following [19] :

* Hypercortisolism
* Aldosteronism (if hypertensive)
* Pheochromocytoma or a malignant tumor

The simplest screening test for autonomous cortisol secretion from an incidentaloma is a 1-mg overnight dexamethasone suppression test. Salivary cortisol, dexamethasone suppression, and urine free cortisol testing can be used if clinical suspicion is high (eg, in patients with hypertension, obesity, diabetes mellitus, or osteoporosis).

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**ADRENAL TUMOR (MALIGNANT)**

*ALTERNATIVE NAMES:* Malignant adrenal tumors are also referred to as “adrenocortical carcinomas”.

These tumors are rare and can be aggressive, growing rapidly and potentially spreading to other parts of the body.

Other terms used to describe malignant adrenal tumors include “adrenocortical carcinoma” and “adrenal cancer”. In some contexts, they may also be described as “malignant adrenal cortical tumors”.

**DEFINITION / DESCRIPTION**

Adrenal cancer is a growth of cells that starts in an adrenal gland. The adrenal glands are small, triangular glands located on top of the kidneys. Although small, these glands control much of what happens in the body. They make hormones that help control metabolism, blood pressure and other important functions.

Adrenal cancer is rare, and it can happen at any age. It's most likely to affect children younger than 5, and adults in their 40s and 50s. Adrenal cancer also is called adrenocortical carcinoma.

When adrenal cancer is found early, a cure may be possible. When the cancer has spread beyond the adrenal glands, a cure becomes less likely. In that situation, treatment may be used to keep the cancer from spreading more.

Most growths that form in the adrenal glands are not cancer. The medical term for that is benign. An example of an adrenal growth that is not cancer is adrenal adenoma.

***What is adrenal cancer?***

Adrenal cancer occurs when cells in your adrenal glands mutate (change) and grow, forming a tumor. You have two adrenal glands — one on top of each kidney. They make hormones that send signals to many different organs to help keep your body healthy.

You can get adrenal cancer in one or both adrenal glands.

**Types of adrenal gland cancer**

There are three main types of adrenal cancer. Each starts in a different area of your adrenal gland:

1. Adrenocortical carcinoma (ACC). This is the most common type of adrenal cancer. It forms in the outer layer of your adrenal gland (the cortex). Your cortex makes steroid hormones that control elements like metabolism, blood pressure, body shape and hair growth. Another name for adrenocortical carcinoma is adrenal cortex cancer.
2. Neuroblastoma. Neuroblastomas form in nerve cells, so they can affect many different parts of your body. However, about one-third form in the inner part of your adrenal gland (the medulla). The medulla makes epinephrine and norepinephrine. These chemicals help control your sympathetic nervous system, which regulates things like sweating, heart rate and blood pressure. Adrenal neuroblastomas usually affect infants and children under the age of 10.
3. Pheochromocytoma. This adrenal gland cancer starts in the center of your medulla, usually in the cells that produce adrenaline. Adrenaline helps regulate your blood pressure and heart rate.

*How common is adrenal gland cancer?*

Adrenal gland cancer is rare, affecting about 200 people in the United States every year.

**CAUSES**

It's not clear what causes adrenal cancer.

Adrenal cancer happens when cells in the adrenal gland develop changes in their DNA. A cell's DNA holds the instructions that tell the cell what to do. In healthy cells, the DNA tells the cells to grow and multiply at a set rate. The DNA also tells the cells to die at a set time.

In cancer cells, the DNA changes give different instructions. The changes tell the cancer cells to grow and multiply quickly. Cancer cells can keep living when healthy cells die. This causes too many cells.

The cancer cells might form a mass called a tumor. The tumor can grow to invade and destroy healthy body tissue. In time, cancer cells can break away and spread to other parts of the body. When cancer spreads, it's called metastatic cancer.

***What causes adrenal cancer?***

Healthcare providers don’t know what causes most adrenal gland cancers. They know that mutations in the DNA can cause cells in your adrenal gland to change, grow and become cancerous. But they don’t know exactly why these DNA mutations happen.

Some people inherit a gene mutation from a biological parent, which increases their risk of adrenal cancer. Others may develop adrenal gland cancer due to exposure to certain cancer-causing substances. But in the majority of cases, these DNA mutations seem to happen for no apparent reason.

**RISK FACTORS**

Adrenal cancer happens more often in people who inherit certain health conditions that raise the risk of some cancers. Those health conditions include:

* Beckwith-Wiedemann syndrome.
* Familial adenomatous polyposis.
* Li-Fraumeni syndrome.
* Lynch syndrome.
* Multiple endocrine neoplasia, type 1, also called MEN 1.

Healthcare professionals haven't found anything that can prevent adrenal cancer.

***Adrenal cancer risk factors***

A risk factor is something that increases your chance of developing a certain cancer or disease. It doesn’t mean that you’ll get the disease. But it helps you know you’re at risk.

Possible environmental risk factors for adrenal cancer include:

* Smoking.
* Exposure to certain chemicals like asbestos and radon.
* Prior radiation therapy to your abdomen, where your adrenal glands are located.

While most adrenal cancers occur for no apparent reason, about 15% of people who develop adrenal tumors have a genetic disorder. This is most common in children. Genetic disorders associated with adrenal gland cancer include:

* Beckwith-Wiedemann syndrome.
* Von Hippel-Lindau syndrome.
* Li-Fraumeni syndrome.
* Familial adenomatous polyposis (FAP).
* Neurofibromatosis type 1.
* Multiple endocrine neoplasia (MEN).
* Carney complex.
* Lynch syndrome.

**SIGNS / SYMPTOMS**

Signs and symptoms of adrenal cancer may include:

* Back pain.
* Belly pain.
* Losing weight without trying.
* Loss of appetite.

Many people who have adrenal cancer develop hormone changes in the body. These changes can happen if the cancer cells make extra hormones. Most often, adrenal cancer makes the hormone cortisol. This can cause symptoms of Cushing syndrome, including:

* Weight gain.
* Muscle weakness.
* Pink or purple stretch marks on the skin.
* Bruises that happen even with a small injury.
* High blood pressure.
* High blood sugar or diabetes.

Less often, an adrenal cancer might make the sex hormones estrogen and testosterone. In females, changes in the sex hormones can cause extra facial hair, hair loss on the head and periods that aren't regular. In males, these hormone changes may cause the testicles to shrink and breast tissue to get bigger.

Rarely, adrenal cancer may make the hormone aldosterone. That can cause high blood pressure and low levels of potassium in the blood.

***Symptoms of adrenal cancer***

Adrenal cancer affects everyone differently. Some people develop pain if the tumor grows and presses on nearby organs. Others may notice symptoms based on the extra hormones the tumor releases.

General adrenal cancer symptoms may include:

* Abdominal pain.
* Back pain.
* Feeling of fullness in your belly.
* Muscle cramps.
* Weakness.
* Headaches.

Hormone-specific adrenal cancer symptoms might include:

* Excess facial or body hair (hirsutism).
* Newly elevated blood sugar (diabetes).
* High blood pressure.
* Low potassium (hypokalemia).
* Unexplained weight loss.
* Unexplained weight gain.
* Fast heartbeat.
* Enlarged breasts.
* Enlarged penis or clitoris.
* Low sex drive (low libido).
* Anxiety.
* Panic attacks.

In some cases, adrenal gland tumors don’t cause any symptoms.

*Metastatic adrenal cancer symptoms*

People with metastatic adrenal cancer (cancer that spreads from your adrenal glands to other parts of your body) might develop more severe symptoms as the disease progresses. Possible Stage 4 adrenal cancer symptoms include:

* Nausea and vomiting.
* Bloating.
* Fatigue.
* Fever.
* Confusion.
* Loss of appetite.

**DIAGNOSIS METHODS AND TESTS**

To diagnose adrenal cancer, a healthcare professional might start with a physical exam and review of your health history and family medical history. Diagnosis also involves blood and urine tests and imaging tests. Sometimes, surgery to remove the adrenal gland may be needed to diagnose adrenal cancer.

**Blood and urine tests**

Lab tests of blood and urine may show levels of hormones made by the adrenal glands that are outside a healthy range. Those hormones include cortisol, aldosterone and androgens.

**Imaging tests**

Imaging tests used to diagnose adrenal cancer include CT, MRI and positron emission tomography scans, also called PET scans. Healthcare professionals might use the images to examine growths on the adrenal glands. Imaging tests also can look for signs that the cancer has spread to other areas of the body.

**Surgery to remove the adrenal gland**

In some situations, to make a diagnosis of adrenal cancer, the adrenal gland that might have cancer is removed with surgery. Then, the gland is examined in a lab by a doctor who studies body tissues, called a pathologist. Testing can show whether the gland has cancer.

***How is adrenal cancer diagnosed?***

Your healthcare provider may suspect cancer in your adrenal glands based on your specific symptoms, such as excessive hair growth or unexplained weight changes. But sometimes, providers find adrenal tumors after taking a CT (computed tomography) scan or MRI (magnetic resonance imaging) for other reasons.

During a visit with your healthcare provider, they’ll:

* Perform a physical examination.
* Review your medical history.
* Ask about your symptoms.
* See if you have any known risk factors for adrenal cancer.
* Review your family history of cancer.

*What tests can help diagnose adrenal cancer?*

After your exam, your healthcare provider will run additional tests to confirm your diagnosis or rule out other conditions. These tests may include:

* Blood tests.
* Urinalysis (urine tests).
* Imaging tests.

***Adrenal cancer staging***

Healthcare providers use a cancer staging system to diagnose adrenal cancer. Staging tells you the size and location of the tumor and whether it has metastasized (spread to other areas of your body).

In general, the higher the number, the more advanced the tumor:

* Stage 1: The tumor measures 5 centimeters or less and hasn’t spread outside of your adrenal gland.
* Stage 2: The tumor measures more than 5 centimeters and hasn’t spread outside of your adrenal gland.
* Stage 3: The cancer is in your adrenal gland and has spread to surrounding tissues or nearby lymph nodes.
* Stage 4: The cancer is in your adrenal gland and has spread to distant areas of your body, such as your lungs or liver.

Staging systems can be complex. If you have specific questions about your diagnosis, you should talk to your healthcare provider.

**TREATMENT OPTIONS**

Treatment for adrenal cancer often includes surgery to remove the adrenal gland. Other treatments also might be used in some situations. Those treatments include radiation therapy and medicines, such as chemotherapy and immunotherapy.

**Surgery**

Surgery for adrenal cancer typically involves removing the entire adrenal gland. This procedure is called an adrenalectomy. The surgery is done for several reasons, including to:

* Confirm a diagnosis of adrenal cancer.
* Remove as much of the cancer as possible.
* See if cancer has spread outside the adrenal gland.
* Ease symptoms. This can include lessening symptoms that happen when the body makes too much of the hormone cortisol due to cancer. Surgery also may help with symptoms such as belly pain and back pain that happen when an adrenal cancer grows large.

It's common for adrenal cancer to spread outside of the adrenal gland. If the surgeon finds evidence that the cancer has spread to nearby organs, such as to the liver or kidney, parts or all of those organs also might need to be removed.

**Radiation therapy**

Radiation therapy treats cancer with powerful energy beams. The energy can come from X-rays, protons or other sources. Radiation therapy sometimes is used after adrenal cancer surgery to kill any cells that might be left behind. It also can help ease pain and other symptoms of cancer that has spread to other parts of the body, such as the bones.

**Chemotherapy**

Chemotherapy treats cancer with strong medicines. For adrenal cancers that can't entirely be removed with surgery or those that come back after surgery, chemotherapy may help keep the cancer from growing and spreading.

**Mitotane**

Mitotane (Lysodren) is an older medicine that has been used to treat advanced adrenal cancer. It also has shown promise in keeping adrenal cancer from coming back after surgery. Mitotane may be used after surgery for people who are at high risk of the cancer coming back. Research into mitotane for this purpose is ongoing.

**Immunotherapy**

Immunotherapy for cancer is a treatment with medicine that helps the body's immune system kill cancer cells. The immune system fights off diseases by attacking germs and other cells that shouldn't be in the body. Cancer cells survive by hiding from the immune system. Immunotherapy helps the immune system cells find and kill the cancer cells.

For adrenal cancer, immunotherapy may be used when the cancer has spread to other parts of the body or in situations where surgery isn't possible.

**Management and Treatment**

*Is adrenal cancer curable?*

There’s a chance for a cure when the tumor is only in your adrenal gland and hasn’t spread to other areas of your body. Surgical removal (adrenalectomy) is the main curative treatment for adrenal cancer.

If the cancer has spread beyond your adrenal gland, a cure becomes less likely. But treatment slows the growth of the tumor and improves your quality of life.

*How is adrenal cancer treated?*

Adrenal cancer treatment depends on the size and location of the tumor, and whether it has spread outside of your adrenal gland. Possible treatments include:

* Surgery.
* Radiation therapy.
* Chemotherapy.
* Other medications.

***Surgery***

If the tumor is in your adrenal gland or has only spread to very nearby tissues or lymph nodes, then your provider will likely recommend surgery. A surgeon will remove your entire adrenal gland (adrenalectomy) and any diseased structures next to it.

If cancer is only in one adrenal gland, then your other adrenal gland should work properly. In many cases, you don’t need to do anything else. If you need to have both adrenal glands removed, then you’ll need to take medicine for the rest of your life to replace the hormones your glands produce.

Sometimes, providers recommend chemotherapy or radiation therapy after surgery to kill any remaining cancer cells and reduce the risk of recurrence (return).

In some cases, providers may recommend surgery even after the cancer has spread to remove as much of the tumor as possible. Providers call this debulking surgery.

***Radiation therapy***

Radiation therapy uses high-energy X-ray beams to kill cancer cells. Providers usually don’t use radiation therapy as the first treatment for adrenal cancer. They might use radiation therapy after surgery to decrease the chance of cancer coming back. If adrenal cancer has spread, they might use radiation therapy to treat sites of spread to reduce symptoms. Healthcare providers may combine radiation with chemotherapy or other medicines.

***Chemotherapy***

Chemotherapy uses drugs to kill cancer cells. Your provider may give chemotherapy drugs in pill form or through a vein (intravenously). Providers often use chemotherapy to treat adrenal cancer that has spread to other areas of your body. Or they may use it following surgery to kill any remaining cancer cells.

Mitotane is the most common chemotherapy drug used to treat cancer in your adrenal glands.

***Other medications***

Healthcare providers may use other medications to treat adrenal gland cancer. Some drugs, like metyrapone, can reduce adrenal steroid hormone production. Other drugs, like spironolactone and mifepristone, block the effects of the hormones that the tumor releases.

These drugs can ease your symptoms, but they don’t shrink or kill cancer cells.

***Who treats adrenal cancer?***

If you have adrenal cancer, your medical team may include several specialists, including:

* Oncologists (surgical, radiation and medical).
* Endocrinologists.

**REOCCURRENCE**

Cancer survivors can be affected by many health problems, but often their greatest concern is facing cancer again. If the same cancer comes back after treatment, it is called a recurrence.

Some cancer survivors may develop a new, unrelated cancer later. This is called a second cancer. Unfortunately, being treated for cancer doesn’t mean you can’t get another cancer. Survivors of adrenal cancer can get any type of second cancer, but they have increased risks of getting:

* Lung cancer
* Bladder cancer
* Prostate cancer

Women who have had adrenal cancer also have an increased risk of melanoma of the skin.

Patients who were under 45 when adrenal cancer was diagnosed have increased risks of breast cancer, bone and soft tissue sarcoma, brain tumors, and acute leukemia. These cancers, along with adrenal cancer, are seen in a family cancer syndrome called Li-Fraumeni syndrome.

**Follow-up after treatment**

After completing treatment for adrenal cancer, you should still see your doctor regularly and might have tests to look for signs the cancer has come back or spread. Experts do not recommend any additional testing to look for second cancers in patients without symptoms. Let your doctor know about any new symptoms or problems, because they could be caused by the cancer coming back or by a new disease or second cancer.

Survivors of adrenal cancer should follow the American Cancer Society guidelines for the early detection of cancer and stay away from tobacco products. Smoking increases the risk of many cancers.

To help maintain good health, adrenal cancer survivors should also:

* Get to and stay at a healthy weight
* Keep physically active and limit the time you spend sitting or lying down
* Eat plenty of fruits, vegetables, and whole grains, and limit or avoid red and processed meats, sugary drinks, and highly processed foods.
* Avoid drinking alcohol. If you do drink, have no more than 1 drink per day for women or 2 drinks per day for men

These steps may also lower the risk of other health problems as well.

**PREVENTION TIPS**

### **Can I prevent adrenal cancer?**

There’s no proven way to prevent adrenal gland cancer. Avoiding environmental risk factors, like smoking, may help reduce your overall risk.

There are no specific prevention tips for malignant adrenal tumors, as there are no modifiable risk factors for this type of tumor.

The majority of adrenal tumors are benign, or non-cancerous, and do not require any treatment. However, sometimes adrenal tumors grow out of control and become malignant (cancerous). Researchers are still trying to determine what causes an adrenal tumor to become cancerous and to establish adrenal cancer prevention guidelines.

While we don’t know exactly what causes adrenal cancer and therefore can’t make specific suggestions on how to prevent it, it’s always a good idea to take steps to lower your overall risk of cancer through lifestyle modification.

**POSSIBLE COMPLICATIONS**

Malignant adrenal tumors can lead to various complications, depending on their type and location. These tumors can cause hormonal imbalances, leading to conditions such as Cushing's syndrome, which is characterized by rapid weight gain, especially in the trunk and face, and the development of fat pads along the back and face.

Additionally, tumors that secrete excess hormones can result in symptoms like high blood pressure, excessive hair growth in women, and breast tenderness or enlargement in men.

Malignant adrenal tumors can also grow large enough to press on nearby organs, causing pain in the abdomen, side, or back.

In some cases, these tumors may spread to other parts of the body, such as the lungs or liver, which can lead to more severe symptoms and complications.

Treatment for malignant adrenal tumors may involve surgery, radiation therapy, and chemotherapy, which can have their own set of side effects. For instance, surgery to remove an adrenal gland may affect hormone production, requiring lifelong hormone replacement therapy if the remaining adrenal gland does not compensate adequately.

Radiation therapy and chemotherapy can also cause various side effects, including fatigue, nausea, and immunosuppression.

**OUTLOOK / PROGNOSIS**

**Does adrenal cancer spread fast?**

It depends on the type of tumor you have:

* Adrenocortical carcinoma, the most common type of adrenal cancer, usually grows rapidly and spreads quickly.
* Some neuroblastomas grow slowly, but others grow quickly.
* Most cancerous pheochromocytomas grow slowly.

Adrenal cancer affects everyone differently. If you have questions about how fast an adrenal tumor may grow, talk to your healthcare provider.

**How serious is cancer in the adrenal gland?**

In general, adrenal gland cancer is difficult to cure. Adrenal cancer prognosis depends on the location and size of the tumor and whether it has spread to other areas of your body.

**Can you survive an adrenal tumor?**

Yes, it’s possible to survive an adrenal gland tumor. The outlook for people with adrenal gland cancer varies significantly depending on the location of the tumor.

**Adrenal cancer survival rates**

The five-year survival rate for early-stage adrenal cancer is between 50% and 60%. This means that up to 60% of people with this disease will still be alive five years after their diagnosis. Once the cancer spreads to other areas of your body, the five-year survival rate drops to 10% to 20%.

Survival rates can’t tell you how long you’ll live or how well a certain treatment will work for you. To learn more about survival rates and what they mean in your specific situation, talk to your healthcare provider.

**WHEN TO SEE A DOCTOR / RED FLAG**

**When should I see my healthcare provider?**

It’s not always possible to spot the symptoms of adrenal cancer. But you should schedule an appointment with your healthcare provider if you develop:

* Abdominal pain.
* Sudden-onset diabetes.
* Unexplained weight loss or weight gain.
* Excessive hair growth.
* Changes to your genitals.

If a first-degree biological relative (parent or sibling) develops adrenal cancer, consider talking to your provider about your risk.

**What questions should I ask my healthcare provider?**

If you or a loved one have an adrenal cancer diagnosis, you may want to ask these questions:

* Where is the tumor?
* What size is the tumor?
* Has the cancer spread outside of my adrenal gland?
* Do I need more testing?
* What are my treatment options?
* Will I be able to work or go to school during treatment?
* When will I start treatment?
* What can I do to ease my symptoms?
* What are the chances that adrenal cancer will come back?

**DIFFERENTIAL DIAGNOSIS**

The differential diagnosis for malignant adrenal tumors involves distinguishing them from benign adrenal tumors and other conditions that may mimic their presentation. Several criteria and methods are used to differentiate benign from malignant adrenal tumors, including imaging, histopathological assessments, and molecular markers.

Imaging modalities such as CT, MRI, and FDG-PET/CT are commonly used to evaluate adrenal tumors. Unenhanced CT can assess lipid content, with a Hounsfield unit (HU) value of ≤10 being specific for lipid-rich lesions, typically indicating benign adenomas.

However, adjustments in cutoff values, such as a tumor diameter of 4 cm and unenhanced CT tumor attenuation of 20 HU, have been proposed to improve specificity for diagnosing adrenocortical carcinoma (ACC).

Histopathological criteria, such as the Weiss score, are used to evaluate tumor characteristics after surgical removal. The Weiss score includes nine histopathological criteria, and a score of ≥3 points is indicative of malignancy.

Other scoring systems, such as the Modified Weiss, Lin-Weiss-Bisceglia, Reticulin Algorithm, and Helsinki Score, also provide thresholds for malignancy.

Molecular markers and genetic alterations are also being explored for their diagnostic potential. For example, IGF2 methylation score combined with tumor size has shown high accuracy (AUC 0.957) in differentiating benign from malignant tumors.

Additionally, molecular studies have identified several targets that may aid in the diagnosis of ACC, including alterations in DNA, methylome, chromosome, or microRNA.

In summary, the differential diagnosis for malignant adrenal tumors involves a combination of imaging, histopathological assessments, and molecular markers to accurately distinguish between benign and malignant lesions.

**RECENT GUIDELINES OR UPDATES**

Recent guidelines for the management of malignant adrenal tumors emphasize a multidisciplinary approach and highlight the importance of accurate diagnosis and treatment strategies. According to the 2023 European Society of Endocrinology (ESE) guidelines, in collaboration with the European Network for the Study of Adrenal Tumors (ENSAT), adrenal incidentalomas should be evaluated with careful clinical assessment, including clinical examination for symptoms and signs of adrenal hormone excess.

The guidelines also recommend the use of steroid metabolomics using tandem mass spectrometry to discriminate malignancy.

For the differentiation of benign from malignant adrenocortical tumors, several scoring systems are used, including the Weiss criteria, modified Weiss criteria, Lin-Weiss-Bisceglia criteria, reticulin algorithm, and Helsinki score.

These criteria help in determining the likelihood of malignancy based on specific histopathological features.

In terms of treatment, the guidelines advocate for more proactive surgical treatment for indeterminate adrenal masses in young patients (<40 years) and pregnant women.

Laparoscopic adrenalectomy is recommended for selected patients with small tumors and no evidence of invasiveness or adrenal incidentalomas.

For patients with advanced adrenal malignant disease, surgery is considered, and factors associated with improved outcomes include complete operative resection, laparoscopic adrenalectomy, and the absence of extra-adrenal disease.

Additionally, the guidelines highlight the importance of high-volume surgeons performing adrenalectomy and emphasize the pivotal role of a multidisciplinary team approach in deciding the treatment plan for indeterminate adrenal masses.

For patients with metastatic disease, systemic therapy, preferably within a clinical trial, is recommended.

**EPIDEMIOLOGY**

Adrenal tumors are found in about 1 in every 10 people who have an imaging test (like a CT or MRI) of the adrenal gland. Most are benign adenomas.

Adrenocortical carcinomas are much less common than adenomas. In fact, they are very rare. The exact number diagnosed in the United States each year is not known. It is probably around 200 per year.

Patients with adrenocortical carcinoma are usually either very young (less than 5 years old) or middle-aged (40 to 50s). Women appear to be more likely to develop this cancer than men.

Malignant adrenal tumors, including adrenocortical carcinomas (ACCs) and pheochromocytomas or paragangliomas (PPGLs), have distinct epidemiological profiles. ACCs are rare, with an estimated annual incidence of 0.7–2 cases per million population in Western countries, although higher rates have been reported in certain regions like south and southeastern Brazil.

The prevalence of ACCs is approximately 4–12 cases per million per year.

Adrenal incidentalomas, which are often benign, are found in about 1 in 10 people undergoing imaging tests of the adrenal gland, but only a small percentage (up to 10%) are functional, and about 2% are ACCs.

PPGLs, which include pheochromocytomas and paragangliomas, have an incidence of 0.2 to 0.9 cases per 100,000 individuals per year.

Pheochromocytomas are present in approximately 4-7% of patients with adrenal incidentalomas.

In terms of prevalence among adrenal incidentalomas, adrenocortical carcinoma accounts for 0.4%-4% of cases.

The epidemiology of malignant adrenal tumors is influenced by factors such as age, mode of discovery, tumor size, imaging modality, and history of extra-adrenal malignancy, which can introduce selection bias in current literature.

The exact number of diagnosed adrenocortical carcinomas in the United States is not known, but it is estimated to be around 200 cases per year.

These tumors are more commonly diagnosed in children and middle-aged adults, with a higher incidence in women compared to men.

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**ADRENAL CRISIS**

ALTERNATIVE NAMES: Other names for adrenal crisis include “Addisonian crisis” and “acute adrenal insufficiency”.

**DEFINITION / DESCRIPTION**

An adrenal crisis is a condition in which your adrenal glands don’t make enough of the hormone cortisol. It’s a life-threatening complication of adrenal insufficiency (Addison’s disease). If you suspect that you have an adrenal crisis, reach out to your healthcare provider immediately.

Your adrenal glands are just above each kidney. They’re small and shaped like triangles. They make hormones, including cortisol. Hormones are chemicals that coordinate different functions in your body by carrying messages through your blood to your organs, skin, muscles and other tissues. These signals tell your body what to do and when to do it.

Cortisol affects almost every organ and tissue in your body. Some of its functions include:

* Regulating your body’s stress response.
* Helping control your metabolism.
* Suppressing inflammation.
* Regulating blood pressure.
* Regulating blood sugar.
* Helping control your sleep-wake cycle.

An adrenal crisis may cause a lack of blood flow (shock). Shock progresses quickly and may damage your organs. Without treatment, up to 20% of people in shock may die from an adrenal crisis.

An adrenal crisis may also cause seizures or a coma.

An adrenal crisis can affect anyone. However, it most commonly affects people between the ages of 30 and 50.

Adrenal crises aren’t common. Studies estimate that 42% of people with adrenal insufficiency will have an adrenal crisis. In the United States, adrenal insufficiencies affect 1 in 100,000 people.

Some studies suggest that up to 25% of people who have an adrenal crisis die from it.

**CAUSES**

The two adrenal glands are located on top of the kidneys. They consist of the outer portion, called the cortex, and the inner portion, called the medulla. The cortex produces three types of hormones, all of which are called corticosteroids.

Cortisol is a glucocortoid, a corticosteroid that maintains glucose (blood sugar) regulation, suppresses the immune response, and is released as part of the body's response to stress. Cortisol production is regulated by a small gland just below the brain called the pituitary gland. Cortisol is essential for life.

*What happens in an adrenal crisis?*

Acute adrenal crisis is a medical emergency caused by a lack of cortisol. Patients may experience lightheadedness or dizziness, weakness, sweating, abdominal pain, nausea and vomiting, or even loss of consciousness.

Adrenal crisis occurs if the adrenal gland is deteriorating (Addison's disease, primary adrenal insufficiency), if there is pituitary gland injury (secondary adrenal insufficiency), or if adrenal insufficiency is not adequately treated.

**What can trigger an adrenal crisis?**

The following stressors may trigger an adrenal crisis:

* Not receiving treatment for an adrenal insufficiency such as Addison’s disease.
* Damage to your adrenal gland, including adrenal gland diseases or surgery.
* Dehydration.
* Hypopituitarism.
* Infection.
* No longer taking glucocorticoid medications (prednisone) after taking them for a long time.
* Mental or emotional stress.

**RISK FACTORS**

Risk factors for adrenal crisis include physical stress such as infection, dehydration, trauma, or surgery, adrenal gland or pituitary gland injury, and ending treatment with steroids such as prednisone or hydrocortisone too early.

Adrenal crisis, also known as Addisonian crisis or acute adrenal insufficiency, is a life-threatening complication of adrenal insufficiency.

The risk factors for adrenal crisis include adrenal insufficiency itself, polyglandular autoimmune syndromes, the use of glucocorticoids, levothyroxine, and rifampin.

Additionally, conditions such as thyrotoxicosis, infections, trauma, pregnancy, and surgery can increase the risk of an adrenal crisis.

Individuals with primary adrenal insufficiency are at a higher risk for an adrenal crisis, and the biggest trigger for adrenal crisis is gastrointestinal illness.

Those with adrenal insufficiency should be aware of the risk factors and take necessary precautions to prevent an adrenal crisis.

***Adrenal Crisis Risk Factors***

The risk factors associated with adrenal crisis are as follows:

* A known history of adrenal insufficiency or previous adrenal crisis
* Primary adrenal insufficiency diagnosis, which carries a higher risk than secondary adrenal insufficiency
* Ongoing glucocorticoid therapy, including topical and inhalation forms, poses a risk for an adrenal crisis due to the potential suppression of the hypothalamic-pituitary-adrenal (HPA) axis if abruptly discontinued
* Medications, including levothyroxine, phenytoin, phenobarbital, rifampin, carbamazepine, St John's wort, ketoconazole, etomidate, and fluconazole, which affect cortisol metabolism or reduce its production
* Anticoagulation agents, which increase the risk of adrenal hemorrhage
* Additional medications, including megestrol acetate and medroxyprogesterone
* Pregnancy, particularly during the third trimester
* Advanced age
* The presence of comorbidities
* Patients with type 1 diabetes
* Adrenal metastasis or adrenal hemorrhage
* Polyglandular autoimmune syndromes 1 and 2

**SIGNS / SYMPTOMS**

The most common symptoms of an adrenal crisis include:

* Abdominal pain or pain in your side (flank).
* Long-lasting fatigue.
* Loss of appetite.
* Darker patches of skin (hyperpigmentation).
* Weakness.
* Unexplained weight loss.

Other warning signs of adrenal crisis may include:

* Dehydration.
* Diarrhea.
* Dizziness, confusion, light-headedness, fainting or coma.
* Fever.
* Headache.
* Joint pain.
* Low blood glucose.
* Low blood pressure.
* Nausea and vomiting.
* Rapid breathing (respiratory rate).
* Rapid heart rate.
* Headache
* Profound weakness
* Fatigue
* Slow, sluggish movement
* Nausea
* Vomiting
* Low blood pressure
* Dehydration
* High fever
* Shaking chills
* Confusion or coma
* Darkening of the skin
* Rapid heart rate
* Joint pain
* Abdominal pain
* Unintentional weight loss
* Rapid respiratory rate (see tachypnea)
* Unusual and excessive sweating on face and/or palms
* Skin rash or lesions may be present
* Flank pain
* Loss of appetite

**Signs and tests:**

* An ACTH (cortrosyn) stimulation test shows low cortisol.
* The baseline cortisol level is low.
* Fasting blood sugar may be low.
* Serum potassium is elevated ( usually primary adrenal insufficiency).
* Serum sodium is decreased (usually primary adrenal insufficiency).

**DIAGNOSIS METHODS AND TESTS**

An adrenal crisis may be difficult to diagnose because it shares many symptoms with other common conditions. However, the following tests can help your healthcare provider properly diagnose an adrenal crisis:

* Adrenocorticotropic hormone (ACTH) blood test.
* Blood sugar tests.
* Cortisol test.
* pH blood test.
* Potassium blood test.
* Sodium blood test.

**MANAGEMENT AND TREATMENT OPTIONS**

In adrenal crisis, an intravenous or intramuscular injection of hydrocortisone (an injectable corticosteroid) must be given immediately. Supportive treatment of low blood pressure with intravenous fluids is usually necessary. Hospitalization is required for adequate treatment and monitoring. If infection is the cause of the crisis, antibiotic therapy may be needed.

Your healthcare provider will immediately use a small needle and tube to deliver a hydrocortisone injection (hydrocortisone phosphate or hydrocortisone sodium succinate) and a saline solution into your vein in your arm or hand (intravenously). The hydrocortisone injection replaces cortisol.

If a bacterial infection causes your adrenal crisis, your healthcare provider might give you antibiotics.

Your provider may also treat any other symptoms related to your adrenal crisis. For dehydration or an electrolyte imbalance, treatments may include water, sports drinks or coconut water. For hypoglycemia, treatment may include consuming carbohydrates.

If you’ve never had an adrenal crisis before, your healthcare provider will conduct ACTH stimulation tests to determine its cause.

Hydrocortisone injection side effects may include:

* Allergic reaction.
* Bloody or black stool (poop).
* Fever.
* Sore throat.
* Cough.
* Mood swings.
* Pain in your hips, back, ribs, arms, shoulders or legs.

Yes, it’s OK to receive a hydrocortisone injection if you’re pregnant and have an adrenal crisis. You can’t transfer hydrocortisone to a developing fetus through your placenta.

If you don’t treat your adrenal crisis, you may die, and your pregnancy would end.

**How soon after treatment will I feel better?**

It may take 24 hours or longer to feel better after receiving treatment for an adrenal crisis.

An adrenal crisis requires prompt identification and treatment. This medical emergency necessitates maximal supportive care and monitoring in the intensive care unit. The administration of glucocorticoids, specifically hydrocortisone, constitutes the definitive treatment for adrenal crisis. In patients with known adrenal insufficiency, symptoms consistent with an adrenal crisis should be sufficient to initiate treatment. If a patient is medically unstable and is strongly suspected of adrenal insufficiency or crisis, stress dose steroids should be administered promptly. The administrative dosing of stress dose steroids and fluid resuscitation differs in children from adults

In cases of adrenal crisis, involving an endocrinologist as soon as possible is crucial to ensure appropriate management of the condition and guidance in patient care. Recent evidence indicates that continuous infusion is a superior delivery method for hydrocortisone in the management of adrenal crises when compared to intermittent boluses. Continuous hydrocortisone infusion has shown better maintenance of cortisol levels within the therapeutic range. Once there is clinical improvement, initiating a gradual tapering of steroids is advisable. This approach helps prevent abrupt discontinuation and enables a smoother transition to lower doses.

The necessity for mineralocorticoid replacement should be assessed individually and in consultation with an endocrinologist. Mineralocorticoid replacement is unnecessary if the glucocorticoid doses administered to patients exceed 50 mg. In situations where hydrocortisone is unavailable, the following alternative parenteral glucocorticoids can be considered:

* **Prednisolone**: A preferred alternative treatment, prednisolone is administered as an initial bolus of 25 mg, followed by 2 additional 25 mg doses within the first 24 hours. Subsequently, this regimen should be continued with a daily dose of 50 mg of prednisone.
* **Methylprednisolone**: This can be administered at a dosage of 40 mg every 24 hours.
* **Dexamethasone**: This alternative is the least preferred, with a recommended dosage of 4 mg every 24 hours.

In patients with an infectious process as the precipitating event for adrenal crisis, prompt administration of appropriate antibiotics is necessary to address the underlying infection.

**OUTLOOK / PROGNOSIS**

If you suspect you’re having an adrenal crisis, seek treatment immediately. High doses of glucocorticoids aren’t harmful over a short period. Death may result if you don’t seek immediate treatment.

Most people who’ve had an adrenal crisis must take hydrocortisone pills for the rest of their lives. Always have extra medicine available in case you become ill and need more.

Despite the potential for successful treatment with prompt administration of glucocorticoids, the associated mortality rate remains unacceptably high for adrenal crisis. Due to its rarity, many healthcare professionals may have limited familiarity with the presentation and management of adrenal crises. A retrospective study in the United Kingdom revealed that adrenal crisis contributed to 10% of the deaths in patients with primary and secondary adrenal insufficiency.

Patients whose adrenal crisis is quickly identified and given prompt treatment with IV fluids and parenteral steroids have a good prognosis and recovery. Those who are critically ill with significantly altered mental status, advanced endocrinopathies (eg, severe diabetes and uncontrolled thyroid disease), or multiple comorbidities have an increased risk of mortality and residual disability. The patient may need physical or occupational therapy and rehabilitation to regain independent function.

The prognosis for adrenal crisis is highly dependent on the promptness of treatment. Adrenal crisis is a life-threatening condition that requires immediate medical attention, as failure to treat it can result in death.

With timely intervention, however, the prognosis is generally good. Treatment typically involves the administration of high doses of glucocorticoids, such as hydrocortisone, either intravenously or intramuscularly, along with fluid resuscitation to address hypotension and electrolyte imbalances.

In cases where adrenal crisis is managed effectively, patients can recover fully, although they may require ongoing monitoring and adjustments to their hormone replacement therapy.

The risk of recurrence can be minimized by educating patients on recognizing early signs of stress or illness and adjusting their medication accordingly.

It is important to note that adrenal crisis can occur in individuals with known adrenal insufficiency, such as those with Addison's disease, if their cortisol replacement therapy is inadequate or if they experience significant physical stressors like infection, trauma, or surgery.

Therefore, patients with adrenal insufficiency must be vigilant and prepared to manage their condition proactively.

In summary, while adrenal crisis is a medical emergency with potentially severe consequences, the prognosis is favorable when treated promptly and appropriately.

Death may occur due to overwhelming shock if early treatment is not provided.

**POSSIBLE COMPLICATIONS**

An adrenal crisis can result in fatal outcomes, even with timely recognition and appropriate treatment. Besides the risk of death, adrenal crisis is associated with other potential complications. Electrolyte abnormalities, such as hyponatremia, hyperkalemia, and hypoglycemia, can lead to various complications, including seizures, arrhythmias, and coma. If left untreated, hypotension can lead to hypoperfusion, potentially resulting in multiple organ failure. Furthermore, the precipitating disease or event that triggered the adrenal crisis can introduce additional complications.

Despite receiving steroid replacement therapy, individuals who have experienced adrenal crises often face significant challenges in their quality of life. Studies have indicated that many individuals suffer from disabilities and are unable to work due to conditions such as depression and chronic fatigue, thereby leading to a poor quality of life.

Adrenal crises continue to maintain an unacceptably high mortality rate. Although the exact cause of mortality may not be apparent in all cases, experts believe it to be attributed to respiratory infections, adverse cardiovascular events, and stroke. Despite extensive efforts in patient education, the incidence of adrenal crisis–related mortality remains significant. A study involving 423 participants reported an adrenal crisis–related mortality rate as high as 6%. In a previous study, patient satisfaction with managing adrenal crises in the emergency setting was as low as 66%.

* Shock
* Coma
* Seizures

**PREVENTION TIPS**

If you have an adrenal insufficiency, learn what stressors may trigger an adrenal crisis. These may include mental or emotional stress, dehydration, infection or not taking your glucocorticoid medications as prescribed by your healthcare provider.

Surgery and pregnancy may trigger adrenal insufficiency. Tell your healthcare provider that you have an adrenal insufficiency before any surgery. Talk to your provider if you’re planning to become pregnant.

Carry a medical identification card, necklace or bracelet that indicates you have adrenal insufficiency. Your identification materials should also include what type of medication you need and the exact dosage. This information can help your healthcare providers administer timely treatment.

Regularly weigh yourself and check your blood pressure. Let your healthcare provider know if you lose weight or if your blood pressure gets too high or too low.

Your provider may give you an emergency shot of cortisol. They’ll teach you when and how to give yourself cortisol. Keep this medication and directions on how to use it handy at all times. Teach a family member or close friend how to give you the cortisol shot in case you’re too weak to administer it yourself.

It’s also a good idea for you and your healthcare provider to create a plan in the event you can’t take your hydrocortisone pills because of nausea or vomiting.

People who have Addison's disease symptoms should be taught to recognize signs of potential stress that may cause an acute adrenal crisis. Most people with Addison's disease are taught to give themselves an emergency injection of hydrocortisone or increase their dose of oral prednisone in times of stress.

It is important for the individual with Addison's disease to always carry a medical identification card that states the type of medication and the proper dose needed in case of an emergency.

Never omit medication. If unable to retain medication due to vomiting, notify the health care provider.

**WHEN TO SEE A DOCTOR / RED FLAG**

**When should I see my healthcare provider?**

Contact your healthcare provider immediately if you have symptoms of an adrenal crisis.

See your healthcare provider if you experience major stress — such as an injury, illness or mental or emotional stress. You may need to adjust your medication.

***Calling your healthcare provider***

Call your healthcare provider if you have Addison's disease and are unable to retain usual medications because of vomiting. Go to the emergency room or call the local emergency number (such as 911) if symptoms of an acute Addisonian crisis develop.

**DIFFERENTIAL DIAGNOSIS**

An adrenal crisis is rarely an isolated event and has a wide array of differential diagnoses, depending on the presentation and underlying etiology. Although symptoms such as altered mental status, abdominal pain, nausea, vomiting, and fever are frequently encountered during presentations, hypotension typically remains the most significant feature. An adrenal crisis should be considered the primary differential diagnosis for patients with a known history of adrenal insufficiency and experiencing related symptoms.

Further investigation is necessary to determine the underlying cause of the adrenal crisis and potential secondary triggers. In patients without a known adrenal pathology and exhibiting hypotension resistant to fluid administration and vasopressor support, the diagnosis of adrenal crisis should be strongly considered. Differential diagnoses that should also be considered include:

* Shock
* Cardiogenic
* Obstructive
* Distributive
* Hypovolemic
* Septic
* Cardiac
* Acute myocardial infarction
* Endocrine
* Thyrotoxicosis
* Diabetic ketoacidosis
* Hyperosmolar hyperglycemic state
* Myxedema coma
* Pituitary adenoma
* Gastrointestinal
* Dehydration
* Gastroenteritis
* Poor oral intake
* Acute abdomen (e.g., appendicitis, diverticulitis, obstruction)
* Hematology and oncology
* History of melanoma, breast cancers, or immunotherapy with a checkpoint inhibitor
* Malignancy
* Obstetrics
* Pregnancy
* Hyperemesis gravidarum
* Infectious
* Acute localized or systemic infection
* Stressors
* Trauma
* Recent surgery
* Psychological stress

**EPIDEMIOLOGY**

Determining the exact frequency of adrenal crises in the general population poses a significant challenge. Patients with adrenal insufficiency have been estimated to experience an adrenal crisis in 6% to 8% of cases annually or 4 to 6 adrenal crises per 100 patient years in those carrying a diagnosis of adrenal insufficiency. The incidence of adrenal crises remains high even among patients who have received extensive education on managing and preventing adrenal insufficiency. A study revealed a 6% mortality rate associated with adrenal crises among this well-informed group of patients. The annual frequency of adrenal crisis in patients with Addison disease remains at 8%.

Adrenal crisis has a significant impact on patients with adrenal insufficiency, with an estimated incidence of 5 to 10 cases per 100 patient years.

Each year, about 6% to 8% of patients with adrenal insufficiency (AI) are reported to suffer an episode of adrenal crisis.

Approximately 42% of people with adrenal insufficiency will have an adrenal crisis during their lifetime, and about 20% of these patients experience more than one adrenal crisis.

Adrenal crisis is slightly more common in patients with primary AI than in those with secondary AI.

Women make up about 60% of patients admitted with adrenal crisis, which reflects the increased prevalence of AI in women due to an increased predisposition to autoimmune disease.

The mortality rate for adrenal crisis is estimated to be between 0.5% and 2%.

Norwegian data indicate that 1 in 7 patients with Addison’s disease eventually dies from adrenal crisis.

It is estimated that the adrenal crisis will account for 5500–10,600 excess deaths in the European Union in the next decade.

Adrenal crisis is a life-threatening medical emergency associated with high mortality unless it is promptly recognized and treated.

The most common causes of AI are outlined in the context, with primary AI most commonly due to autoimmune adrenalitis (Addison’s disease) in the United States and other first-world countries.

Secondary AI is more common than primary AI and is caused by any process that leads to deficiency of ACTH.

**RECENT GUIDELINE OR UPDATES**

**If you suspect an established or developing adrenal crisis in a patient**

Please immediately inject 100 mg hydrocortisone i.v. or i.m. followed by rapid rehydration with i.v. Administration of 0.9% saline solution (or equivalent).

Please maintain the patient on hydrocortisone at a dose of 200mg hydrocortisone per 24 hours (preferably by continuous i.v. infusion, alternatively by i.v. or i.m. injection of 50mg hydrocortisone every 6 hours) until clinical recovery and further guidance by an endocrinologist.

Adrenal crisis can be a manifestation of previously undiagnosed adrenal failure. Patients taking exogenous glucocorticoids across any route (oral, intra-articular, intramuscular, inhaled, nasal and topical preparations) being used to treat a variety of medical conditions can cause adrenal insufficiency by suppressing the hypothalamo-pituitary-adrenal axis. Adrenal crisis can also occur in patients with known adrenal insufficiency if existing cortisol replacement does not meet the increased need for cortisol, e.g. due to illness with fever, persistent vomiting or diarrhea, trauma or childbirth. Preparation for invasive diagnostic procedures such as colonoscopy and surgery requiring general anesthesia are further risk factors for adrenal crises.

To prevent adrenal crisis in all these situations, hydrocortisone needs to be administered and maintained as per above.

Do not hesitate to give high doses of hydrocortisone to a pregnant woman; hydrocortisone is inactivated in the placenta and does NOT affect the unborn baby. However, failure to treat a pregnant woman with adrenal insufficiency can result in the death of the mother and/or loss of the child.

Children can be given i.v. or i.m. hydrocortisone as follows:

* Infants up to 1 year - 25mg
* children 1 to 5 years - 50mg
* children over 6 years - 100mg

These doses can be repeated three or four times in 24 hours, depending upon the condition being treated and the patient's response.

*REFERENCES:*

[Adrenal Crisis - StatPearls - NCBI Bookshelf](https://www.ncbi.nlm.nih.gov/books/NBK499968/#article-17224.s10)

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**HYPERALDOSTERONISM**

*ALTERNATIVE NAMES:* Alternative names for hyperaldosteronism include “primary aldosteronism”, also known as “Conn’s syndrome”.

This condition is characterized by the overproduction of aldosterone by the adrenal glands, leading to high blood pressure and low potassium levels.

“Secondary hyperaldosteronism” refers to cases where the “excess aldosterone production” is due to factors outside the adrenal glands, such as reduced blood flow to the kidneys or other underlying health issues.

**DEFINITION / DESCRIPTION**

**Hyperaldosteronism is a condition in which one or both of your** adrenal glands produce too much aldosterone. Aldosterone is a hormone that helps regulate your blood pressure by controlling the levels of potassium and sodium in your blood.

Your adrenal glands are part of your endocrine system. They make hormones your body needs to carry out daily functions. You have two adrenal glands — one atop each kidney.

*There are two main types of hyperaldosteronism:*

* Primary hyperaldosteronism (Conn’s syndrome): An issue within your adrenal glands causes them to release too much aldosterone.
* Secondary hyperaldosteronism: An issue somewhere else in your body causes your adrenal glands to make too much aldosterone.

Hyperaldosteronism causes high blood pressure (hypertension) and low potassium levels in your blood.

Hyperaldosteronism mostly affects people 30 to 50 years old. It more often affects women than men.

It’s difficult for researchers to estimate how common hyperaldosteronism is. Some studies suggest that 5% to 10% of people with high blood pressure have primary hyperaldosteronism. Experts estimate that as many as 25% of people who have medication-resistant high blood pressure may have hyperaldosteronism.

**CAUSES**

**Causes hyperaldosteronism**

Hyperaldosteronism has different causes depending on the type: primary or secondary.

Causes of primary hyperaldosteronism

Primary hyperaldosteronism happens when there’s an issue within your adrenal glands that causes them to produce too much aldosterone.

Adrenal adenomas (noncancerous tumors) are the most common cause of primary hyperaldosteronism.

Rarer causes of primary hyperaldosteronism include:

* Unilateral adrenal hyperplasia (one enlarged adrenal gland).
* Aldosterone-producing adrenocortical carcinomas (cancerous tumors).
* Familial hyperaldosteronism type 1 (a condition you inherit from your biological parents).

**Causes of secondary hyperaldosteronism**

Reduced blood flow to your kidneys causes secondary aldosteronism.

To understand why this happens, it’s important to know that aldosterone is part of a complex chain of hormone reactions that regulates your blood pressure.

This is known as the renin-angiotensin-aldosterone system, and it involves the following steps:

* Your kidneys release renin (an enzyme) when your body detects low blood pressure or low sodium in your blood. Renin converts angiotensinogen (a precursor of angiotensin that’s produced by your liver) to angiotensin I (angiotensin is a hormone that narrows your blood vessels).
* Angiotensin I is converted to angiotensin II.
* Angiotensin II narrows your blood vessels and stimulates the release of aldosterone.

Reduced blood flow to your kidneys “mistakenly” triggers the renin-angiotensin-aldosterone system, which results in excess aldosterone in your body.

Causes of reduced kidney blood flow and secondary hyperaldosteronism include:

* Obstructive renal artery disease.
* Renal hypertension.
* Conditions that cause fluid retention (edema), such as heart failure, cirrhosis of the liver and nephrotic syndrome.

**RISK FACTORS**

Hyperaldosteronism, characterized by excessive secretion of aldosterone, has several risk factors. One of the key risk factors is age, with the condition most commonly affecting individuals between the ages of 30 and 50 years old.

Additionally, there is a noted greater risk for hypertension-related morbidity and mortality in blacks compared to whites, although no studies indicate that the prevalence of primary hyperaldosteronism is significantly higher in blacks.

Inherited forms of primary hyperaldosteronism account for only 1% of cases but are more likely to occur during childhood years.

Other risk factors include the presence of a tumor in the adrenal gland, which can lead to primary hyperaldosteronism, or conditions that cause secondary hyperaldosteronism such as cardiac failure, cirrhosis of the liver, and nephrotic (kidney) syndrome.

Moreover, the risk of developing hyperaldosteronism can be influenced by genetic factors, as mutations in certain genes, such as the KCNJ5 gene, have been associated with aldosterone-producing adenomas.

It is also important to note that the duration of the disease before diagnosis is a significant prognostic factor, with longer durations potentially leading to more severe complications.

***Risk Factors for Hyperaldosteronism***

Factors associated with an increased risk for hyperaldosteronism include:

* Family history of hypertension or cardiovascular events at young ages
* Hypertension, diagnosed before age 40
* Hypokalemia, whether spontaneous or induced by thiazide diuretics
* Incidental discovery of an adrenal adenoma in a patient with hypertension, particularly if the blood pressure is difficult to control
* Resistant or intractable hypertension, which remains poorly controlled despite the use of 3 or more standard antihypertensive medications, including a diuretic

**SIGNS / SYMPTOMS**

The symptoms of hyperaldosteronism can vary based on the severity of the condition. Some people with mild cases of hyperaldosteronism have no symptoms (are asymptomatic).

The most common symptom of hyperaldosteronism is high blood pressure (hypertension), especially medication-resistant hypertension.

If you experience other symptoms, they’ll probably be caused by having moderate to severe high blood pressure and/or low potassium levels (hypokalemia).

Symptoms of high blood pressure include:

* Headaches.
* Dizziness.
* Vision changes.
* Difficulty breathing.

Symptoms of low potassium include:

* Muscle weakness (which can lead to temporary paralysis in severe cases).
* Muscle spasms.
* Tingling and numbness.
* Fatigue.
* Extreme thirst (polydipsia).
* Frequent urination (peeing).

**DIAGNOSIS METHODS AND TESTS**

A healthcare provider will diagnose hyperaldosteronism with blood tests. However, many people never have hyperaldosteronism diagnosed because several conditions and risk factors can cause high blood pressure.

General signs of hyperaldosteronism include medication-resistant high blood pressure and the following results of an electrolyte blood panel:

* Mildly high sodium level (hypernatremia).
* Mildly low magnesium level (hypomagnesemia).

If your healthcare provider thinks you might have hyperaldosteronism based on these signs and your symptoms, they’ll likely order one of two blood tests: plasma renin concentration (PRC) or plasma renin activity (PRA).

If you have primary hyperaldosteronism, your PRC and PRA levels will be lower than normal. In secondary hyperaldosteronism, the levels will be higher than normal.

You may also need an aldosterone suppression test. This test involves consuming a certain amount of sodium (salt) orally or through an IV over a certain amount of time. You’ll then provide urine (pee) samples over a 24-hour period so that a laboratory can measure the amount of aldosterone in your pee.

If these tests confirm you have hyperaldosteronism, your provider will order additional tests to determine the cause. For example, they may recommend an imaging test such as a CT (computed tomography) scan to check for a tumor that could be causing hyperaldosteronism.

**MANAGEMENT AND TREATMENT OPTIONS**

The treatment of hyperaldosteronism depends on what’s causing it. But the main goal is to manage your blood pressure.

Healthcare providers usually recommend treating primary hyperaldosteronism caused by an adrenal gland tumor by surgically removing the tumor. In some cases, these tumors can be treated with only medication. Even after surgery, you might still have high blood pressure and need to take medicine to manage it.

Providers treat secondary hyperaldosteronism by managing your blood pressure with medications and treating the underlying cause (such as heart failure).

Medications that can help treat hyperaldosteronism include:

* Spironolactone (Aldactone®).
* Eplerenone (Inspra®).
* Amiloride (Midamor®).

Men may experience erectile dysfunction and gynecomastia (enlarged male breast tissue) with long-term use of medicines that block the effects of aldosterone, such as spironolactone.

***Unilateral Primary Hyperaldosteronism Management***

Primary hyperaldosteronism caused by unilateral disease is best treated surgically. Robotic or laparoscopic adrenalectomy is preferred as these procedures are associated with fewer complications and a shorter hospital stay compared to open surgery.Complete adrenalectomy is preferred to partial gland removal due to greater efficacy and resolution of symptoms. Primary hyperaldosteronism is the most frequently encountered surgically curable etiology of hypertension.

Preoperative spironolactone to control blood pressure for 4 to 6 weeks is recommended. Patients who fail to normalize their blood pressure on spironolactone preoperatively are likely to continue to be hypertensive even after surgery. Following surgery, about two-thirds of patients will eventually develop stable, normal blood pressure, although this may take a year. Please see the companion StatPearls' reference resource, "Conn Syndrome," for more information.

Patients with hyperaldosteronism due to unilateral disease fare better long-term with surgery than with medical therapy regarding blood pressure control, maintaining serum potassium levels, and improved vascular remodeling. Failure of surgery to control hypertension despite the normalization of aldosterone levels suggests the following:

* An erroneous or inadequate initial diagnosis of unilateral hyperaldosteronism
* Underlying essential hypertension
* Vascular abnormalities or damage from chronic hyperaldosteronism
* Other unrelated causes of hypertension (eg, pheochromocytoma or renovascular disease)

Good outcomes from surgery without adequate localization occur in less than 20% of patients. The medical therapy of choice for nonsurgical candidates is mineralocorticoid receptor antagonists, such as spironolactone and eplerenone.

Amiloride, a potassium-sparing diuretic, may also be used.

Transcatheter and percutaneous adrenal ablation appear to be acceptable, less invasive surgical therapies for primary unilateral hyperaldosteronism, with a clinical success rate reported at about 75%.These procedures are currently recommended for suitable patients unwilling to have surgery or take long-term medications.Partial adrenalectomy may be possible in some patients as it provides similar outcomes with fewer postoperative complications, but it carries a potential risk of leaving part of the abnormal aldosterone-secreting tissue behind

***Treatment of Primary Hyperaldosteronism Secondary to Bilateral Hyperplasia***

Mineralocorticoid receptor antagonists are the treatments of choice for primary hyperaldosteronism caused by bilateral hyperplasia and for patients who are not surgical candidates. Spironolactone or eplerenone are most commonly used. The selection of these agents depends on the adverse effect profile, physician experience, and individual patient characteristics.

* **Spironolactone** is usually the preferred medical therapy, starting at 12.5 to 25 mg daily and titrated upward every 2 weeks according to the 2016 Endocrine Society Guidelines.Maintenance is often reached at a daily dosage of about 100 mg of spironolactone. Gynecomastia is a significant known adverse effect of spironolactone use in men, which may occur in up to 50% of male patients who take more than 150 mg daily.
* **Eplerenone** is a more specific medication that, unlike spironolactone, does not block androgen receptors. This makes it more acceptable and preferred for long-term treatment in men as it avoids possible gynecomastia and erectile dysfunction, especially if low-dose spironolactone is not effective. Eplerenone has a relatively short half-life of about 4 hours, which is longer than spironolactone's half-life of only 1.4 hours. However, spironolactone is more effective in controlling blood pressure. Eplerenone is usually started at 50 mg daily and titrated upward, up to a maximum of about 200 mg twice a day.

Patients with bilateral or idiopathic hyperaldosteronism are typically treated medically with either spironolactone or eplerenone for blood pressure control but still tend to have higher rates of cardiovascular events than other hypertensive patients, as higher levels of serum aldosterone correspond to a greater cardiovascular risk. This has led to investigations into alternative therapies where standard surgery could not be utilized.

The feasibility of bilateral superselective adrenal artery embolization for treating idiopathic primary hyperaldosteronism has been demonstrated. Early studies indicate that such selective embolization therapy produces long-term, sustained improvement in serum aldosterone levels, aldosterone: renin ratios, hypokalemia, and blood pressure with no significant side effects or adverse events after 1 year of follow-up.This suggests that bilateral superselective adrenal artery embolization could represent a reasonable and effective alternative therapy for idiopathic primary hyperaldosteronism.

***Other Potassium-Sparing Diuretics***

The clinical course ultimately dictates the drug selection, dosage, and frequency. Reports of spontaneous remission of primary hyperaldosteronism after long-term therapy with mineralocorticoid receptor antagonist medications are rare. Triamterene and amiloride are potassium-sparing diuretics that may have an adjunctive role in managing aldosterone-related hypertension. However, amiloride is preferred as triamterene may form urinary calculi.

Canrenone is an active metabolite of spironolactone with similar activity but a much longer half-life (16.5 hours versus 1.4 hours) and fewer sexual adverse effects.Canrenone appears to have a direct beneficial myocardial effect beyond its antihypertensive actions. Although currently available in Europe, canrenone is not yet available in the United States. Medications specifically targeting aldosterone-producing adrenal CYP-11B2 cells are being developed and investigated, though this is complex due to the close similarity between CYP-11B2 and CYP-11B1 cells.

***Combination therapy***

Combination therapy, including medications, sodium restriction (usually <100 mEq/d), avoidance of alcohol, smoking cessation, aerobic exercise, and maintaining ideal body weight, generally yields the best results.Additional treatments, such as glucocorticoids, amiloride, and calcium channel blockers, may be used to manage hypertension and other symptoms not adequately controlled by mineralocorticoid receptor antagonists alone. In rare cases, surgery involving bilateral adrenalectomies may be considered for patients with hyperaldosteronism secondary to bilateral adrenal hyperplasia who are refractory to maximum medical treatment.

***Secondary Hyperaldosteronism Management***

Secondary hyperaldosteronism is best managed by addressing the underlying disease, which typically resolves the symptoms. ACE inhibitors (ACE I) and angiotensin receptor blockers are preferred for blood pressure control in these patients due to their renal protective benefits. In addition, salt restriction is recommended for better control of blood pressure.

Potassium supplements and potassium-sparing diuretics may also be used to manage secondary hyperaldosteronism. The treatment approach is similar to that for primary hyperaldosteronism caused by idiopathic adrenal hyperplasia. In cases of renal artery stenosis, surgical intervention or revascularization may be necessary to achieve optimal blood pressure control.

**OUTLOOK / PROGNOSIS**

The prognosis of hyperaldosteronism varies depending on what caused it.

The outlook for primary hyperaldosteronism is generally good if it’s diagnosed and treated early. The outlook for secondary hyperaldosteronism depends on the cause of the condition.

The most common complications of hyperaldosteronism are cardiovascular issues caused by high blood pressure, including:

* Atrial fibrillation.
* Left ventricular hypertrophy.
* Heart attack.
* Stroke.

Few studies have examined mortality rates for either form of hyperaldosteronism, but results suggest that the reported 10-year survival rates for treated patients range from 90% to 95%. The most common morbidity associated with hyperaldosteronism is cardiovascular-related, although overall mortality rates do not significantly differ from those of the general population.

If hypokalemia persists, it can lead to symptoms such as weakness, paralysis, constipation, and polyuria. Additionally, primary hyperaldosteronism and hypokalemia can impair insulin secretion, increasing the risk of developing diabetes mellitus. About two-thirds of patients become normotensive after adrenal surgery, although this improvement may take up to a year. By 5 years post-surgery, about half of these patients remain normotensive without medication. Untreated hyperaldosteronism is associated with significant morbidity and mortality, largely due to uncontrolled hypertension and cardiac arrhythmias.

**POSSIBLE COMPLICATIONS**

The most common complication and comorbidity associated with hyperaldosteronism is the increased risk of cardiovascular mortality due to excessive aldosterone secretion. Clinical manifestations can include atrial fibrillation, left ventricular hypertrophy, hypertension, myocardial infarction, and stroke. In addition, myocardial fibrosis has been reported in patients with long-standing hyperaldosteronism.

Hyperaldosteronism, also known as primary aldosteronism or Conn's syndrome, can lead to several serious complications if left untreated. The most common complications are cardiovascular issues caused by high blood pressure, including atrial fibrillation, left ventricular hypertrophy, heart attack, and stroke.

Additionally, untreated primary aldosteronism can lead to life-threatening complications like stroke, heart attack, and kidney failure.

The condition can also result in electrolyte imbalances, such as low potassium levels, which can cause heart rhythm irregularities (arrhythmia).

Secondary hyperaldosteronism, on the other hand, is generally related to hypertension and other underlying conditions such as cardiac failure, cirrhosis of the liver, and nephrotic syndrome.

The main complication of hyperaldosteronism is cardiovascular disease, which increases the risk of heart attack, stroke, and death.

**PREVENTION TIPS**

There is no known way to prevent hyperaldosteronism, as it is typically caused by underlying conditions such as adrenal gland tumors or genetic disorders.

However, managing risk factors associated with high blood pressure may help in reducing the impact of the condition. These include maintaining a healthy lifestyle with regular exercise, a balanced diet low in salt, limiting alcohol and caffeine intake, and quitting smoking.

Additionally, monitoring blood pressure regularly and seeking medical attention if symptoms of high blood pressure or low potassium levels occur can aid in early detection and management.

In most cases, there’s nothing you can do to prevent hyperaldosteronism.

**WHEN TO SEE A DOCTOR / RED FLAG**

***When should I see my healthcare provider about hyperaldosteronism?***

If you’ve been diagnosed with hyperaldosteronism, you’ll need to see your healthcare provider regularly to make sure your medication dosage is working.

Visit a healthcare provider if you notice any new symptoms or if your symptoms are changing

**DIFFERENTIAL DIAGNOSIS**

**Differential Diagnosis of Hyperaldosteronism**

1. Primary Hyperaldosteronism Causes

* Aldosterone-producing adenoma (Conn syndrome)
* Bilateral adrenal hyperplasia (idiopathic hyperaldosteronism)
* Adrenal carcinoma (rare)
* Adrenal incidentaloma with aldosterone secretion
* Familial hyperaldosteronism types I, II, III
* Congenital adrenal hyperplasia (e.g., 11β-hydroxylase deficiency, 17α-hydroxylase deficiency)

***2. Secondary Hyperaldosteronism Causes***

* Renovascular hypertension (renal artery stenosis)
* Heart failure, cirrhosis, nephrotic syndrome (edematous states causing renin activation)
* Bartter syndrome and Gitelman syndrome (mimic secondary hyperaldosteronism but with normal/low blood pressure)
* Excessive licorice consumption (inhibits 11β-HSD2 causing apparent mineralocorticoid excess)
* Cushing syndrome (excess cortisol with mineralocorticoid effects)
* Apparent mineralocorticoid excess syndrome (genetic or acquired)
* Liddle syndrome (pseudo aldosteronism with low renin and aldosterone)
* Acromegaly (can stimulate renin-angiotensin-aldosterone system)

***3. Other Conditions to Consider***

* Adrenal surgery or trauma history
* Medication effects (diuretics, beta-blockers, ACE inhibitors affecting renin-aldosterone axis)
* Non-aldosterone mineralocorticoid excess states

Presentations similar to hyperaldosteronism can be observed in various conditions, including essential hypertension, Liddle syndrome, syndrome of apparent mineralocorticoid excess, congenital adrenal hyperplasia, primary glucocorticoid resistance, Cushing syndrome (hypercortisolism), aldosterone-producing renin-responsive adenomas, adrenocortical carcinomas, metabolic alkalosis, diabetes insipidus, preeclampsia, Gitelman syndrome, renal artery stenosis, Bartter syndrome, pheochromocytoma, Chrétien syndrome, excessive licorice intake, and ectopic ACTH syndrome.

The following presentations are some of the shared clinical features:

* 17-Alpha-hydroxylase deficiency: This condition can closely mimic hyperaldosteronism Patients typically present with hypogonadism and immature genitalia. Genetic testing may be required for a definitive diagnosis.
* Chrétien syndrome: This syndrome is a rare disorder caused by excess secretion of proopiomelanocortin, a precursor of ACTH, from a pituitary adenoma. This results in adrenocortical hypertension.
* Congenital adrenal hyperplasia: This condition is typically associated with a family history of 11-beta-hydroxylase or 17-alpha-hydroxylase deficiency and is characterized by low aldosterone levels.
* Ectopic ACTH syndrome: This condition is characterized by elevated ACTH levels that cannot be suppressed with high-dose dexamethasone. These patients often have an underlying tumor.
* Essential hypertension: This condition typically presents with a normal PAC/PRA ratio.
* Excessive licorice intake: This condition inhibits the renal conversion of cortisol to cortisone, producing a cortisol excess, which acts as a mineralocorticoid agonist simulating hyperaldosteronism.
* Liddle syndrome: This syndrome is a rare genetic disorder that presents with low aldosterone levels and typically manifests in childhood. Symptoms include hypertension, hypokalemia, and metabolic alkalosis, which are similar to mineralocorticoid excess disorders. Liddle syndrome is often referred to as pseudohyperaldosteronism, which is characterized by high urinary potassium secretion and sodium reabsorption in the renal collecting tubules despite low aldosterone levels.
* Primary glucocorticoid resistance: This condition features low aldosterone levels, elevated ACTH and cortisol, and often has a family history of the syndrome.
* Syndrome of apparent mineralocorticoid excess: This syndrome presents with hypertension, low aldosterone levels, high urinary free cortisol levels, hypokalemia, ACTH suppression, hereditary implications, and a history of excessive licorice consumption. Genetically, it is an autosomal recessive disorder.

***Hyperaldosteronism and Hypercortisolism***

Hyperaldosteronism and hypercortisolism (ie, Cushing syndrome and disease) share several clinical and laboratory features due to their involvement with abnormal adrenal function. Both conditions are 3 times more common in women than in men, are most frequently diagnosed in patients aged 25 to 50, and typically present with hypertension, hypokalemia, and hypernatremia.

In hyperaldosteronism, patients typically present with intractable hypertension resistant to standard drug therapies. Hyperaldosteronism is a relatively common disorder, affecting approximately 10% of all hypertensive individuals, with over 20% experiencing resistant hypertension.Therefore, hyperaldosteronism should be considered in any patient with hypertension that is difficult to control. Diagnosis often begins with a blood test showing a high aldosterone-to-renin ratio and low plasma renin levels, as previously described.

Conversely, patients with hypercortisolism often exhibit less severe hypertension. Hypercortisolism is rare, occurring at an estimated rate of 60 cases per million individuals.Hypercortisolism is initially suspected based on clinical features such as weight gain, muscle weakness, thin extremities, a rounded face, a fat pad at the base of the neck, easy bruising, thin skin, acne, hirsutism, and purplish stretch marks. A 24-hour urine test for free cortisol is typically used for the initial diagnosis, while a dexamethasone suppression test serves as a confirmatory measure.

**RECENT GUIDELINES OR UPDATES**

The recent guidelines for hyperaldosteronism, specifically primary aldosteronism (PA), emphasize the importance of case detection, diagnosis, and treatment. According to the Endocrine Society's clinical practice guidelines, primary aldosteronism is a common cause of secondary hypertension and has a higher cardiovascular risk profile compared to essential hypertension.

The guidelines recommend screening for PA in patients with sustained blood pressure above 150/100 mm Hg on three separate measurements, hypertension resistant to three conventional antihypertensive drugs, or controlled BP on four or more medications.

The plasma aldosterone/renin ratio (ARR) is recommended as the initial test for detecting PA in these patient groups.

For patients with a positive ARR, confirmatory tests are advised to definitively confirm or exclude the diagnosis. However, in cases of spontaneous hypokalemia with plasma renin below detection levels and plasma aldosterone concentration (PAC) >20 ng/dL (550 pmol/L), further confirmatory testing may not be necessary.

For patients with unilateral PA, unilateral laparoscopic adrenalectomy is recommended as a curative treatment. For those with bilateral adrenal disease, medical treatment with a mineralocorticoid receptor antagonist is advised.

In patients with glucocorticoid-remediable aldosteronism (GRA), the first-line treatment is the lowest dose of glucocorticoid to lower ACTH and normalize blood pressure and potassium levels.

The guidelines also highlight the importance of genetic testing for familial hyperaldosteronism type 1 in patients with early-onset PA or a family history of early-onset hypertension or stroke.

Additionally, the guidelines emphasize the need for regular follow-up in adrenalectomized patients to confirm biochemical cure and monitor for potential complications.

Recent updates also include the use of adrenal venous sampling (AVS) to differentiate between unilateral and bilateral adrenal disease, which is crucial for determining the appropriate treatment.

The guidelines also address the management of PA in special populations, such as pregnant women, where systematic exclusion of PA is recommended due to the risks associated with undiagnosed PA.

**EPIDEMIOLOGY**

Primary hyperaldosteronism can be seen in at least 10% of all patients with hypertension. The incidence of primary hyperaldosteronism increases with the severity of the associated hypertension. The prevalence is over 20% in patients with resistant hypertension, especially in those younger than 40 or those who exhibit hypokalemia. Earlier studies grossly underestimated the incidence of hyperaldosteronism due to differences in patient selection, diagnostic methods, definitions of hypertension, and a general failure to test patients who met the currently recommended criteria for screening.

Secondary hyperaldosteronism is diagnosed less often than primary hyperaldosteronism. Both primary and secondary hyperaldosteronism are more prevalent in women. Africans and Black Americans tend to have a higher prevalence of hyperaldosteronism than the general population, particularly idiopathic bilateral adrenal hyperplasia.

Primary hyperaldosteronism is a rare condition in children. The youngest child reported with an aldosterone-secreting adenoma was aged 3 years. Earlier use of hypokalemia as a diagnostic requirement, as advocated by some authorities, may have led to under recognition of the contribution of primary hyperaldosteronism to hypertension.

The prevalence rate for PA in hypertensive patients varies between studies, ranging from 4.6% to 16.6% in reports using confirmatory tests to diagnose PA.Patients with PA also make up 17-23% of the treatment-resistant hypertensive population.

Most of the hyperaldosteronism observed in the general population is sporadic, with most cases due to bilateral adrenal hyperplasia. APAs are likely to be diagnosed earlier than IHA because they are more likely than IHA to produce early symptomatic hypertension and hypokalemia. APAs account for 40% of cases of primary hyperaldosteronism.

It is possible that the distinction between adenoma and hyperplasia is not as clear as was once assumed. In one third of cases, associated hyperplasia or nodules of the adjacent zona glomerulosa is present, implying that the adenoma may have arisen in previously hyperplastic tissue.

Inherited forms of primary hyperaldosteronism (ie, FH-I [GRA], FH-II, and a very rare form known as FH type III [FH-III]) account for approximately 1% of cases of primary hyperaldosteronism, though they are more likely to occur during childhood and adolescent years than other forms of primary hyperaldosteronism are.

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**HYPOALDOSTERONISM**

*ALTERNATIVE NAMES:* Hypoaldosteronism is also known as “low aldosterone syndrome”. Other terms used to describe this condition include “aldosterone deficiency”, and it can be classified into different types such as “hyporeninemic hypoaldosteronism”. Additionally, it is sometimes referred to as “type 4 renal tubular acidosis”.

**DEFINITION / DESCRIPTION**

Hypoaldosteronism is a condition characterized by the insufficient production or action of aldosterone, a crucial hormone in the regulation of sodium and potassium balance within the body. This inadequacy can precipitate a range of clinical manifestations and pose significant health risks if left unmanaged.

Aldosterone, a mineralocorticoid hormone produced by the adrenal glands, plays an indispensable role in maintaining electrolyte balance by promoting sodium retention and potassium excretion in the kidneys.

**SIGNS / SYMPTOMS**

Hypoaldosteronism is characterized by low levels of the hormone aldosterone, leading to electrolyte imbalances and various symptoms. The signs and symptoms of hypoaldosteronism include muscle weakness, nausea, palpitations, irregular heartbeat, and abnormal blood pressure.

Additionally, patients may experience hyponatremia (low sodium levels), hyperkalemia (high potassium levels), and metabolic acidosis.

These biochemical changes can result in weakness, postural hypotension (a decrease in blood pressure upon standing), salt craving, and heart block, which may be fatal.

In some cases, hypoaldosteronism may present with high blood potassium and is associated with 'type 4 renal tubular acidosis'.

**Symptoms of Hypoaldosteronism**

The clinical presentation of hypoaldosteronism can be subtle, often overlapping with other conditions. Common symptoms include:

* Fatigue
* Muscle weakness
* Nausea
* Heart palpitations
* Low blood pressure

These symptoms stem from the body’s inability to maintain proper sodium and potassium levels, resulting in electrolyte imbalances that can affect various bodily functions.

**CAUSES**

**Causes of Hypoaldosteronism**

Hypoaldosteronism can be attributed to several underlying causes, which can be broadly categorized into primary and secondary forms.

***Primary Hypoaldosteronism***

Primary hypoaldosteronism results from intrinsic defects within the adrenal gland itself. Causes may include:

* Congenital adrenal hyperplasia
* Autoimmune adrenalitis
* Genetic mutations affecting aldosterone synthesis

***Secondary Hypoaldosteronism***

Secondary hypoaldosteronism, on the other hand, is often a consequence of factors extrinsic to the adrenal glands. These may involve:

* Renal tubular disorders
* Diabetic nephropathy
* Medications such as ACE inhibitors and nonsteroidal anti-inflammatory drugs (NSAIDs)

Understanding the etiology is crucial as it guides the diagnostic and therapeutic approach to managing the condition.

**RISK FACTORS**

Hyperaldosteronism, characterized by excessive secretion of aldosterone, has several risk factors. One of the key risk factors is age, with the condition most commonly affecting individuals between the ages of 30 and 50 years old.

Additionally, there is a noted greater risk for hypertension-related morbidity and mortality in blacks compared to whites, although no studies indicate that the prevalence of primary hyperaldosteronism is significantly higher in blacks.

Inherited forms of primary hyperaldosteronism account for only 1% of cases but are more likely to occur during childhood years.

Other risk factors include the presence of a tumor in the adrenal gland, which can lead to primary hyperaldosteronism, or conditions that cause secondary hyperaldosteronism such as cardiac failure, cirrhosis of the liver, and nephrotic (kidney) syndrome.

Moreover, the risk of developing hyperaldosteronism can be influenced by genetic factors, as mutations in certain genes, such as the KCNJ5 gene, have been associated with aldosterone-producing adenomas.

It is also important to note that the duration of the disease before diagnosis is a significant prognostic factor, with longer durations potentially leading to more severe complications.

**DIAGNOSIS METHODS**

**Diagnosis of Hypoaldosteronism**

The diagnostic process for hypoaldosteronism involves a combination of clinical evaluation, laboratory testing, and imaging studies.

**Clinical Evaluation**

A thorough clinical assessment is essential to identify symptoms and potential risk factors associated with hypoaldosteronism. A detailed medical history and physical examination can provide initial clues.

**Laboratory Tests**

Laboratory investigations are pivotal in confirming the diagnosis of hypoaldosteronism. Key tests include:

* Serum electrolytes to check for hyperkalemia and hyponatremia
* Plasma aldosterone concentration (PAC)
* Plasma renin activity (PRA)
* The aldosterone-to-renin ratio (ARR) is a critical parameter, with a low ratio indicative of hypoaldosteronism.

**Imaging Studies**

In certain cases, imaging studies such as a CT scan of the adrenal glands may be warranted to identify structural abnormalities or adrenal hyperplasia.

**TREATMENT OPTIONS**

**Management of Hypoaldosteronism**

The management of hypoaldosteronism is multifaceted, focusing on correcting electrolyte imbalances and addressing the underlying cause.

**Electrolyte Management**

The primary aim is to restore normal sodium and potassium levels. This can be achieved through dietary modifications and the use of mineralocorticoid replacement therapy, such as fludrocortisone, which mimics the action of aldosterone.

**Addressing Underlying Causes**

Effective management also necessitates addressing the root cause of hypoaldosteronism. For instance, in cases secondary to medication use, altering the medication regimen might be necessary.

**Monitoring and Follow-up**

Regular monitoring of serum electrolytes and blood pressure is essential to ensure therapeutic efficacy and prevent complications.

The treatment of HA presenting in infancy and childhood with a salt-wasting crisis in ALD synthase deficiency and PHA AD is aggressive rehydration with NaCl. Before a definitive diagnosis of HA is made, after drawing a 'critical sample' of blood, the infants are treated for presumed CAH with intravenous hydrocortisone (HC) in stress doses. This also has adequate mineralocorticoid activity and will tide over the crises. If 17 OHP levels are in range, the HC can be discontinued after the infant stabilizes, and the mineralocorticoid fludrocortisone (FC) can be substituted orally at doses starting at 150 micrograms / m2 body surface area in ALD synthase deficiency. The younger the child, the greater are the doses of fludrocortisone because of drug insensitivity in infants and young children. Fludrocortisone is ineffective in PHA and NaCl, sodium bicarbonate, cation exchange resins, and in very severe cases, peritoneal dialysis is needed to counter hyperkalemia; thiazide diuretics to reduce hyperkalemia and hypercalciuria and indomethacin to counter polyuria, Na loss and reduce hypercalciuria are useful in PHA AD.

PHA AR is a much more severe disease with multi-organ involvement and may need very high doses of salt replacement and often show resistance to therapy. Carbenoxolone, an 11 beta HSD 2 inhibitor, prevents cortisol degradation and allows it to stimulate the MR receptor and function as a mineralocorticoid that may be useful in PHA AR.

In Conn syndrome, preoperatively, spironolactone, if used to control hypertension, should be stopped at least 3 days before surgery and any volume expansion corrected. Post adrenalectomy hypoaldosteronism is managed with fludrocortisone. Some patients may need extended support until the suppressed adrenal recovers.

Renal transplant patients treated with calcineurin inhibitors present with hyperkalemia secondary to HA and respond to a low dose of fludrocortisone.

In type 4 RTA, fludrocortisone is useful in reducing hyperkalemia, but caution is required as Na retention, fluid overload, and precipitation of congestive heart failure are side-effects. The addition of a loop diuretic or even better thiazides that block the NCCT in the distal renal tubules may be necessary. Precipitating medications like NSAID and K+ sparing diuretics must be carefully reviewed and discontinued.

**PREVENTION TIPS**

Hypoaldosteronism is a condition characterized by decreased levels of the hormone aldosterone, which can lead to imbalances in electrolytes such as sodium and potassium, as well as metabolic acidosis. While there is no specific information on prevention tips for hypoaldosteronism in the provided context, managing underlying conditions and avoiding certain medications may help reduce the risk of developing the condition.

Hypoaldosteronism can be caused by various factors, including adrenal insufficiency, congenital adrenal hyperplasia, and certain medications such as diuretics, NSAIDs, and ACE inhibitors.

Therefore, managing these underlying conditions and being cautious with medication use may be important in preventing hypoaldosteronism.

In addition, maintaining a balanced diet with adequate sodium intake may be beneficial for individuals at risk of hypoaldosteronism. However, it is important to consult with a healthcare provider before making any significant changes to diet or medication regimen.

Overall, while there are no specific prevention tips for hypoaldosteronism, managing underlying conditions and being cautious with medication use may help reduce the risk of developing the condition.

**POSSIBLE COMPLICATIONS**

Hypoaldosteronism can lead to several complications, primarily due to the imbalance of electrolytes and the resulting effects on the body. One of the main complications is hyperkalemia, which is an elevated level of potassium in the blood. This can lead to muscle weakness, palpitations, and irregular heartbeat.

Additionally, hypoaldosteronism can cause hyponatremia (low sodium levels) and metabolic acidosis, which can result in symptoms such as nausea and abnormal blood pressure.

In severe cases, particularly in newborns and infants, hypoaldosteronism can lead to salt wasting, hypovolemia, and failure to thrive.

Furthermore, the condition can contribute to cardiovascular issues, similar to those seen in hyperaldosteronism, although the specific complications may vary depending on the underlying cause and severity of the hypoaldosteronism.

It is important to manage hypoaldosteronism with appropriate treatment, such as mineralocorticoids like fludrocortisone, to prevent these complications.

**Complications of Hypoaldosteronism**

Without appropriate management, hypoaldosteronism can lead to severe complications, including:

* Persistent hyperkalemia, which can cause cardiac arrhythmias
* Hypotension and its associated risks
* Adrenal crisis in severe cases, necessitating emergency intervention

In patients treated for HA, overdosage with fludrocortisone can cause fluid retention, low K+, very suppressed PRC and precipitate congestive heart failure. Less severe but clinically significant side-effects include constipation due to increased colonic mucosal Na and water reabsorption, weight gain due to fluid retention and muscle weakness due to hypokalemia. Dosing should be titrated to PRC levels in the upper limits of the normal range. Undertreated children will have poor growth. When the diagnosis is delayed in infants with severe disease, mortality is increased.

**OUTLOOK / PROGNOSIS**

**Prognosis of Hypoaldosteronism**

The prognosis of hypoaldosteronism largely depends on the underlying cause and the timeliness of intervention. With adequate treatment and monitoring, individuals can maintain a good quality of life. However, those with genetic or chronic forms may require long-term management to mitigate potential complications.

Prognosis is good in ALD synthase deficiency and PHA AD when identified early and promptly treated. Many children can be weaned off medications, and some go into remission as they grow. Older children who are inadequately treated have retarded growth or failure to thrive but adequately treated grow normally and have a good catch up growth. PHA AR patients do not as a rule improve and will need close monitoring. PHA III patients will be cured once their primary renal infection or obstruction is resolved.

Diligent management of medications causing HA will reduce morbidity considerably. Most patients with HA post-adrenalectomy for Conn's syndrome resolve early, while some at high-risk need surveillance.

**DIFFERENTIAL DIAGNOSIS**

Hypoaldosteronism can be differentiated from global adrenal failure by the presence of genital ambiguity in female infants and a high 17 OHP in both sexes in CAH. Addison's disease in older children and adults will have decreased serum cortisol and increased ACTH, present dramatically, and have physical findings like hyperpigmentation. Infants with congenital adrenal hypoplasia (AHC) present with salt-wasting and hyperpigmentation; cortisol deficiency appears later. It may be necessary to perform a cosyntropin stimulation test to confirm cortisol deficiency. Deficiency of cholesterol sidechain cleaving enzymes produce deficiencies in all three adrenal axes. Thus, salt-wasting, low cortisol, and ambiguous genitalia in male infants are seen.

Decreased ALD and increased PRC is a feature of ALD synthase deficiency, whereas PHA has very high PRC and ALD, although both conditions have low Na, high K+, and acidosis.

In the two forms of ALD synthase deficiency, 18 OHC is low to normal in type 1 and high in type 2 ALD synthase deficiency, and the urinary tetrahydro-aldosterone (THA), the metabolite of ALD is decreased in type 1 and low normal or normal in type 2 ALD synthase deficiency.

A definitive diagnosis of biosynthetic defects causing HA is by gene sequencing.

A preoperative aldosterone contralateral suppression index (*CSI -see image 1*) during adrenal venous sampling (AVS) is the ratio of ALD to Cortisol in the ipsilateral adrenal vein divided by a similar ratio in the external iliac vein. Patients with a contralateral suppression index of <0.47 are at risk for prolonged adrenal suppression and require close monitoring of serum K+ after unilateral adrenalectomy for Conn syndrome.

HA in the critically ill is not clinically significant due to high cortisol levels acting on the MR compensating for the absence of mineralocorticoid.

Some conditions have a low ALD level due to Na+ retention, hypertension, hypokalemia, suppressed PRC, and volume expansion. They should be distinguished from salt-losing causes of HA by the features mentioned. Examples are Liddle syndrome and the syndrome of mineralocorticoid excess due to 11 beta HSD2 inhibition. In Gordon syndrome, hypertension is accompanied by hyperkalemia, hyperchloremic acidosis, and suppressed renin due to volume expansion.

**RECENT GUIDELINES OR UPDATES**

The initial presentation of the salt-wasting crisis is to the pediatric emergency physician. The general pediatrician takes over the infant's care after stabilization and provides follow-up with periodic input from the pediatric endocrinologist. A clinical geneticist may be necessary to confirm a diagnosis of causes of HA. Pediatric nephrologists are involved when intractable hyperkalemia needs dialysis therapy. Coordinated care by all specialties and effective communication among them will reduce mortality and morbidity, ensure the growth and development of these affected children. [Level 5] In every step, nursing and clinical psychology play important roles.

Adults with Conn syndrome will need coordinated care of the endocrinologist, endocrine surgeon, laboratory medicine personnel, interventional radiologist, and nurses skilled in the post-operative care to manage HA in these patients effectively.

Adults and older adults with type 4 RTA can be effectively managed by the primary care physician in coordination with other specialists and improve patient outcomes.

Primary aldosteronism (PA) is a common secondary cause of hypertension, and recent guidelines emphasize the importance of early detection and targeted treatment to prevent cardiovascular and renal complications.

The Endocrine Society's updated guidelines recommend screening high-risk hypertensive patients and those with hypokalemia using the aldosterone-renin ratio (ARR) as the gold standard for case detection.

Confirmatory tests are necessary for patients with a positive ARR to definitively diagnose PA.

For patients with unilateral PA, adrenal vein sampling (AVS) is crucial for identifying the cause and achieving optimal outcomes, although it is technically challenging and not widely available.

Surgical treatment, such as laparoscopic adrenalectomy, is recommended for patients with documented unilateral PA, while medical treatment with mineralocorticoid receptor antagonists is advised for those who are not surgical candidates.

The guidelines also highlight the importance of genetic testing for familial forms of PA, particularly in young patients or those with a family history of early-onset PA or stroke.

Additionally, the 2016 update broadened the indications for screening to include patients with sustained blood pressure above 150/100 mm Hg, recognizing PA as a more common condition than previously thought.

These recommendations aim to improve the detection, diagnosis, and treatment of PA, ultimately reducing the risk of adverse cardiovascular events.

**EPIDEMIOLOGY**

The prevalence of congenital causes of selective HA is low, and that of PHA AD type I is less than 1:80000. Some causes of genetically inherited PHA I may be found in higher frequencies in certain ethnic populations.

Acquired causes are more frequent and commoner in hospitalized patients, children with type1 diabetes or sickle cell disease, adults with type 1 and 2 diabetes, and older adults on multiple medications known to affect the RAA axis. The incidence of contralateral adrenal suppression after adrenalectomy for Conn's syndrome is estimated at around 5 percent.

Hyperkalemia occurs with increased frequency in recipients of solid organ transplantation and subsequent use of calcineurin inhibitors and is estimated between 40 and 70 percent.

Hypoaldosteronism is a condition characterized by decreased levels of the hormone aldosterone, which plays a crucial role in regulating sodium and potassium levels in the blood. The epidemiology of hypoaldosteronism indicates that it affects both men and women equally, with a higher prevalence in middle-aged and older individuals. It is more commonly observed in African-American, Native American, and Hispanic populations.

In hospitalized patients, the incidence of hypoaldosteronism is approximately 3000 per 100,000 individuals, and the prevalence rate in the United States is estimated to be 200,000 cases.

The condition is also more prevalent in elderly patients who are on multiple medications, as polypharmacy increases the risk of drug-induced hypoaldosteronism.

In younger patients, hypoaldosteronism is seen in those with underlying conditions such as diabetes mellitus type I or sickle cell disease.

The epidemiology of hypoaldosteronism is influenced by various factors, including the presence of chronic diseases and the use of medications that affect the renin-angiotensin-aldosterone system.

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**PRIMARY ALDOSTERONISM**

**DEFINITION / DESCRIPTION**

Primary aldosteronism, also known as **Conn’s syndrome**, is a condition that occurs when your adrenal glands make too much aldosterone. Aldosterone is a steroid hormone that helps regulate sodium and potassium in your blood.

High blood pressure (hypertension) and low blood potassium levels (hypokalemia) are the defining features of primary aldosteronism. People with the condition may have other symptoms, too, like headaches, muscle cramps or excessive thirst.

Untreated primary aldosteronism can lead to serious complications like heart attack and kidney failure. But prompt treatment can manage the condition successfully.

Primary aldosteronism used to be a rare disorder. But today, 5% to 10% of adults with high blood pressure have it. It’s more common in women. Most people with this condition get a diagnosis in their 30s or 40s.

**SIGNS / SYMPTOMS**

People with primary aldosteronism usually develop high blood pressure and low potassium levels. Left unchecked, high blood pressure raises your risk for complications, including heart attack and stroke, while low potassium can cause heart rhythm irregularities (arrhythmia).

Other primary aldosteronism symptoms may include:

* Fatigue.
* Excessive thirst.
* Frequent urination (peeing more than you used to).
* Headache.
* Muscle cramps.
* Muscle weakness.
* Blurred vision.

**CAUSES**

**Causes primary aldosteronism**

Primary aldosteronism happens when your adrenal glands produce too much aldosterone. This hormone helps regulate your body’s balance of water, sodium (salt), blood volume and blood pressure.

Issues that can cause an overproduction of aldosterone include:

* Benign (noncancerous) tumors in one or both adrenal glands.
* Inherited disorders (like congenital adrenal hyperplasia).
* Adrenal cancer (rare).

***Secondary aldosteronism***

Primary aldosteronism occurs when there’s an issue with your adrenal glands themselves. But sometimes, underlying conditions can cause excess aldosterone production. When this happens, providers call it secondary aldosteronism. Conditions related to secondary aldosteronism include:

* Liver disease.
* Renal artery stenosis (a narrowing of the arteries that carry blood to your kidneys).
* Heart failure.
* Some types of kidney cancer.
* Pregnancy.

**RISK FACTORS**

**Risk factors for primary aldosteronism**

Anyone can develop primary aldosteronism. But it’s more common in people with:

* Low blood potassium levels.
* High blood pressure starting before age 30.
* High blood pressure requires three or more medications to manage.
* An adrenal tumor.

**POSSIBLE COMPLICATIONS**

***Complications of primary aldosteronism***

If you don’t treat primary aldosteronism, your blood pressure may increase to dangerous levels. It also disrupts the balance of electrolytes in your body. (Electrolytes are minerals that help balance the amount of water in your body.)

Electrolyte imbalances and prolonged high blood pressure increase your risk for serious complications like:

* Heart attack or heart failure.
* Irregular heartbeat.
* Kidney failure.
* Stroke.
* Temporary paralysis or the inability to move.

**DIAGNOSIS METHODS AND TESTS**

Healthcare providers use blood tests to diagnose primary aldosteronism. These tests measure:

* Levels of hormones (like aldosterone and renin) in your blood.
* Electrolytes, including sodium and potassium.

It might take several blood tests to get an accurate diagnosis. This is because many blood pressure medications can interfere with blood test results. To counteract this, your provider might switch up your medication occasionally to ensure accuracy.

***What tests will be done to diagnose primary aldosteronism?***

Your healthcare provider may recommend further testing to rule out adrenal gland tumors. These tests may include:

* Computed tomography (CT) scans, which use X-rays to create pictures of internal body structures.
* Magnetic resonance imaging (MRI), which uses radio waves and high-powered magnets to visualize the inside of your body.

**MANAGEMENT AND TREATMENT OPTIONS**

Primary aldosteronism treatment typically involves medication and/or surgery.

**Medication**

If both adrenal glands produce excess aldosterone, healthcare providers typically treat it with medications like spironolactone (Aldactone®) or eplerenone (Inspra®), which block the effects of aldosterone.

**Surgery**

If only one adrenal gland makes excess aldosterone, removing that gland (adrenalectomy) is an alternative to medication. In these cases, healthcare providers may suggest surgery.

Even after surgery, you might need medication until your blood pressure returns to normal. Your healthcare provider can tell you what to expect in your situation.

**OUTLOOK / PROGNOSIS**

Underlying hypertension (high blood pressure) — a hallmark of this condition — increases your risk for stroke, heart failure, kidney disease and other conditions. People with primary aldosteronism usually notice reduced symptoms with treatment. Serious long-term effects typically only occur in those with untreated primary aldosteronism.

***Outlook for primary aldosteronism***

The outlook for primary aldosteronism is excellent with appropriate treatment. That’s why it’s important to schedule a visit with a provider as soon as you notice symptoms.

Left untreated, primary aldosteronism can lead to life-threatening complications like stroke, heart attack and kidney failure.

**POSSIBLE COMPLICATIONS**

Hypoaldosteronism can lead to several complications, primarily due to the imbalance of electrolytes and the resulting effects on the body. One of the main complications is hyperkalemia, which is an elevated level of potassium in the blood. This can lead to muscle weakness, palpitations, and irregular heartbeat.

Additionally, hypoaldosteronism can cause hyponatremia (low sodium levels) and metabolic acidosis, which can result in symptoms such as nausea and abnormal blood pressure.

In severe cases, particularly in newborns and infants, hypoaldosteronism can lead to salt wasting, hypovolemia, and failure to thrive.

Furthermore, the condition can contribute to cardiovascular issues, similar to those seen in hyperaldosteronism, although the specific complications may vary depending on the underlying cause and severity of the hypoaldosteronism.

It is important to manage hypoaldosteronism with appropriate treatment, such as mineralocorticoids like fludrocortisone, to prevent these complications

People with Conn's syndrome, also known as primary aldosteronism, may experience several possible complications if left untreated. High blood pressure, a common symptom, can lead to serious health issues such as heart attack, stroke, and heart failure.

Additionally, low potassium levels can cause heart rhythm irregularities (arrhythmia).

Over time, untreated hyperaldosteronism can result in direct injury to heart tissues, leading to scarring and enlargement of the left side of the heart. It can also increase the risk of kidney failure and other cardiovascular diseases.

Furthermore, hypertension can lead to retinopathy and end-stage renal disease. Complications may also arise from the surgery used to treat Conn's syndrome.

**PREVENTION TIPS**

There is currently no known way to prevent Conn's syndrome, as it is primarily caused by factors beyond an individual's control, such as adrenal gland tumors or genetic conditions.

However, monitoring blood pressure regularly can help detect issues early, which is crucial for timely intervention.

While there are no specific prevention strategies, maintaining a healthy lifestyle may help manage risk factors associated with the condition. This includes eating nutritious foods, engaging in regular physical activity, and limiting sodium intake to help manage blood pressure.

It is also important to be aware of symptoms such as fatigue, excessive thirst, or frequent urination, and to consult a healthcare provider if these occur, as early diagnosis and treatment can significantly improve outcomes.

Currently, there’s no way to prevent this condition. Monitoring your blood pressure frequently can help spot issues.

You may be able to reduce your risk for primary aldosteronism by:

* Increasing your physical activity.
* Limiting alcohol intake.
* Reducing sodium in your diet.
* Stopping smoking.

**WHEN TO SEE A DOCTOR / RED FLAG**

If you develop symptoms like fatigue, excessive thirst or frequent urination, call a healthcare provider. They’ll need to run tests to determine a diagnosis; if there is an underlying issue, such as Conn’s syndrome.

Additionally, if you have consistently high blood pressure or low potassium, ask your provider if you should have testing for primary aldosteronism or related conditions.

If you have been diagnosed with primary aldosteronism, it is crucial to follow up with your healthcare provider regularly to monitor your condition and adjust treatment as needed.

If you notice any new symptoms or if your symptoms are changing, it is also advisable to visit a healthcare provider

**EPIDEMIOLOGY**

**Frequency**

*United States*

The exact prevalence of primary aldosteronism is unclear, but estimates suggest that 10-20% of essential hypertension cases, and up to 40% of resistant hypertension cases, may be due to primary aldosteronism. The prevalence of primary aldosteronism is probably higher in patients who have a low serum potassium level, in individuals who are elderly, and in persons who have HTN that is resistant to several medications.

*International*

No evidence demonstrates that primary aldosteronism, in its more common forms, occurs in relative excess in any part of the world.

*Race-, sex-, and age-related demographics*

Primary aldosteronism occurs worldwide. Several reports suggest a higher prevalence in African Americans, persons of African origin, and, potentially, other Black persons. (This appears to be particularly true of the IHA variant of the disease.) The greater prevalence may stem from genetic variation in the *ARMC5* gene that may be associated with primary hyperaldosteronism and is more common in the African American population.

APAs are more common in women than in men, with a female-to-male ratio of 2:1. The typical patient with an APA is a woman aged 30-50 years.

Accumulating data for IHA suggest different demographics for this condition, with the idiopathic disease being four times more prevalent in men than in women and peaking in the sixth decade of life.

**DIFFERENTIAL DIAGNOSIS**

**Differential Diagnoses of Primary Aldosteronism**

*1. Common Causes of Primary Aldosteronism*

* Aldosterone-Producing Adenoma (APA) / Conn Syndrome
  + Usually, a unilateral benign adrenal tumor produces excess aldosterone.
* Bilateral Adrenal Hyperplasia (Idiopathic Hyperaldosteronism, IHA)
  + Bilateral adrenal gland enlargement causing aldosterone overproduction.
* Unilateral Adrenal Hyperplasia (less common)
* Familial Hyperaldosteronism (Genetic Forms)
  + Type 1: Glucocorticoid-Remediable Aldosteronism (GRA)
  + Type 2, 3, 4, 5: Various genetic mutations (e.g., KCNJ5, CACNA1H, CACNA1D)

*2. Rare Causes of Primary Aldosteronism*

* Aldosterone-Producing Adrenal Cortical Carcinoma (very rare)
* Aldosterone-Producing Micronodules (<10 mm)
* Ectopic Aldosterone Secretion (extremely rare; reported from ovaries or kidneys in neoplastic disease)
* Co-secreting Adrenal Adenomas (producing both glucocorticoids and mineralocorticoids)

*3. Conditions to Differentiate from Primary Aldosteronism (Mimics or Secondary Causes)*

* Secondary Hyperaldosteronism
  + Renovascular hypertension (renal artery stenosis)
  + Edematous states: congestive heart failure, cirrhosis, nephrotic syndrome
  + Renin-driven aldosterone excess with elevated plasma renin activity
* Non-Aldosterone Mineralocorticoid Excess Syndromes
  + Apparent mineralocorticoid excess (e.g., licorice ingestion, 11β-HSD2 deficiency)
  + Liddle syndrome (ENaC channel mutation causing pseudo aldosteronism)
* Congenital Adrenal Hyperplasia (CAH)
  + Enzyme defects (e.g., 11β-hydroxylase or 17α-hydroxylase deficiency) causing mineralocorticoid excess
* Cushing Syndrome
  + Excess cortisol with mineralocorticoid effects

**RECENT GUIDELINES OR UPDATES**

Primary aldosteronism, also known as Conn's syndrome, is a condition characterized by the overproduction of aldosterone by the adrenal glands, leading to high blood pressure and low potassium levels.

Recent guidelines for the management of primary aldosteronism emphasize the importance of case detection, diagnosis, and treatment. These guidelines, developed by the Endocrine Society, provide recommendations for the diagnosis and management of patients with primary aldosteronism, including the use of blood tests to measure aldosterone and renin levels.

The diagnosis of Conn's syndrome typically involves measuring the levels of aldosterone and renin in the blood. In primary hyperaldosteronism, the aldosterone level is high while renin is low or undetectable.

Additional tests may be needed to confirm the diagnosis, such as a test to measure the body's response to captopril, a medication used to treat high blood pressure. Patients may also undergo a 24-hour urine test to check for high levels of aldosterone.

Treatment for primary aldosteronism depends on the underlying cause. If the condition is caused by a benign tumor on one of the adrenal glands, surgery to remove the affected gland may be recommended. For patients with bilateral adrenal hyperplasia, medication to block the effects of aldosterone may be prescribed.

The guidelines also highlight the importance of monitoring patients after treatment to ensure that blood pressure and potassium levels remain stable.

In addition to medical treatment, lifestyle changes may be recommended to help manage high blood pressure and low potassium levels. These may include reducing sodium intake, increasing potassium intake, and engaging in regular physical activity.

The guidelines also emphasize the importance of regular follow-up with a healthcare provider to monitor for any changes in symptoms or blood pressure.

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**ADRENOLEUKODYSTROPHY**

*ALTERNATIVE NAMES:* Adrenoleukodystrophy is also known by several alternative names, including “X-linked adrenoleukodystrophy”, “ALD”, “X-ALD”, “Siemerling–Creutzfeldt disease”, and bronze “Schilder disease”.

**DEFINITION / DESCRIPTION**

Adrenoleukodystrophy (uh-dree-noh-loo-koh-DIS-truh-fee) is a type of hereditary (genetic) condition that damages the membrane (myelin sheath) that insulates nerve cells in your brain.

In adrenoleukodystrophy (ALD), your body can't break down very long-chain fatty acids (VLCFAs), causing saturated VLCFAs to build up in your brain, nervous system and adrenal gland.

The most common type of ALD is X-linked ALD, which is caused by a genetic defect on the X chromosome. X-linked ALD affects males more severely than females, who carry the disease.

Forms of X-linked ALD include:

* **Childhood-onset ALD.** This form of X-linked ALD usually occurs between ages 4 and 10. The white matter of the brain is progressively damaged (leukodystrophy), and symptoms worsen over time. If not diagnosed early, childhood-onset ALD may lead to death within five to 10 years.
* **Addison's disease.** Hormone-producing glands (adrenal glands) often fail to produce enough steroids (adrenal insufficiency) in people who have ALD, causing a form of X-linked ALD known as Addison's disease.
* **Adrenomyeloneuropathy.** This adult-onset form of X-linked ALD is a less severe and slowly progressive form that causes symptoms such as a stiff gait and bladder and bowel dysfunction. Women who are carriers for ALD may develop a mild form of Adrenomyeloneuropathy.

**CAUSES**

The cause of ALD is a mutation in a particular gene. Your genes are the instruction manual for creating proteins that have critical roles in how the body works. With a genetic mutation, the gene may create faulty protein.

With ALD, there’s a problem with the ABCD1 gene, which creates the ALDP protein. This protein helps break down VLCFAs. Because of the faulty protein, VLCFAs accumulate in the body’s tissues.

***The most common forms of ALD are:***

* Childhood cerebral ALD: Boys with this form of ALD usually start showing neurological symptoms between ages 3 and 10. As infants, these children develop typically. Then they begin to regress, losing skills. Children often display behavioral problems, such as having difficulty paying attention in school. They may also have seizures. Children with this type typically pass away within a few years of developing symptoms.
* ALD plus Addison’s disease: Along with neurological symptoms, ALD may cause adrenal insufficiency, or Addison’s disease. This condition means your adrenal glands don’t make enough of the hormone cortisol. Symptoms include decreased appetite and muscle weakness.
* Adrenomyeloneuropathy (AMN) or adult-onset ALD: This milder form of ALD begins between ages 21 and 35. People with AMN have both adrenal and neurological problems. Adult-onset ALD progresses more slowly than childhood cerebral ALD, but adults can also have deteriorated brain function. Other symptoms include leg stiffness and pain in the hands and feet.

***Less-common types of ALD include:***

* Adrenal insufficiency-only ALD: Some people have only Addison’s disease, without any neurological problems. About 1 in 10 people with ALD have this type.
* Adult cerebral ALD: About 1 in 5 affected adult males develop cognitive problems similar to childhood cerebral ALD. Over time, they lose most of their mental and neurological function. Many adults with this type eventually pass away from the disease.
* Females with ALD: By age 40, about 1 in 5 women who are ALD carriers have symptoms, but 90% have symptoms by age 60. Symptoms are generally less severe, such as mild weakness and stiffness in their legs.

ALD symptoms often appear between the ages of 3 and 10, though they can start later in life. The childhood form of ALD is the most severe.

**RISK FACTORS**

Adrenoleukodystrophy (ALD) is a rare genetic disorder primarily caused by an inherited mutation in the ABCD1 gene. The primary risk factor for ALD is having a family history of the condition, as it is an X-linked recessive disorder.

Males are more severely affected due to having only one X chromosome, making them more susceptible to the disorder when they inherit the mutated gene. Females can be carriers and may develop milder symptoms, but they are less likely to exhibit the full range of symptoms compared to males.

Additionally, the risk of developing ALD is influenced by genetic factors and the presence of specific mutations in the ABCD1 gene.

Early diagnosis through newborn screening is critical, as it can significantly impact the management and outcome of the disease. Individuals with a family history of ALD should consider genetic counseling to understand their risk and potential implications for future generations.

***Risk Factors and Genetic Considerations***

The primary risk factor is an inherited mutation in the *ABCD1* gene. A family history of adrenoleukodystrophy also increases the risk.

**SIGNS / SYMPTOMS**

**What are the common symptoms of ALD?**

Each type has its own symptoms. People often have both neurological and hormonal symptoms.

ALD Symptoms

Symptoms of ALD often begin between the ages of 4 and 10 but can also present much later in life. ALD symptoms include:

* loss of vision
* learning disabilities
* dysphagia (difficulty swallowing)
* Seizures
* Deafness
* lack of coordination and balance
* Fatigue
* intermittent vomiting
* weight loss
* lack of appetite
* Nausea
* darkening of the skin
* progressive dementia
* muscle weakness
* low blood glucose (blood sugar)
* headaches in the morning

***Adrenomyeloneuropathy***

Adrenomyeloneuropathy is an adult-onset form of ALD that progresses slowly over decades. Symptoms may include a stiff gait when walking and bladder and bowel dysfunction. Many male patients often end up in need of a wheelchair. The adrenal glands often fail to produce enough steroid (cortisol) in people who have ALD, causing Addison’s disease.

***Childhood cerebral ALD symptoms:***

Early symptoms include:

* Behavioral problems, such as attention deficit hyperactivity disorder (ADHD) and learning disabilities.
* Cognitive deficits, or problems with thinking and processing new information. Children may “space out” at school. They may have trouble with reading, handwriting and solving spatial problems.
* Regression, when children lose skills.

As the disease progresses, symptoms include:

* Vision problems.
* Hearing loss
* Trouble walking.
* Weak and stiff limbs.
* Convulsions and seizures.
* Dementia.
* Trouble eating.
* Vomiting.

Eventually, children lose most of their neurological abilities. They lose sight, hearing and voluntary movements. As the disease progresses, children end up in a vegetative state. They often pass away within two to three years of the neurological symptoms’ starting.

***Addison’s disease symptoms:***

Symptoms of adrenal insufficiency include:

* Fatigue.
* Weight loss.
* Nausea and vomiting.
* Digestive problems.
* Feeling weak.
* Headaches in the morning.
* Hypotension.
* Hypoglycemia.
* Hyperpigmented skin, when the skin darkens unrelated to sun exposure.

***Adrenomyeloneuropathy symptoms:***

Symptoms include:

* Spasticity (muscle stiffness), weakness or paralysis of the lower limbs.
* Ataxia, neurological conditions affecting movement.
* Numbness and pain.
* Erectile dysfunction.
* Bowel incontinence.
* Bladder control problems.
* Premature baldness.

ALD is an X-linked genetic disorder. It results from a mutated gene on the X chromosome.

Females, who have two X chromosomes, can be carriers of the disorder. One of the X chromosomes is “shut off.” That means the genes on that chromosome aren’t active.

Females usually don’t have symptoms because the “shut-off” X chromosome carries the mutated gene. Females who have symptoms usually get a milder form that develops during adulthood.

Males have only one X chromosome. The mutated X chromosome can cause more severe ALD because males lack the protective effect of the extra X chromosome.

**DIAGNOSIS METHODS**

*ALD Diagnosis*

After a thorough evaluation of the patient’s medical history, if doctors think the patient may have ALD, they will request additional testing: First, a blood test is performed to measure the levels of VLCFA. High levels of VLCFA suggest a possible ALD diagnosis. To confirm this diagnosis, a genetic test is ordered. If ALD is diagnosed, the doctor may recommend that the patient’s family members receive genetic testing. Many states have also started newborn screening for ALD.

To diagnose ALD, your doctor will review your symptoms and your medical and family history. Your doctor will conduct a physical examination and order several tests, including:

* **Blood testing.** These tests check for high levels of very long-chain fatty acids (VLCFAs) in your blood, which are a key indicator of adrenoleukodystrophy.  
  Doctors use blood samples for genetic testing to identify defects or mutations that cause ALD. Doctors also use blood tests to evaluate how well your adrenal glands work.
* **MRI.** Powerful magnets and radio waves create detailed images of your brain in an MRI scan. This allows doctors to detect abnormalities in your brain that could indicate adrenoleukodystrophy, including damage to the nerve tissue (white matter) of your brain. Doctors may use several types of MRI to view the most-detailed images of your brain and detect early signs of leukodystrophy.
* **Vision screening.** Measuring visual responses can monitor disease progression in males who have no other symptoms.
* **Skin biopsy and fibroblast cell culture.** A small sample of skin may be taken to check for increased levels of VLCFA in some cases.

**TREATMENT OPTIONS**

Adrenoleukodystrophy has no cure. However, stem cell transplantation may stop the progression of ALD if done when neurological symptoms first appear. Doctors will focus on relieving your symptoms and slowing disease progression.

Treatment options may include:

* **Stem cell transplant.** This may be an option to slow or halt the progression of adrenoleukodystrophy in children if ALD is diagnosed and treated early. Stem cells may be taken from bone marrow through bone marrow transplant.
* **Adrenal insufficiency treatment.** Many people who have ALD develop adrenal insufficiency and need to have regular adrenal gland testing. Adrenal insufficiency can be treated effectively with steroids (corticosteroid replacement therapy).
* **Medications.** Your doctor may prescribe medications to help relieve symptoms, including stiffness and seizures.
* **Physical therapy.** Physical therapy may help relieve muscle spasms and reduce muscle rigidity. Your doctor may recommend wheelchairs and other mobility devices if needed.

In a recent clinical trial, boys with early-stage cerebral ALD were treated with gene therapy as an alternative to stem cell transplantation. Early results from gene therapy are promising. Disease progression stabilized in 88 percent of boys who participated in the trial. Additional research is necessary to assess long-term results and safety of gene therapy for cerebral ALD.

Adrenoleukodystrophy has no effective cure. Supportive care, including optimizing nutrition, occupational therapy, and respiratory support, can help alleviate some of the severe consequences of the disorder but typically does not significantly impact survival or long-term outcomes. Corticosteroid and mineralocorticoid replacement therapy is recommended for patients with impaired adrenal gland function. Some studies report that allogeneic hematopoietic stem cell transplantation (HSCT) can halt cerebral demyelination if performed before advanced brain disease develops, highlighting the importance of early screening for at-risk babies. Gene therapy trials using autologous stem cell transplants have shown short-term improvements without the significant risks of HSCT.

Adrenoleukodystrophy gained recognition through the movie "Lorenzo's Oil." However, this mixture of oleic and erucic triglycerides has not been proven effective in randomized controlled trials and is not approved by the US Food and Drug Administration (FDA). Bezafibrate and statin therapy have also been studied but have not yet been proven effective. Crossing the blood-brain barrier is a pharmacodynamic challenge.

A multicenter, open-label phase I trial using lentiviral vectors carrying the *ABCD1* gene is currently underway in China. So far, significant adverse events have not been noted. Recent trials exploring docosahexaenoic acid use to induce peroxisome proliferation have yielded inconclusive results.

Physical therapy, management of urologic complications, and vocational counseling are adjunctive treatments that help improve patients' overall functional status. Given the multiple organs affected and the diverse needs of patients with adrenoleukodystrophy, an interprofessional team approach is recommended. This healthcare team should include, at a minimum, endocrinologists, neurologists, geneticists, and psychologists.

**OUTLOOK / PROGNOSIS**

The prognosis for people with ALD depends on the type. Children with childhood cerebral X-ALD generally have a poor prognosis. Unless they receive a stem cell transplant early in the disease, their neurological function deteriorates. In many cases, children pass away within a few years after symptoms begin.

For people with adult-onset AMN, the disease can progress over many decades.

The prognosis for neonatal adrenoleukodystrophy and most forms of X-ALD is generally poor. However, patients with adrenomyeloneuropathy can survive past age 65, although often with significant morbidity. Treatment is usually limited to symptomatic supportive management. Replacement therapy is effective for patients with Addison disease, while HSCT may benefit asymptomatic patients identified through newborn screening or incidental imaging, as well as those with mild symptoms.

**POSSIBLE COMPLICATIONS**

Patients with adrenomyeloneuropathy have significantly increased other comorbid conditions that have not been fully characterized yet. These include increased levels of pulmonary disease, liver disease, cerebrovascular disease, and cancer.

**PREVENTION TIPS**

There is no known way to prevent ALD. If a family member has ALD, follow your provider’s recommendation for genetic testing and counseling.

**WHEN TO SEE A DOCTOR / RED FLAG**

Early intervention may offer the best chance for successful treatment. If you notice signs in your child, including behavioral or cognitive changes, talk to your healthcare provider. Also talk to your provider if your child seems to lose abilities they once had.

Your child’s care team should include:

* Pediatrician.
* Pediatric and adult neurologist (specialist in the brain and nervous system).
* Urologist (specialist in the urinary system).
* Endocrinologist (specialist in the endocrine system).
* Psychiatrist.
* Physical therapist.
* Genetic counselor.
* Other specialists as needed.

**DIFFERENTIAL DIAGNOSIS**

The differential diagnosis of neonatal adrenoleukodystrophy is comprehensive and includes several other genetic syndromes that present with neurological signs and symptoms in the neonatal period. These conditions include Angelman syndrome, Prader-Willi syndrome, Zellweger spectrum disorders (such as Zellweger syndrome, infantile Refsum disease, and rhizomelic chondrodysplasia punctata type 1), hypoxic-ischemic encephalopathy, metabolic disorders, and myotonic dystrophy.

For X-linked adrenoleukodystrophy (X-ALD), differential diagnoses include conditions characterized by demyelination, such as acute disseminated encephalomyelitis and multiple sclerosis.

**RECENT GUIDELINES OR UPDATES**

Adrenoleukodystrophy is a rare genetic peroxisomal disorder characterized by the abnormal metabolism of very long-chain fatty acids (VLCFAs) due to mutations in the *ABCD1* gene. This leads to the accumulation of VLCFAs, particularly affecting the brain, spinal cord, adrenal glands, and testes. The condition is classified into various subtypes based on inheritance patterns, clinical presentation, age of onset, and affected organs. Diagnosis typically involves clinical suspicion prompted by neurological symptoms and biochemical testing showing elevated VLCFAs. Genetic confirmation through DNA analysis of *ABCD1* gene mutations is crucial for a definitive diagnosis.

Management focuses on early detection through newborn screening programs in some regions, followed by regular monitoring of VLCFA levels. Symptoms typically include progressive neurological dysfunction and adrenal insufficiency, which is managed with glucocorticoid and mineralocorticoid replacement therapies. Hematopoietic stem cell transplantation (HSCT) remains the primary therapeutic option for early-stage adrenoleukodystrophy, offering the best chance to halt disease progression and improve outcomes. Despite these interventions, the prognosis is generally poor, with most patients developing severe neurological disabilities and a shortened lifespan. This activity reviews the pathophysiology, clinical manifestations, and genetic basis of adrenoleukodystrophy and provides clinicians with a comprehensive understanding of the condition. This activity also highlights the crucial role of the multidisciplinary healthcare team in recognizing the symptoms of progressive neurological dysfunction and adrenal insufficiency through early diagnosis and in becoming familiar with current management strategies. Additionally, this activity will offer clinicians insights into the therapeutic potential of HSCT for managing early-stage adrenoleukodystrophy.

**Objectives:**

* Identify early signs and symptoms of adrenoleukodystrophy to facilitate timely diagnosis and intervention.
* Implement appropriate diagnostic tests, including very long-chain fatty acids measurement and genetic analysis, to confirm adrenoleukodystrophy and guide treatment.
* Apply current evidence-based guidelines for the management of adrenoleukodystrophy, including glucocorticoid and mineralocorticoid replacement therapies.
* Collaborate with a multidisciplinary healthcare team, including neurologists, endocrinologists, and geneticists, to provide comprehensive care for adrenoleukodystrophy patients.

Providing patient-centered care for individuals with adrenoleukodystrophy requires a collaborative effort among healthcare professionals, including physicians, advanced practice practitioners, nurses, and pharmacists. Healthcare providers must possess the necessary clinical skills and expertise in diagnosing, evaluating, and treating this condition. This includes proficiency in interpreting genetic testing, recognizing potential complications, and understanding the nuances of disease progression.

An interprofessional healthcare team consisting of neurologists, endocrinologists, geneticists, dieticians, and psychologists is recommended to provide comprehensive care to individuals with adrenoleukodystrophy. This collaborative approach should address both the medical and psychosocial aspects of living with adrenoleukodystrophy. Moreover, a strategic approach involving evidence-based guidelines and individualized care plans tailored to each patient's unique circumstances is vital.

Ethical considerations are crucial when determining treatment options and respecting patient autonomy in shared decision-making. Responsibilities within the interprofessional team should be clearly defined, with each member contributing their specialized knowledge and skills to optimize patient care. Effective interprofessional communication fosters a collaborative environment where information is shared, questions are encouraged, and concerns are addressed promptly.

Lastly, care coordination is pivotal in ensuring seamless and efficient patient care. Physicians, advanced practitioners, nurses, pharmacists, and other healthcare professionals must collaborate to streamline the patient’s journey from diagnosis through treatment and follow-up. This coordination helps minimize errors, reduce delays, and enhance patient safety, ultimately leading to improved outcomes and patient-centered care that prioritizes the well-being and satisfaction of those affected by adrenoleukodystrophy.

**EPIDEMIOLOGY**

**Epidemiology of Adrenoleukodystrophy (ALD)**

Adrenoleukodystrophy is the most common genetic disorder affecting peroxisomes, with an estimated prevalence of 1 in 14,700. The disease incidence is higher in patients of Latino or African descent.Neonatal adrenoleukodystrophy has a prevalence of 1 in 50,000.

* *Prevalence:*  
  Adrenoleukodystrophy affects approximately 1 in 20,000 to 1 in 50,000 individuals worldwide. Some studies report a broader range, with prevalence estimates from about 1 in 62,847 to 1 in 486,088 depending on the population and country. The median prevalence is roughly 1 in 255,000 based on multi-country data.
* *Incidence at Birth:*  
  Newborn screening data from New York State estimate the incidence of ALD at birth to be approximately 1 in 15,000 newborns.
* *Genetics and Risk:*  
  ALD is an X-linked recessive disorder caused by mutations in the *ABCD1* gene on the X chromosome. Males are at higher risk of developing the disease, while females are typically carriers but may develop milder symptoms later in life. The prevalence is similar across ethnicities and geographic regions
* *Disease Types and Distribution:*  
  ALD manifests mainly as:
  + Childhood cerebral ALD (cALD): Most common form, accounting for about 33–57% of cases globally
  + Adrenomyeloneuropathy (AMN): Represents approximately 25–46% of cases
  + Addison’s disease only: The least common presentation, about 10% of cases
* *Geographic Distribution:*  
  The United States, Europe (notably Germany, France, UK), and Japan have documented ALD prevalence and patient registries. For example, in 2017, the US had about 2,248 diagnosed male ALD cases including childhood and adult forms.
* *Gender-Specific Prevalence:*  
  In the US, estimated prevalence is about 1 in 21,000 males affected and 1 in 16,800 females as carriers

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**PHEOCHROMOCYTOMA**

A pheochromocytoma (fee-o-kroe-moe-sy-TOE-muh) is a rare tumor that grows in an adrenal gland. Most often, the tumor is not cancer and has not spread to other parts of the body. This is called benign or non metastatic pheochromocytoma. Rarely, the tumor is cancer and has spread to other parts of the body. This is called malignant or metastatic pheochromocytoma.

You have two adrenal glands — one at the top of each kidney. The adrenal glands make hormones that help control key processes in the body, such as blood pressure. Usually, a pheochromocytoma forms in only one adrenal gland. But tumors can grow in both adrenal glands.

With a pheochromocytoma, the tumor releases hormones that can cause various symptoms. They include high blood pressure, headache, sweating and symptoms of a panic attack. If a pheochromocytoma isn't treated, serious or life-threatening damage to other body systems can happen.

Surgery to remove a pheochromocytoma often returns blood pressure to a healthy range.

**CAUSES**

Researchers don't know exactly what causes a pheochromocytoma. The tumor forms in cells called chromaffin cells. These cells are located in the center of an adrenal gland. They release certain hormones, mainly adrenaline and noradrenaline. These hormones help control many body functions, such as heart rate, blood pressure and blood sugar.

Adrenaline and noradrenaline trigger the body's fight-or-flight response. That response happens when the body thinks there is a threat. The hormones cause blood pressure to rise and the heart to beat faster. They also prepare other body systems so you can react quickly. A pheochromocytoma causes more of these hormones to be released. And it causes them to be released when you're not in a threatening situation.

Most of the chromaffin cells are in the adrenal glands. But small clusters of these cells also are in the heart, head, neck, bladder, stomach area and along the spine. Chromaffin cell tumors located outside of the adrenal glands are called paragangliomas. They may cause the same effects on the body as a pheochromocytoma.

**Risk factors**

A person's age and certain medical conditions can raise the risk of a pheochromocytoma.

Most pheochromocytomas are found in people between the ages of 20 and 50. But the tumor can form at any age.

People who have certain rare genetic conditions have a higher risk of pheochromocytomas. The tumors usually are not cancer and haven’t spread in the body. This type of tumor is called benign or non metastatic pheochromocytoma. Rarely, the tumors are cancer and are spreading in the body. This type of tumor is called malignant or metastatic pheochromocytoma. Often, benign tumors related to these rare genetic conditions form in both adrenal glands. Genetic conditions linked with pheochromocytoma include:

* **Multiple endocrine neoplasia, type 2 (MEN 2).** This condition can cause tumors in more than one part of the body's hormone-making system, called the endocrine system. There are two types of MEN 2, including type 2A and type 2B. Both can involve pheochromocytomas. Other tumors linked with this condition can appear in other parts of the body. These body parts include the thyroid, parathyroid glands, lips, mouth and digestive system.
* **Von Hippel-Lindau disease.** This condition can cause tumors in many parts of the body. Possible sites include the brain and spinal cord, endocrine system, pancreas and kidneys.
* **Neurofibromatosis 1.** This condition causes tumors in the skin called neurofibromas. It also can cause tumors of the nerve at the back of the eye that connects to the brain, called the optic nerve.
* **Hereditary paraganglioma syndromes.** These conditions are passed down in families. They can result in pheochromocytomas or paragangliomas.

**Symptoms**

A pheochromocytoma often causes the following symptoms:

* High blood pressure.
* Headache.
* Heavy sweating.
* Rapid heartbeat.

Some people with pheochromocytomas also have symptoms such as:

* Nervous shaking.
* Skin that turns a lighter color, also called pallor.
* Shortness of breath.
* Panic attack-type symptoms, which can include sudden intense fear.
* Anxiety or a sense of doom.
* Vision problems.
* Constipation.
* Weight loss.

Some people with pheochromocytomas have no symptoms. They don't realize they have the tumor until an imaging test happens to find it.

**Symptom spells**

Most often, the symptoms of pheochromocytoma come and go. When they start suddenly and keep coming back, they're known as spells or attacks. These spells may or may not have a trigger that can be found.

Certain activities or conditions can lead to a spell, such as:

* Physical hard work.
* Anxiety or stress.
* Changes in body position, such as bending over, or going from sitting or lying down to standing.
* Labor and delivery.
* Surgery and a medicine that causes you to be in a sleep-like state during surgery, called an anesthetic.

Foods high in tyramine, a substance that affects blood pressure, also can trigger spells. Tyramine is common in foods that are fermented, aged, pickled, cured, overripe or spoiled. These foods include:

* Some cheeses.
* Some beers and wines.
* Soybeans or products made with soy.
* Chocolate.
* Dried or smoked meats.

Certain medicines and drugs that can trigger spells include:

* Depression medicines called tricyclic antidepressants. Some examples of tricyclic antidepressants are amitriptyline and desipramine (Norpramin).
* Depression medicines called monoamine oxidase inhibitors (MAOIs), such as phenelzine (Nardil), tranylcypromine (Parnate) and isocarboxazid (Marplan). The risk of spells is even higher if these medicines are taken with foods or drinks high in tyramine.
* Stimulants such as caffeine, amphetamines or cocaine.

**Diagnosis**

To find out if you have a pheochromocytoma, your healthcare professional likely will order various tests.

Lab tests

These tests measure levels of the hormones adrenaline and noradrenaline, and substances that can come from those hormones called metanephrines. Raised levels of metanephrines are more common when a person has a pheochromocytoma. Metanephrine levels are less likely to be high when a person has symptoms due to something other than pheochromocytoma.

* 24-hour urine test. In this test, you collect a urine sample every time you urinate over 24 hours. Ask for written directions about how to store, label and return the samples.
* Blood test. A healthcare professional takes a sample of blood to be tested in the lab.

For both types of tests, ask your healthcare professional if you need to do anything to prepare. For example, you may be asked not to eat for a certain amount of time before the test. This is called fasting. Or you may be asked to skip taking a certain medicine. Don't skip a medicine dose unless a member of your healthcare team tells you to and gives you directions.

Imaging tests

If the lab test results find signs of a pheochromocytoma, imaging tests are needed. Your healthcare professional likely will order one or more of these tests to find out if you have a tumor. These tests may include:

* CT scan, which combines a series of X-ray images taken from different angles around your body.
* MRI, which uses radio waves and a magnetic field to make detailed images.
* M-iodobenzylguanidine (MIBG) imaging, a scan that can detect tiny amounts of an injected radioactive compound. The compound is taken up by pheochromocytomas.
* Positron emission tomography (PET), a scan that also can detect radioactive compounds taken up by a tumor.

A tumor in an adrenal gland might be found during imaging studies done for other reasons. If that happens, healthcare professionals often will order more tests to find out if the tumor needs to be treated.

Genetic testing

Your healthcare professional might recommend genetic tests to see whether a pheochromocytoma is related to a genetic condition. Information about possible genetic factors can be important for many reasons:

* Some genetic conditions can cause more than one medical problem. So, test results may suggest the need to screen for other medical conditions.
* Some genetic conditions are more likely to happen again or be cancer. So, your test results may affect treatment decisions or long-term plans to track your health.
* Results from tests may suggest that other family members should be screened for pheochromocytoma or related conditions.

Genetic counseling can help you understand the results of your genetic testing. It also can help your family manage any mental health issues tied to the stress of genetic testing.

**Treatment**

The main treatment for a pheochromocytoma is surgery to remove the tumor. Before you have surgery, your healthcare professional likely will prescribe certain blood pressure medicines. These medicines block high-adrenaline hormones to lower the risk of dangerously high blood pressure during surgery.

Preparing before surgery

You'll likely take medicines for 7 to 14 days before surgery to help lower blood pressure. These medicines will either replace or be added to other blood pressure medicines you take. You also may be told to eat a high-sodium diet.

Medicines such as alpha blockers, beta blockers and calcium channel blockers keep smaller veins and arteries open and relaxed. This improves blood flow and lowers blood pressure. Some of these medicines also may cause the heart to beat more slowly and with less force. This can lower blood pressure more.

Because these medicines widen the blood vessels, they cause the amount of fluid within the blood vessels to be low. This can cause dangerous drops in blood pressure when you stand up. A high-sodium diet can draw more fluid inside the blood vessels. This helps prevent low blood pressure during and after surgery.

Surgery

Most often, a surgeon makes a few small cuts called incisions in the stomach area. Wandlike devices equipped with video cameras and small tools are placed through the cuts to do the surgery. This is called laparoscopic surgery. Some surgeons do the procedure with robotic technology. They sit at a nearby console and control robotic arms, which hold a camera and surgery tools. If the tumor is very large, surgery that involves a larger incision and opening the abdominal cavity may be needed.

Often, the surgeon removes the entire adrenal gland that has the pheochromocytoma. But the surgeon might remove only the tumor, leaving some healthy adrenal gland tissue. This may be done when the other adrenal gland also has been removed. Or it may be done when there are tumors in both adrenal glands.

If you have metastatic pheochromocytoma, which means the tumor has spread to other organs, surgery may not be able to remove all of the cancer tissue. Removing as much of the tumor as possible along with medical therapy might ease pheochromocytoma symptoms. It also makes blood pressure easier to control.

After surgery

If one healthy adrenal gland remains, it can carry out the functions usually done by two glands. Blood pressure usually returns to a healthy range after surgery. You'll need regular checkups and blood tests with your healthcare professional for the rest of your life. These appointments help track your health, find other health concerns and check to see if the tumor has come back.

If both adrenal glands are removed, you'll need to take steroid medicines for the rest of your life. These medicines replace certain hormones that the adrenal glands make.

Cancer treatments

Very few pheochromocytomas spread through the body as cancer, called metastatic pheochromocytomas. Because they are rare, research about the best treatments is limited. Treatments for metastatic pheochromocytoma may include:

* Targeted therapies. These use a medicine combined with a radioactive substance that seeks out cancer cells and kills them.
* Chemotherapy. This treatment uses powerful drugs that kill fast-growing cancer cells. It may help ease symptoms in people with pheochromocytomas whose cancer has spread.
* Radiation therapy. This treatment uses beams of intense energy to kill cancer cells. It may relieve symptoms of tumors that have spread to the bone and cause pain.
* Ablation. This treatment can destroy cancer tumors with freezing temperatures, high-energy radio waves or ethanol alcohol.

**Complications**

A pheochromocytoma can lead to other health problems. The high blood pressure linked with a pheochromocytoma can damage organs, especially tissues of the heart and blood vessel system, brain and kidneys. This damage can cause dangerous conditions, including:

* Heart disease.
* Stroke.
* Kidney failure.
* Vision loss.

Cancerous tumors

Rarely, a pheochromocytoma spreads to other parts of the body. This tumor is then considered cancerous, also called malignant, and is referred to as metastatic pheochromocytoma. Cancer cells from a pheochromocytoma or paraganglioma most often travel to the lymph system, bones, liver or lungs.

**When to see a doctor**

High blood pressure is one of the main symptoms of a pheochromocytoma. But most people who have high blood pressure don't have an adrenal tumor. Talk to your healthcare professional if any of these factors apply to you:

* Spells of symptoms linked with pheochromocytoma, such as headaches, sweating and a fast, pounding heartbeat.
* Trouble controlling high blood pressure with your current treatment.
* High blood pressure that starts before the age of 20.
* Recurring large rises in blood pressure.
* A family history of pheochromocytoma.
* A family history of a related genetic condition. These include multiple endocrine neoplasia, type 2 (MEN 2), von Hippel-Lindau disease, inherited paraganglioma syndromes and neurofibromatosis

**Epidemiology**

Pheochromocytomas are rare, reportedly occurring in 0.05–0.2% of hypertensive individuals. This accounts for only a portion of cases, however, as patients may be completely asymptomatic. A retrospective study from the Mayo Clinic revealed that in 50% of cases of pheochromocytoma, the diagnosis was made at autopsy.Approximately 10% of pheochromocytomas are discovered incidentally.

A Dutch study, by Berends et al, found an increase in the age-standardized incidence rate (ASR) of pheochromocytomas and sympathetic paragangliomas in the Netherlands between 1995 and 2015. The investigators reported that the ASR between 1995 and 1999 was 0.29 per 100,000 person-years, compared with 0.46 per 100,000 person-years between 2011 and 2015. The ASRs for sympathetic paragangliomas rose between these same two periods from 0.08 to 0.11 per 100,000 person-years. There was also a trend during this 20-year period towards patients being older and tumor size smaller at diagnosis. The investigators suggested that clinical practice changes, along with greater use of imaging and biochemical studies, were at least partially responsible for the incidence increases.

Race- and age-related demographics

Pheochromocytomas occur in people of all races, although they are diagnosed less frequently in the black population. Pheochromocytomas may occur in persons of any age, but the peak incidence is from the third to the fifth decades of life.

**Differential Diagnosis of Pheochromocytoma**

Pheochromocytoma, a catecholamine-secreting tumor of the adrenal medulla, must be differentiated from a variety of conditions that cause similar symptoms such as paroxysmal hypertension, palpitations, headaches, and sweating.

1. Endocrine Disorders

* Hyperthyroidism / Thyroid storm
* Carcinoid syndrome (can cause flushing and hypertension)
* Medullary thyroid carcinoma (especially in MEN 2 syndromes)
* Cushing syndrome (hypertension and metabolic symptoms)
* Hypoglycemia (can mimic adrenergic symptoms)

2. Cardiovascular Causes

* Essential hypertension (including labile and white coat hypertension)
* Renovascular hypertension (renal artery stenosis)
* Heart failure
* Arrhythmias
* Ischemic heart disease
* Baroreflex failure

3. Neurologic and Psychiatric Conditions

* Migraine headaches
* Stroke and lateral medullary syndrome
* Seizures (focal or generalized)
* Postural orthostatic tachycardia syndrome (POTS)
* Panic disorder and anxiety attacks
* Factitious disorder (including factitious hypertension)
* Substance use (e.g., sympathomimetic drugs)

4. Other Causes

* Pseudopheochromocytoma (idiopathic paroxysmal hypertension)
* Drugs that mimic catecholamine excess (e.g., cocaine, amphetamines, decongestants)
* Porphyria
* Compression of the lateral medulla (Wallenberg syndrome)
* Adrenal tumors other than pheochromocytoma:
  + Adrenocortical adenoma
  + Adrenal metastases
  + Adrenal cortical carcinoma

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