**PITUITARY ADENOMA**

A pituitary adenoma is a benign (noncancerous) growth on your pituitary gland. Unlike cancer, it doesn’t spread to other parts of your body. But as pituitary adenomas grow, they can put pressure on nearby structures and cause symptoms.

Your pituitary is a small gland about the size of a pea that’s joined to your hypothalamus (the base of your brain) right behind your nose. It has two lobes: the anterior (front) lobe and the posterior (back) lobe. Each lobe releases different hormones.

Hormones are chemicals that coordinate different functions in your body by carrying messages through your blood to your organs, muscles and other tissues.

Your pituitary gland releases several important hormones, including:

* Adrenocorticotropic hormone (ACTH or corticotropin).
* Antidiuretic hormone (ADH, or vasopressin).
* Follicle-stimulating hormone (FSH).
* Growth hormone (GH).
* Luteinizing hormone (LH).
* Oxytocin.
* Prolactin.
* Thyroid-stimulating hormone (TSH).

Your pituitary gland also tells other endocrine system glands to release hormones. Of note, pituitary adenomas can affect the production and release of a single hormone or a combination of hormones.

Healthcare providers categorize pituitary adenomas based on whether or not they produce extra hormones.

* Functioning (secreting) adenomas: These adenomas release extra pituitary hormones, which cause certain symptoms and/or conditions depending on the hormone it releases.
* Nonfunctioning (non-secreting) adenomas: These adenomas don’t release hormones, but they can compress nearby structures if they grow (see below). The most common adenomas most healthcare providers diagnose are nonfunctioning pituitary adenomas.

Healthcare providers also categorize pituitary adenomas based on their size:

* Microadenomas: These adenomas are smaller than 10 millimeters or 1 centimeter.
* Macroadenomas: These adenomas are larger than 10 millimeters. Macroadenomas are twice as common compared to microadenomas. They’re also more likely to cause lower than normal levels of one or more pituitary hormones. This is known as hypopituitarism.

Even though your pituitary gland is an endocrine structure that’s not technically a part of your brain (it’s actually attached to your brain), healthcare providers consider pituitary adenomas brain tumors. They represent about 10% of primary brain tumors.

Pituitary adenomas can occur at any age but are more common in people in their 30s or 40s. Women are more likely to have pituitary adenomas.

Pituitary adenomas make up 10% to 15% of all tumors that develop within your skull. About 77 out of 100,000 people have a pituitary adenoma, but researchers think adenomas actually occur in as many as 20% of people at some point in their lives. As many people with pituitary adenomas, especially microadenomas, are asymptomatic, they’re usually never found.

**Symptoms and Causes**

The symptoms of pituitary adenomas can vary widely depending on several factors, including:

* If it’s large enough to damage your pituitary gland or nearby structures (mass effect).
* If it’s a functioning (hormone secreting) pituitary adenoma with symptoms based on the type of hormone it secretes.

Pituitary macroadenomas typically present with mass effects — meaning their large size can apply pressure to or damage nearby tissues, causing compressive symptoms, including:

Vision problems

Approximated 40% to 60% of people with a pituitary macroadenoma have impaired vision (blurry or double vision) from the adenoma. The adenoma compresses your optic chiasm, leading to visual field defects like the loss of peripheral vision (side vision).

Headaches

People with pituitary adenomas often report having headaches. This could be due to pressure on nearby tissues, but as headaches are a common symptom in general, people could have them for other reasons as well.

Hormonal deficiency

Pituitary macroadenomas can cause one or more pituitary hormone deficiencies due to damage to your pituitary gland tissue. This can result in an underactive pituitary gland, also known as hypopituitarism.

Each pituitary hormone deficiency causes different symptoms.

* A deficiency of LH and FSH hormones leads to low testosterone (LH) and estrogen (FSH), a condition known as hypogonadism. Symptoms of hypogonadism include hot flashes and vaginal dryness, erectile dysfunction and decreased facial/body hair growth in men,, mood swings, decreased libido/sex drive and fatigue.
* A deficiency of TSH results in low thyroid hormone production, a condition known as hypothyroidism. Symptoms of hypothyroidism include fatigue, constipation, slow heart rate, dry skin, swelling of extremities and diminished reflexes.
* A deficiency of ACTH means you don’t produce as much cortisol, a condition known as adrenal insufficiency. Symptoms of adrenal insufficiency include low blood pressure, nausea, vomiting, abdominal pain and poor appetite.
* A deficiency of GH results in low growth hormone production, also known as growth hormone deficiency. You’ll have different symptoms depending on how old you are. In adults, a lack of GH results in fatigue and decreased muscle mass.

What symptoms do functioning pituitary adenomas cause?

A functioning, or secreting, pituitary adenoma releases excess hormone(s). Functioning pituitary adenomas can cause several different symptoms depending on which pituitary hormone(s) they release.

As your body normally regulates the hormone levels in your body for optimum health, extra pituitary hormones from a functioning adenoma can lead to the following conditions:

Prolactinomas (lactotroph adenomas)

Prolactinomas (lactotroph adenomas) make excess prolactin, a condition known as hyperprolactinemia. Prolactinomas account for about 4 out of 10 pituitary tumors. They’re the most common type of pituitary adenoma.

High prolactin levels can disrupt normal reproductive functions by interfering with hormones produced by your testicles or ovaries. Symptoms include:

* Male and female infertility.
* Milky discharges from your nipples when not pregnant, which is known as (galactorrhea).

Somatotroph adenomas

Somatotroph adenomas make excess growth hormone (also known as somatotropin) and make up about 2 in 10 pituitary tumors.

Somatotroph adenomas cause different symptoms depending on your age.

In adults, these adenomas are a common cause of acromegaly, a rare but serious condition that results from too much growth hormone. It affects your body’s bones and tissues and causes them to grow in abnormal ways. Over time, it can lead to enlarged hands, feet or head size and a rounded face with poorly defined features. It also affects important metabolic functions like blood sugar (glucose) regulation and can increase the size of your heart muscle.

In children and adolescents, somatotroph adenomas are the cause of gigantism (also called pediatric acromegaly and pituitary gigantism). High levels of growth hormone in their body cause them to grow very tall.

**Corticotroph adenomas**

**Corticotroph adenomas make extra adrenocorticotropic hormone (ACTH). They account for about 1 in 10 pituitary tumors. ACTH triggers your adrenal glands to make steroid hormones, including cortisol.**

**Corticotroph adenomas cause** Cushing’s syndrome (excess cortisol). This causes several symptoms, including:

* High blood pressure.
* Muscle weakness.
* Easy bruising.
* Wide (> 1 centimeter), purple stretch marks over your belly.
* Osteoporosis.
* Compression fractures.
* Type 2 diabetes mellitus.

Thyrotroph adenomas

Thyrotroph adenomas make excess thyroid-stimulating hormone (TSH) and are very rare. TSH stimulates your thyroid gland to make and release thyroid hormone.

Excess TSH results in excess thyroid hormone, which causes a condition called hyperthyroidism and speeds up your metabolism. This results in symptoms like:

* Rapid heart rate.
* Unexplained weight loss.
* Loose stools (poop).
* Sweating.
* Hand tremors.
* Anxiety.

Hyperthyroidism has many other causes — pituitary adenomas are a rare cause of the condition.

Gonadotroph adenomas

Gonadotroph adenomas make excess gonadotropins, which are luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Gonadotroph adenomas are very rare.

These adenomas can cause irregular menstruation (periods) and ovarian hyperstimulation syndrome (OHSS). It can also cause enlarged testicles, a deeper voice, balding on your temples and rapid facial hair growth.

They can also cause precocious (early) puberty in children.

**What causes pituitary adenomas?**

Scientists aren’t sure of the exact cause of pituitary adenomas.

But some adenomas have been linked to accidental changes, or mutations in DNA, the material within a cell that makes up our genes. These changes cause the cells in your pituitary gland to grow out of control, making a mass (growth). The genetic changes can be passed down from parents to children (inherited), but they usually happen randomly.

Pituitary adenomas are also associated with certain genetic conditions, including:

* Multiple endocrine neoplasia type 1.
* Multiple endocrine neoplasia type 4.
* Carney complex.
* X-LAG syndrome.
* Succinate dehydrogenase-related familial pituitary adenoma.
* Neurofibromatosis type 1.
* Von Hippel–Lindau syndrome.

Having one of these conditions makes it more likely that you’ll develop a pituitary adenoma, but you can still have an adenoma without having one of these conditions.

**Diagnosis and Tests**

The diagnostic process for pituitary adenomas depends on what kind of adenoma you have and if it’s causing symptoms or not.

If you have a hormone-secreting pituitary adenoma, your healthcare provider will likely diagnose you with the condition it causes based on your symptoms before diagnosing the adenoma. This is because many conditions that result from excess hormones can have many different causes — not just pituitary adenomas. This is also true of hypopituitarism (pituitary hormone deficiency) causes.

Sometimes, healthcare providers find pituitary adenomas by accident when you get an imaging test of your brain for another condition. In these cases, the adenoma is usually small and nonfunctioning.

What tests will be done to diagnose a pituitary adenoma?

If your healthcare provider thinks you might have a pituitary adenoma, they’ll do a full review of your symptoms and your medical background and will perform a physical exam.

They may order any of the following tests:

* Blood tests: Depending on your symptoms, your healthcare provider may order blood tests to check certain hormone levels.
* Imaging tests: An MRI (magnetic resonance imaging) scan or CT (computed tomography) scan of your head can provide images of the structures inside of your head. These tests can confirm the diagnosis of a pituitary adenoma.
* Eye exam: If you’re having problems with your vision, your healthcare provider might have you take a visual field test to check your eye function. Large pituitary adenomas can put pressure on the nerves that connect your eyes to your brain and cause vision issues.

**Management and Treatment**

Healthcare providers usually treat pituitary adenomas with surgery, medicine, radiation or a combination of these therapies. As each pituitary adenoma is different, you and your healthcare team will come up with a treatment plan that works best for you.

Surgery to remove pituitary adenomas

If you have a pituitary adenoma that’s causing a hormonal imbalance, your healthcare provider will likely recommend surgery to remove all or part of the adenoma. Depending on the size of the adenoma and the severity of your symptoms, you may need multiple surgeries.

Your surgeon will likely use a type of surgery called transsphenoidal surgery to remove the pituitary adenoma, which involves going through your nose and sphenoid sinus, a hollow space in your skull behind your nasal passages and below your brain, to perform surgery. Surgeons use this technique for 95% of pituitary tumors.

If the adenoma is too large to remove through your sinus cavity, your surgeon may open your skull (transcranial surgery) to get to your pituitary and the adenoma. This is a rare surgery technique for pituitary adenomas.

Medication to treat pituitary adenomas

Healthcare providers can treat some types of pituitary adenomas with medication that shrinks the adenoma and relieves symptoms.

If you have a prolactinoma (the most common kind of pituitary adenoma), you’ll likely receive dopamine agonist therapy medications, such as cabergoline (Dostinex®) or bromocriptine (Cycloset®), as the first course of treatment for several months.

In 80% of cases, these medications shrink the prolactinoma, and prolactin levels return to normal. If the medication doesn’t work, your healthcare provider will likely recommend surgery.

Radiation therapy for pituitary adenomas

Radiation therapy uses high-energy X-rays to shrink adenomas or tumors. Healthcare providers use a special form of radiation therapy called stereotactic radiosurgery for pituitary adenomas, which uses a high dose of radiation aimed precisely at the adenoma from more than one direction to keep the adenoma from growing.

Side effects of pituitary adenoma treatment

As a result of surgeries and/or radiation therapy, approximately 60% of people with pituitary adenomas develop hypopituitarism after treatment, a condition in which there’s a lack of production of one, multiple, or all of your pituitary hormones. Hypopituitarism is treatable with hormone replacement medications.

Complications from surgery to remove a pituitary adenoma can include:

* Bleeding.
* Cerebrospinal fluid (CSF) leaks.
* Meningitis.
* Diabetes insipidus, which is a condition that results in partial or complete antidiuretic hormone deficiency from the posterior pituitary gland. This condition causes you to urinate large quantities of diluted urine resulting in sodium (salt) excess in your body.

Common side effects of dopamine agonists that healthcare providers prescribe to treat prolactinomas include headaches, nausea, vomiting, dizziness and sometimes increased compulsive behavior.

Possible side effects of radiation therapy include:

* Pituitary hormone deficiency.
* Impaired fertility.
* Vision loss and brain injury (rare).
* Tumor development several years after treat**ment (rare).**

**Outlook / Prognosis**

The prognosis (outlook) depends on the size and type of pituitary adenoma you have.

When treatment destroys the adenoma, most people with adenomas can return to full, healthy lives. In some cases, adenoma treatment results in low hormone levels, and you have to take lifelong hormone medicines to replace what you’ve lost.

Adenomas tend to recur (come back), which means you may need treatment again. About 18% of people with non functioning adenomas and 25% of people with prolactinomas will need more treatment at some point.

As long as a pituitary adenoma is small and doesn’t cause any symptoms, you can live with it. In fact, most people find out they have a pituitary adenoma when they get an imaging test of their head for another reason. But if the adenoma continues to grow, you may need to eventually receive treatment for it.

If you have a large and/or functioning pituitary adenoma, you’ll likely need treatment as some pituitary adenomas can cause symptoms that greatly impact your health and quality of life.

**Complications of an untreated pituitary adenoma**

If left untreated, some pituitary adenomas — mainly macroadenomas and functioning (secreting) adenomas — can cause serious health issues. The health issues largely depend on which hormone the adenoma secretes (see Causes and Symptoms section above).

A very rare complication of untreated pituitary adenomas is pituitary apoplexy. This is a medical emergency that’s caused by bleeding either into or out of your pituitary gland.

Pituitary apoplexy is commonly caused by bleeding inside a pituitary adenoma. Your pituitary is damaged when the tumor suddenly enlarges. It either causes bleeding into your pituitary gland or blocks the blood supply to your pituitary. The larger the adenoma, the higher the risk for pituitary apoplexy.

Pituitary apoplexy usually has a quick onset of symptoms, which can be life-threatening. Symptoms often include:

* Severe headache.
* Paralysis of the eye muscles, causing double vision or problems opening an eyelid.
* Loss of peripheral vision or loss of all vision in one or both eyes.
* Low blood pressure, nausea and vomiting due to acute adrenal insufficiency.
* Personality changes due to the sudden narrowing of one of the arteries in your brain (anterior cerebral artery).

**Although pituitary apoplexy is rare, it’s serious. If you have symptoms of pituitary apoplexy, call 911 or have a loved one take you to the nearest emergency room as soon as possible.**

**Prevention**

Unfortunately, there’s nothing you can do to prevent developing a pituitary adenoma. Most pituitary adenomas occur randomly, but they’re also associated with certain rare genetic conditions as noted above.

If you have a first-degree relative (sibling or parent) who has one of these conditions, you may want to get genetic testing to check to see if you have it as well. This may help screen for and catch a pituitary adenoma in its early phases. Your healthcare provider may recommend regular blood tests of your pituitary hormone levels to increase the odds of finding and treating a pituitary tumor before it creates problems.

**Living With**

**When should I see my healthcare provider about a pituitary adenoma?**

Call your healthcare provider if you have problems with your vision and/or have headaches that don’t go away or keep coming back, particularly if they’re toward your forehead.

If you’ve been diagnosed with a pituitary adenoma, you’ll likely need to see your healthcare provider regularly to monitor the adenoma and to make sure your treatment is working.

## **Differential Diagnosis of Pituitary Adenoma**

1. Primary Brain Tumors
   * Glioblastoma multiforme
   * Oligodendroglioma
   * Pilocytic astrocytoma
   * Medulloblastoma
   * Ependymoma
   * Schwannoma
   * Primary CNS lymphoma
   * Germ cell tumors (germinomas)
   * Chordoma
2. Other Sellar and Parasellar Lesions
   * Craniopharyngioma
   * Rathke cleft cyst
   * Meningioma
   * Pituitary carcinoma (rare)
   * Pituitary hyperplasia (e.g., secondary to ectopic GHRH secretion)
   * Pituitary abscess
   * Pituitary apoplexy
   * Empty sella syndrome
   * Lymphocytic hypophysitis (autoimmune inflammation)
   * Drug-induced hypophysitis
3. Vascular Lesions
   * Arteriovenous (AV) malformation
   * Brain aneurysm (especially in sellar region)
4. Infectious and Granulomatous Diseases
   * Bacterial brain abscess
   * Tuberculosis (tuberculoma)
   * Syphilitic gumma
   * Sarcoidosis
   * Toxoplasmosis
   * Hydatid cyst
   * CNS cryptococcosis
   * CNS aspergillosis
5. Metastatic Disease
   * Metastasis to pituitary or parasellar region from systemic cancers
6. Other Considerations
   * Basilar artery thrombosis
   * Brainstem gliomas
   * Cavernous sinus syndromes
   * Cerebral venous thrombosis

**EPIDEMIOLOGY**

Pituitary adenomas are usually nonmalignant, but have a heavy burden on patients and health care systems. Increased availability of MRI has led to an increase in incidentally found pituitary lesions and clinically relevant pituitary adenomas. Epidemiologic studies show that pituitary adenomas are increasing in incidence (between 3.9 and 7.4 cases per 100,000 per year) and prevalence (76 to 116 cases per 100,000 population) in the general population (approximately 1 case per 1000 of the general population). Most new cases diagnosed are prolactinomas and non secreting pituitary adenomas. Most clinically relevant pituitary adenomas occur in females, but pituitary adenomas are clinically heterogeneous.

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**PROLACTINOMA**

**Prolactinoma** is a noncancerous tumor of the pituitary gland. This tumor causes the pituitary gland to make too much of a hormone called prolactin. The major effect of a prolactinoma is decreased levels of some sex hormones — namely, estrogen and testosterone.

A prolactinoma isn't life-threatening. But it can cause vision difficulties, infertility and other problems. Prolactinoma is the most common type of hormone-producing tumor that can develop in the pituitary gland.

A prolactinoma can usually be treated with medications to bring the prolactin level down into the standard range and shrink the tumor. In some cases, surgery to remove the tumor might be an option.

**CAUSES**

Prolactinoma is one type of tumor that develops in the pituitary gland. The cause of prolactinoma is usually unknown.

The pituitary gland is a small bean-shaped gland located at the base of your brain. Despite its small size, the pituitary gland has an effect on nearly every part of your body. Its hormones help control important functions such as growth, metabolism, blood pressure and reproduction.

A prolactinoma causes the pituitary gland to make too much of a hormone called prolactin. This results in a decreased level of some sex hormones — namely, estrogen and testosterone.

Making too much prolactin (hyperprolactinemia) can also happen for reasons other than a prolactinoma. These can include:

* Medications
* Other types of pituitary tumors
* Kidney disease
* Underactive thyroid gland
* Pregnancy and breastfeeding

**Risk factors**

More prolactinomas occur in females than males. The disorder is rare in children.

Rarely, an inherited disorder such as multiple endocrine neoplasia, type 1 — a disorder that causes tumors in hormone-producing glands — may increase the risk of a prolactinoma.

**Symptoms**

A prolactinoma might not cause any signs or symptoms. However, too much prolactin in your blood (hyperprolactinemia) can cause symptoms. So can pressure on surrounding tissues from a large tumor.

Because too much prolactin can disrupt the reproductive system (hypogonadism), some of the signs and symptoms of a prolactinoma are specific to females or males.

In females, prolactinoma can cause:

* Irregular menstrual periods or no menstrual periods
* Milky discharge from the breasts when not pregnant or breastfeeding
* Painful intercourse due to vaginal dryness
* Acne and excessive body and facial hair growth

In males, prolactinoma can cause:

* Erectile dysfunction
* Decreased body and facial hair
* Smaller muscles
* Enlarged breasts

In both females and males, prolactinoma can cause:

* Infertility
* Weak and brittle bones that break easily (osteoporosis)
* Loss of interest in sexual activity

Pressure from tumor growth can cause:

* Vision problems
* Headache
* Reduction of other hormones produced by the pituitary gland

Females who are premenopausal tend to notice signs and symptoms early, when tumors are smaller in size. This is probably because of missed or irregular menstrual periods. Females who are postmenopausal are more likely to notice signs and symptoms later, when tumors are larger and more likely to cause headache or vision problems. Males are also more likely to notice signs and symptoms later.

**Complications**

Complications of prolactinoma may include:

* **Infertility.** A prolactinoma can interfere with reproduction. Too much prolactin reduces the production of the hormones estrogen and testosterone. Too much prolactin also can prevent the release of an egg during the menstrual cycle (anovulation) in females. In males, too much prolactin also can lead to decreased sperm production.
* **Bone loss (osteoporosis).** Reduced estrogen and testosterone also cause decreased bone strength. This results in weak and brittle bones that can break easily.
* **Pregnancy complications.** During a typical pregnancy, the production of estrogen increases. This may cause tumor growth. This can result in signs and symptoms such as headaches and changes in vision in pregnant females who have large prolactinomas.
* **Vision loss.** Left untreated, a prolactinoma may grow large enough to press on your optic nerve. This nerve sits near the pituitary gland. The nerve sends images from your eye to your brain so that you can see. The first sign of pressure on the optic nerve is a loss of your side (peripheral) vision.
* **Low levels of other pituitary gland hormones.** Larger prolactinomas can put pressure on the healthy part of the pituitary gland. This can lead to lower levels of other hormones controlled by the pituitary gland. These include thyroid hormones and cortisol. Cortisol is a stress-response hormone.

**Diagnosis**

If you have signs and symptoms that suggest you have a prolactinoma, your health care provider may recommend:

* **Blood tests.** Blood tests can show if too much prolactin is being made. They can also show whether levels of other hormones controlled by the pituitary gland are within the standard range. A pregnancy test is typically recommended for females of childbearing age.
* **Brain imaging.** Your provider may be able to detect a prolactinoma using a magnetic resonance imaging (MRI) scan of your brain.
* **Vision tests.** These can determine if a prolactinoma is affecting your sight.

Your provider may also refer you for additional testing with a specialist in treating disorders that affect the endocrine glands and hormones (endocrinologist).

**Treatment**

Goals in the treatment of a prolactinoma include:

* Return the production of prolactin to within the standard range
* Reduce the size of the prolactinoma
* Restore healthy pituitary gland function

For most people, treatment can eliminate or improve:

* Problems caused by increased prolactin levels, such as irregular menstrual periods, infertility and loss of interest in sexual activity
* Signs or symptoms from tumor pressure, such as headaches or vision problems

Prolactinoma treatment includes two main therapies: medications and surgery.

**Medications**

Oral medications known as dopamine agonists are generally used to treat a prolactinoma. These drugs mimic the effects of dopamine — the brain chemical that controls how much prolactin is made. Dopamine agonists can decrease the production of prolactin and shrink the size of the tumor. Drugs can eliminate symptoms for most people with prolactinomas. However, you'll generally need long-term treatment with drugs.

Commonly prescribed drugs include cabergoline and bromocriptine (Cycloset, Parlodel).

If a drug shrinks the tumor significantly and your prolactin level remains within the standard range for two years, you may be able to taper off the drug. Only taper off your drug with your health care provider's guidance. Your provider monitors your prolactin levels during this process. Don't stop taking your drug without talking to your provider first.

Prolactin levels commonly rise after stopping the drug. If this happens, your provider will likely ask you to restart taking the drug.

**Common medication side effects**

Common side effects of these medications include nausea and vomiting, dizziness, nasal stuffiness, and headache. However, these side effects often can be less bothersome if your health care provider starts you with a very low dose of the drug. Then your provider can gradually increase the dose. It may also help if you take the drug with food or if you take it at bedtime.

People have rarely had heart valve damage with cabergoline. But it's usually in people taking much higher doses for Parkinson's disease. Some people may develop impulse control disorders, such as compulsive gambling, while taking these drugs.

**Medication during pregnancy**

Both bromocriptine and cabergoline treat prolactinomas in people who want to become pregnant. But the medications have different advantages and disadvantages. Discuss the pros and cons of these options with your healthcare provider. Together you can decide which drug may work best for you.

In most situations, a provider typically advises stopping the drug when pregnancy is confirmed. Although both drugs are considered safe in pregnancy, your provider will generally recommend avoiding any drug during pregnancy when possible. However, if you have a large prolactinoma or you develop signs and symptoms such as headaches or vision changes, your provider may recommend that you restart the drug. This can prevent further tumor growth and complications.

If you're being treated for a prolactinoma and you'd like to start a family, it's best to discuss your options with your provider before you become pregnant.

**Surgery**

Surgery to remove a prolactinoma is generally an option if drug therapy doesn't work or you can't tolerate the drug. Surgery may be necessary to relieve pressure on the nerves that control your vision.

The type of surgery you have will depend largely on the size and extent of your tumor:

* **Nasal surgery.** For most people who need surgery, the procedure involves removing the tumor through the nose (nasal cavity). This surgery is called transsphenoidal surgery. Complication rates are low because the surgeon doesn't touch other areas of the brain during surgery. This surgery leaves no visible scars.
* **Transcranial surgery.** If your tumor is large or has extended to nearby brain tissue, you may need this procedure, also known as a craniotomy. The surgeon removes the tumor through the upper part of the skull.

Surgery outcomes depend on the size and location of the tumor and prolactin levels before surgery. The surgeon's skill and experience with this specific type of surgery also is a factor. Sometimes an MRI scan shows that a prolactinoma has extended to areas in the brain where it's unsafe to attempt removal. When this happens, the surgeon can only partially remove the prolactinoma.

Surgery corrects the prolactin level in most people with small prolactinomas. However, tumors may come back within several years of surgery. For people with larger tumors that can only be partially removed, drug therapy often can return the prolactin level to the standard range after surgery.

**Radiation**

Rarely, radiation therapy to kill tumor cells may be an option for a large prolactinoma. You may have radiation if you don't respond to medication, if you aren't able to have surgery, or if your surgery didn't remove all of a large tumor.

**Outlook / Prognosis**

The prognosis (outlook) for someone with prolactinoma is generally good. Medication (dopamine agonists) shrinks small prolactinoma tumors and brings prolactin levels back to normal for 4 out of 5 people receiving this treatment.

Prolactinoma surgery is also often successful. When an experienced surgeon performs the surgery, it corrects prolactin levels in about 90% of people with small tumors and in 50% of those who have large tumors. If you have a large tumor that can only be partially removed, medications can often return your prolactin levels to a normal range after surgery.

**Prevention**

Unfortunately, there’s nothing you can do to prevent developing prolactinoma. A known risk factor is having an inherited (passed through your biological family) condition called multiple endocrine neoplasia (MEN) type 1.

If you have a first-degree relative (biological sibling or parent) who has this condition, you may want to get genetic counseling to check if you have it as well. This may help screen for and catch prolactinoma in its early phases.

**When to see a doctor**

If you develop signs and symptoms that may be caused by a prolactinoma, see your health care provider to determine the cause.

If you have a prolactinoma and you want to become or are already pregnant, talk to your health care provider. Adjustments in your treatment and monitoring may be necessary.

**DIFFERENTIAL DIAGNOSIS**

* Pregnancy
* Hypothyroidism
* Renal failure
* Breast stimulation
* Pituitary tumors

**EPIDEMIOLOGY**

Prolactinomas account for up to 40% of all clinically recognized pituitary adenomas. The mean prevalence of prolactinoma is estimated to be approximately 10 per 100,000 in men and 30 per 100,000 in women, with a peak prevalence in women aged 25 to 34 years. Among patients with prolactinomas, as many as 60% of the males present with macroprolactinomas, while 90% of the females present with microprolactinomas.

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**Hyperprolactinemia**

Hyperprolactinemia happens when you have high levels of prolactin in your blood. Prolactin is a hormone that’s responsible for breast tissue development and lactation.

Hyperprolactinemia isn’t life-threatening. But it can cause infertility and other issues that can impact your quality of life. The good news is that it’s treatable.

Hyperprolactinemia affects less than 1% of the general population. Women are more likely to have the condition than men.

**Symptoms and Causes**

Hyperprolactinemia happens when you have high levels of prolactin in your blood. It isn’t life-threatening, but it can cause issues that can impact your quality of life.

**Symptoms of hyperprolactinemia**

Some people who have hyperprolactinemia have very mild or no symptoms (are asymptomatic).

For anyone, hyperprolactinemia can cause the following symptoms:

* Infertility
* Loss of interest in sex (low libido)
* Low bone mass (osteopenia)
* Milky discharge from your nipples when not pregnant or breastfeeding (galactorrhea)

For women, symptoms of hyperprolactinemia include:

* Changes in menstruation not related to menopause, like irregular periods or no periods
* Pain during penetrative sex due to vaginal dryness

For men, common symptoms of hyperprolactinemia include:

* Erectile dysfunction (ED)
* Low levels of testosterone
* Enlarged breast tissue (gynecomastia)

**Causes hyperprolactinemia**

Several factors and conditions can cause hyperprolactinemia, including:

* Prolactinoma (a pituitary gland tumor)
* Other pituitary gland tumors
* Certain medications
* Certain health conditions

Sometimes, healthcare providers can’t find the cause. They call this idiopathic hyperprolactinemia. It usually goes away without treatment after several months.

Prolactinomas

A prolactinoma is the most common cause of hyperprolactinemia. A prolactinoma is a benign (noncancerous) tumor (adenoma). It forms in your pituitary gland. It causes excess production of prolactin.

Other pituitary gland tumors

Large tumors (other than prolactinomas) in or near your pituitary gland may cause hyperprolactinemia. This is usually because the tumor prevents dopamine from reaching your pituitary gland. Dopamine stops prolactin production.

Radiation therapy for tumors on or near your pituitary gland may also cause hyperprolactinemia.

**Medications**

The brain chemical dopamine helps suppress (stop) prolactin production. Any medication that affects dopamine production can make your prolactin levels rise.

Medications that can cause hyperprolactinemia include:

* Birth control pills
* Certain antipsychotic medications, like risperidone and haloperidol
* High blood pressure medications, like methyldopa and verapamil
* Medications that treat heartburn and gastroesophageal reflux disease (GERD) (H2 antihistamines)
* Medications that treat depression, like tricyclic antidepressants and SSRIs
* Medications that treat menopause symptoms, like estrogen therapy
* Medications that treat nausea and vomiting (antiemetics)
* Pain relievers that contain opioids

Your prolactin levels will usually return to normal three to four days after you stop taking the medication. Never stop taking a prescribed medication unless your healthcare provider tells you to.

**Health conditions**

Health conditions other than a prolactinoma that may cause hyperprolactinemia include:

* Chest wall injuries, like fractured ribs or sternum (breastbone)
* Chronic kidney disease
* Chronic liver disease
* Cushing disease
* Hypothyroidism (underactive thyroid)
* Shingles, especially if the rash or blisters are on your chest
* Polycystic ovary syndrome (PCOS)

**Risk factors for hyperprolactinemia**

The only known risk factor for hyperprolactinemia is having multiple endocrine neoplasia (MEN) type 1 (MEN1). MEN1 is an inherited condition that can cause prolactinoma.

If you have a first-degree relative (biological sibling or parent) who has MEN1, you may want to get genetic testing. It might help screen for and catch a prolactinoma in its early phase.

**Diagnosis and Tests**

Your healthcare provider will start with a prolactin (PRL) blood test.

If your results show that you have hyperprolactinemia, the next step will be to determine the cause. Your provider may recommend additional testing, like other blood tests and imaging tests.

**Management and Treatment**

The treatment for hyperprolactinemia depends on its cause. If you have high prolactin levels but have few or no symptoms, you may not need treatment.

Treatment options for prolactinomas (the most common cause of hyperprolactinemia) include:

* Medication. Medications called dopamine agonists regulate your prolactin levels. They’re very effective in shrinking prolactinoma tumors. This is the most common form of treatment for prolactinomas.
* Surgery. If medication isn’t working to shrink your prolactinoma, you may need to have surgery to remove it.
* Radiation therapy. This is a rare third option for treating prolactinomas if other methods don’t work.

If a medication is causing hyperprolactinemia, your healthcare provider may prescribe a different one that doesn’t affect your prolactin levels as much.

**Outlook / Prognosis**

The prognosis (outlook) for hyperprolactinemia is generally good. Treatment for its most common cause is usually effective.

Although hyperprolactinemia isn’t life-threatening, it can cause certain issues like infertility and irregular periods. Because of this, it’s important to receive treatment if you have hyperprolactinemia.

**Epidemiology**

Frequency

*United States*

This condition occurs in less than 1% of the general population and in 5-14% of patients presenting with secondary amenorrhea.Approximately 75% of patients presenting with galactorrhea and amenorrhea have hyperprolactinemia. Of these patients, approximately 30% have prolactin-secreting tumors.

Mortality/Morbidity

Mortality is unlikely, although a study by Soto-Pedre et al (discussed below) did report increased mortality depending on the cause of hyperprolactinemia.In cases where the condition is due to a large prolactin-secreting tumor,local mass effect can lead to significant morbidity.

The condition causes systemic complaints that often resolve when the prolactin level returns to normal or once the tumor shrinks.

Rare cases of metastatic malignant prolactinoma have been described in the literature, but they number less than 50.

Bone resorption can be seen due to sex steroid attenuation mediated by the hyperprolactinemic state. A 25% decrease in spinal bone density can be seen in women with hyperprolactinemia and may be irreversible, even with normalization of prolactin levels.

**Differential DiagnosIs**

* Acute Kidney Injury (AKI)
* Erectile Dysfunction
* Gigantism and Acromegaly
* Herpes Zoster
* Hypothyroidism
* Pituitary Macroadenomas
* Pituitary Microadenomas
* Prolactinoma

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**panhypopituitarism**

Panhypopituitarism is a rare condition in which there’s a lack (deficiency) of all of the hormones your pituitary gland makes. It can affect infants, children and adults.

Hormones are chemicals that coordinate different functions in your body by carrying messages through your blood to your organs, muscles and other tissues. These signals tell your body what to do and when to do it.

Your pituitary gland is a pea-sized gland located at the base of your brain below your hypothalamus (the part of your brain that controls your autonomic nervous system). It’s a part of your endocrine system.

The pituitary hormones are in charge of several important functions in your body, such as metabolism, growth and reproduction.

Normally, your body carefully controls hormone levels. If the levels of any of these hormones are unbalanced, it causes symptoms and health issues. Panhypopituitarism causes several symptoms since all of your pituitary hormone levels are lower than what they should be.

Panhypopituitarism is a type of hypopituitarism.

If you have a deficiency (lack) of one or multiple hormones your pituitary gland makes, you have hypopituitarism.

Panhypopituitarism happens when there’s a deficiency in all of the hormones your pituitary makes. The prefix “pan-” means “all.”

Your pituitary gland makes and releases the following hormones:

* Adrenocorticotropic hormone (ACTH or corticotropin): This hormone stimulates your adrenal glands to produce cortisol (the “stress hormone”), which helps maintain blood pressure and blood glucose (blood sugar) levels.
* Follicle-stimulating hormone (FSH): This hormone stimulates sperm production in males and stimulates the ovaries to produce estrogen and egg development in females.
* Growth hormone (GH): In children, growth hormone stimulates growth. In adults, growth hormone helps maintain healthy muscles and bones and impacts fat distribution. GH also impacts your metabolism.
* Luteinizing hormone (LH): This hormone stimulates ovulation in females and testosterone production in males.
* Prolactin: This hormone stimulates breast milk production after giving birth and can affect menstrual periods in females. It can affect fertility and sexual functions in adults.
* Thyroid-stimulating hormone (TSH): This hormone stimulates your thyroid to produce hormones that manage metabolism, energy and your nervous system.

Your pituitary gland stores and releases the following hormones, but your hypothalamus produces them:

* Antidiuretic hormone (ADH or vasopressin): This hormone regulates the water balance and sodium (salt) levels in your body.
* Oxytocin: In females, oxytocin helps labor to progress during childbirth and causes breast milk to flow. It also influences the bonding between parent and baby.

Panhypopituitarism can affect anyone at any age.

Panhypopituitarism is rare. There are approximately four cases of panhypopituitarism per 100,000 people across the globe per year.

Yes, panhypopituitarism can be life-threatening, especially if you have a significant deficiency of adrenocorticotropic hormone (ACTH or corticotropin).

Adrenal crisis (acute cortisol insufficiency) is a life-threatening complication of panhypopituitarism. The cause is a lack of ACTH, which is a hormone that controls your cortisol levels. It’s treatable but requires immediate medical treatment.

Signs and symptoms of adrenal crisis include:

* Fever.
* Weakness.
* Confusion.
* Low blood pressure (hypotension).
* Fast heart rate (tachycardia).
* Vomiting.
* Diarrhea.
* Low blood sugar (hypoglycemia).

If you or your child are experiencing these symptoms, call 911 or get to the nearest hospital as soon as possible.

**Symptoms and Causes**

The signs and symptoms of panhypopituitarism vary widely based on how much of each of the pituitary hormones is lacking and whether the condition develops rapidly or slowly.

Symptoms of panhypopituitarism that children and adults can have include:

* Nausea or dizziness.
* Fatigue.
* Depression and/or anxiety.
* Frequent infections.
* Low blood sugar (hypoglycemia).
* Sensitivity to cold.
* Unusually dry skin.
* Unexplained weight loss or weight gain.
* Irregular lipid and cholesterol levels (dyslipidemia).
* Fast heart rate (tachycardia).
* Excessive thirst and excessive urination.
* Irregular menstruation (periods).
* Female infertility.
* Male infertility.

Additional symptoms of panhypopituitarism that are specific to infants, children and/or adolescents include:

* Prolonged jaundice in newborns.
* Small penis in male infants (micropenis).
* Slowed growth.
* Delayed puberty.

These symptoms may resemble other conditions or medical issues. It’s important to always consult your healthcare provider if you’re experiencing new or prolonged symptoms to get a proper diagnosis.

**Causes panhypopituitarism**

Many conditions and situations can cause panhypopituitarism. In some cases, healthcare providers can’t determine the cause. This is called idiopathic panhypopituitarism.

In general, the cause of panhypopituitarism is some type of damage to your hypothalamus and/or pituitary gland that causes either or both of them to not function properly.

Understanding the possible causes of panhypopituitarism involves understanding how your hypothalamus and pituitary gland work together.

**The hypothalamus-pituitary gland connection**

Together, your pituitary gland and hypothalamus form a hypothalamus-pituitary complex that serves as your brain’s central command center to control vital bodily functions.

Your hypothalamus is the part of your brain that’s in charge of some of your body’s basic operations. It sends messages to your autonomic nervous system. Your hypothalamus also tells your pituitary gland to produce and release hormones that affect other areas of your body.

Your pituitary gland connects to your hypothalamus through a stalk of blood vessels and nerves (the pituitary stalk). Through that stalk, your hypothalamus communicates with your pituitary gland.

Your hypothalamus makes the following hormones to communicate with and stimulate your pituitary gland:

* Corticotropin-releasing hormone.
* Dopamine.
* Gonadotropin-releasing hormone.
* Growth hormone-releasing hormone.
* Somatostatin.
* Thyrotropin-releasing hormone.

Since your pituitary gland and hypothalamus work together so closely, if one of them becomes damaged, it can affect the hormonal function of the other. This can result in panhypopituitarism.

**Pituitary-related causes of panhypopituitarism**

Conditions or situations that can damage your pituitary gland and cause panhypopituitarism include:

* Pituitary adenomas (noncancerous tumors).
* Pituitary gland surgery, typically for adenoma removal.
* Radiation therapy for a pituitary adenoma.
* Pituitary apoplexy (sudden destruction of pituitary gland tissue due to a lack of blood supply to your pituitary or bleeding into your pituitary).
* Underdeveloped or poorly formed pituitary gland at birth.

**Hypothalamus-related causes of panhypopituitarism**

Conditions or situations that can damage your hypothalamus and cause panhypopituitarism include:

* Traumatic brain injury (TBI).
* Brain surgery on or near your hypothalamus.
* Benign (noncancerous) tumors that form in your hypothalamus, such as craniopharyngiomas.
* Malignant (cancerous) tumors that metastasize (spread) to your hypothalamus from cancer elsewhere in your body, such as lung and breast cancers.
* Pressure from hydrocephalus.
* Stroke.
* Tuberculous meningitis.

**Diagnosis and Tests**

If you’re experiencing symptoms of panhypopituitarism, your healthcare provider will ask detailed questions about your symptoms and medical history and perform a physical exam.

They’ll then order tests to confirm a panhypopituitarism diagnosis and/or to rule out other conditions that could be causing your symptoms.

**Test to diagnose panhypopituitarism**

Healthcare providers typically order multiple tests to diagnose panhypopituitarism, including imaging and hormone levels tests.

**Imaging tests for diagnosing panhypopituitarism**

Since panhypopituitarism results from damage to your hypothalamus or pituitary gland, your provider may order the following imaging tests to help determine the cause of panhypopituitarism:

* Brain MRI (magnetic resonance imaging) scan: An MRI scan uses radio waves and strong magnets to create detailed images of the inside of your body. Brain MRIs are considered the best way to find pituitary tumors that could be causing panhypopituitarism. An MRI scan can also help identify other issues with your hypothalamus or pituitary gland.
* Brain CT (computed tomography) scan: A brain CT scan uses X-rays and a computer to create detailed images of your brain. Your provider may use this test to see if you have a brain tumor or pituitary adenoma (noncancerous tumor) that’s causing panhypopituitarism. A CT scan can also help identify other issues with your hypothalamus or pituitary gland.

**Hormone tests for diagnosing panhypopituitarism**

If you have symptoms of panhypopituitarism, your provider will need to measure the levels of all the hormones your pituitary gland releases to check how deficient each one is and to help rule out other conditions.

While some pituitary hormones normally maintain a fairly stable level in your bloodstream, other pituitary hormone levels normally vary widely throughout the day. Because of this, some hormone tests are simple blood tests and others are specialized stimulation tests.

Hormone level tests include:

* Blood tests: Pituitary gland hormones that providers can measure through simple blood tests include thyroid-stimulating hormone (TSH), prolactin, follicle-stimulating hormone (FSH) and luteinizing hormone (LH). They may also measure other hormones that your pituitary hormones affect, such as thyroxine, estrogen and testosterone.
* ACTH stimulation test: This test measures how well your adrenal glands respond to adrenocorticotropic hormone (ACTH). It involves an injection of synthetic ACTH and timed blood draws.
* Growth hormone (GH) stimulation test: For this test, your provider injects medicine that would normally stimulate your pituitary gland to release growth hormone. They then take samples of your blood to measure your GH levels.
* Insulin tolerance test: An insulin tolerance test can help diagnose GH and ACTH deficiencies.

**Management and Treatment**

The treatment for panhypopituitarism greatly depends on how deficient each pituitary hormone is and the cause of the condition. Because of this, treatment is very individualized. Your healthcare team will determine what the best treatment plan is for you. Common treatment options for panhypopituitarism include:

* Hormone replacement therapy: Hormone replacement therapy aims to restore the deficient pituitary hormones to healthy levels. People with panhypopituitarism require lifetime hormone replacement therapy unless the underlying cause of the condition is reversible or treatable. Some hormone replacement medications are pills and others are injections (shots).
* Surgery: If you have a brain tumor or pituitary adenoma that’s causing panhypopituitarism, your provider may recommend surgery to remove the tumor or adenoma.
* Radiation therapy: If you have a brain tumor or pituitary adenoma that’s causing panhypopituitarism, your provider may recommend radiation therapy to treat and/or shrink the tumor.
* Corticosteroids: You may need increased doses of corticosteroids before and/or during any stressful event, whether physical or emotional. Physical stressors include illness, infection and surgery. Corticosteroids replace the adrenal hormones that aren't being produced because of an adrenocorticotropic hormone (ACTH) deficiency. Your body needs these hormones when it’s under stress.

In some cases, panhypopituitarism is reversible by treatment of the underlying cause, such as surgically removing a pituitary adenoma that was compressing the pituitary gland without causing damage. But in most cases, the hormone deficiencies from panhypopituitarism require lifelong treatment.

**Outlook / Prognosis**

The prognosis (outlook) for panhypopituitarism depends on several factors, including:

* How much of each of your pituitary hormones is lacking (deficient).
* Your age at the onset (beginning) of panhypopituitarism.
* If panhypopituitarism develops slowly or rapidly.
* How quickly you get a diagnosis and receive treatment.

Panhypopituitarism is associated with significant decreases in quality of life and life expectancy.

People with panhypopituitarism often develop obesity, decreased lean body mass and an increased risk of cardiovascular disease. People with panhypopituitarism may also have an increased risk of osteoporosis and bone fractures.

Careful, thorough treatment with hormone replacements and aggressive monitoring and treatment for cardiovascular disease risk factors may improve outcomes.

**Prevention**

In most cases, you can’t prevent panhypopituitarism. But there are ways to catch it in its early phase if you’re at risk for developing it.

If you’ve experienced any of the following situations, you’re at greater risk for developing panhypopituitarism:

* Brain or pituitary gland surgery.
* Radiation therapy for your brain and/or pituitary gland.
* Traumatic brain injury.
* Hydrocephalus (buildup of fluid in your brain).

Your healthcare provider will likely recommend regular testing to check the function and health of your pituitary gland and/or hypothalamus if you’re at a greater risk for developing panhypopituitarism.

**Living With**

If you have symptoms of panhypopituitarism or received a diagnosis of the condition, you’ll likely need to see an endocrinologist — a healthcare provider who specializes in treating hormone-related conditions.

You’ll need to see your endocrinologist regularly throughout your life to ensure that your hormone replacement therapy is working well and to prevent excessive hormone replacement.

**Epidemiology**

Frequency

Hypopituitarism is caused by various conditions and is associated with various hormonal deficiencies. Thus, data are limited regarding frequency rates of the various etiologies and components.

In the United States, data from the Northwest Regional Screening program was used to estimate the frequency of congenital TSH deficiency at 1 case per 29,000 live births.

An Italian study reported GH deficiency prevalence to be approximately 9 cases per 1000 individuals in a pediatric population.

A study by Jakobsen et al reported that in Denmark between 1996 and 2020, the incidence of congenital combined pituitary hormone deficiency (cCPHD) diagnosed prior to age 18 years was 7.38 cases per 100,000 live births. This came to an incidence of 4.10 cases per million live births annually, with cCPHD defined as a congenital deficiency of two or more pituitary hormones.

Mortality and morbidity

Morbidity and mortality due to hypopituitarism are caused by the individual hormone deficiencies or the underlying cause of hypopituitarism. Individual hormonal deficiencies are discussed in greater detail in specific articles, and the underlying causes of death are not discussed here.

Acute mortality due to hormonal deficiencies is rare. When deaths occur due to hormonal deficiencies, they are usually caused by

**Differential Diagnosis**

* Craniopharyngioma Imaging
* Diabetes Insipidus
* Histiocytosis
* Hypogonadism
* Pediatric Adrenal Insufficiency (Addison Disease)
* Pediatric Growth Hormone Deficiency
* Pediatric Hypoglycemia
* Pediatric Hypothyroidism

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**HYPOPITUITARISM**

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.

**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.

**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.

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.

**Diagnosis**

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**

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 somatropin (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.

**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.

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.

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.

**When to see a doctor**

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.

**EPIDEMIOLOGY**

Hypopituitarism is considered to be a rare disorder. There are less than 200,000 patients with hypopituitarism 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

**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

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**CUSHING SYNDROME**

Cushing syndrome happens when the body has too much of the hormone cortisol for a long time. This can result from the body making too much cortisol, or from taking medicines called glucocorticoids, which affect the body the same way as cortisol.

Too much cortisol can cause some of the main symptoms of Cushing syndrome — a fatty hump between the shoulders, a rounded face, and pink or purple stretch marks on the skin. Cushing syndrome also can cause high blood pressure or bone loss. Sometimes, it can cause type 2 diabetes.

Treatments for Cushing syndrome can lower the body's cortisol levels and improve symptoms. The sooner treatment starts, the better the chances for recovery.

**Symptoms**

Symptoms of Cushing syndrome can vary depending on the level of extra cortisol.

**Common symptoms of Cushing syndrome**

* Weight gain in the trunk, with thin arms and legs.
* Weight gain in the face. This is sometimes called the moon face.
* A fatty lump between the shoulders. This may be referred to as a buffalo hump.
* Pink or purple stretch marks on the stomach, hips, thighs, breasts and underarms.
* Thin, frail skin that bruises easily.
* Slow wound healing.
* Acne.

**Symptoms women with Cushing syndrome may experience**

* Thick, dark hair on the face and body. This condition is called hirsutism.
* Periods that are irregular or that stop.

**Symptoms men with Cushing syndrome may experience**

* Lower sex drive.
* Reduced fertility.
* Problems getting an erection.

**Other possible symptoms of Cushing syndrome**

* Extreme tiredness.
* Muscle weakness.
* Depression, anxiety and irritability.
* Emotions that are hard to control.
* Trouble concentrating or remembering.
* Sleeplessness.
* High blood pressure.
* Headache.
* Infections.
* Skin darkening.
* Bone loss, which can lead to broken bones.
* Stunted growth in children.

**CAUSES**

Cushing syndrome is caused by having too much cortisol in the body. Cortisol is a hormone that is made in the adrenal glands. It helps the body respond to stress and plays many other important roles, including:

* Controlling blood pressure.
* Reducing inflammation.
* Helping the heart and blood vessels work correctly.
* Controlling blood sugar.
* Helping the body use food for energy.

**The role of glucocorticoid medicines (exogenous Cushing syndrome)**

Cushing syndrome can happen from taking glucocorticoid medicines. These are often used to treat inflammatory diseases such as rheumatoid arthritis, lupus and asthma. Pain or injury in the back or joints and many skin rashes may be treated with glucocorticoids. They also may be used to stop the body from rejecting a new organ after a transplant.

Glucocorticoids may be taken by mouth, given as a shot, rubbed into the skin or breathed into the lungs by an inhaler. Any form of glucocorticoid, if taken in large amounts for a long time, can cause Cushing syndrome.

**When the body makes too much cortisol (endogenous Cushing syndrome)**

A hormone made in the pituitary gland controls how much cortisol the body makes. This is called adrenocorticotropic hormone (ACTH). Some tumors make ACTH, which creates more cortisol and can cause Cushing syndrome. Problems with the adrenal glands also can affect cortisol and cause Cushing syndrome.

When Cushing syndrome happens this way, it may be caused by:

* **ACTH-producing pituitary adenoma.** Pituitary adenomas are tumors that grow in the pituitary gland. They are found at the base of the brain and are usually not cancer. These tumors sometimes make too much ACTH. This causes the adrenal glands to make extra cortisol. When Cushing syndrome happens this way, it's called Cushing disease. It happens more often in women and is the most common type of endogenous Cushing syndrome.
* **Ectopic ACTH-producing tumor.** Rarely, a tumor that makes too much ACTH grows in an organ that usually doesn't make ACTH. This is called ectopic ACTH production. It causes the body to make too much cortisol. These tumors can be cancerous, but aren't always. They are usually found in the lungs, pancreas, thyroid or thymus gland.
* **Adrenal gland tumors or disease.** Problems with the adrenal glands can cause them to make too much cortisol. The most common is a tumor in the outer part of the adrenal gland called an adrenal adenoma. These tumors are not cancer, and only some make too much cortisol.  
  Cancerous tumors in the outer part of the adrenal glands, known as adrenocortical carcinoma, are rare. But they can make cortisol and cause Cushing syndrome. Sometimes, several lumps that make cortisol can grow in the adrenal glands and cause Cushing syndrome. This is called adrenal nodular hyperplasia.
* **Familial Cushing syndrome.** Rarely, people inherit a tendency to get tumors on one or more of their endocrine glands, which are glands that make hormones. If these tumors make ACTH or cortisol, Cushing syndrome can happen.

**Diagnosis**

Taking glucocorticoid medicines is the most common way to get Cushing syndrome. Your health care provider can look at all your medicines — pills, injections, creams and inhalers — to see if you're taking medicines that can cause the syndrome. If you are, you won't need other tests.

When Cushing syndrome is caused by the body making too much cortisol, it can be hard to diagnose. That's because other illnesses have similar symptoms. Diagnosing Cushing syndrome can be a long and complex process. You'll need to see a doctor who specializes in hormonal diseases, called an endocrinologist.

The endocrinologist likely will do a physical exam and look for signs of Cushing syndrome, such as a round face, a hump on the back of the neck, and thin, bruised skin with stretch marks.

If you haven't been using a glucocorticoid medicine, these tests may help pinpoint the cause of Cushing syndrome:

* **Urine and blood tests.** These tests measure hormone levels and show if the body is making too much cortisol. For the urine test, you may be asked to collect your urine over a 24-hour period. Cortisol, ACTH and other hormones are be measured in urine and blood samples.  
  Your health care provider also might recommend other tests. These tests measure cortisol levels before and after using hormone medicines to trigger or block cortisol.
* **Saliva test.** Cortisol levels typically rise and fall during the day. In people without Cushing syndrome, cortisol drops in the evening. By looking at cortisol levels from a small sample of saliva collected at night, the health care team can see if cortisol levels are too high.
* **Imaging tests.** CT or MRI scans can take pictures of the pituitary and adrenal glands to see if anything shows up, such as tumors.
* **Inferior petrosal sinus sampling.** This test can help decide if Cushing syndrome is caused by an ACTH-producing pituitary adenoma, or ACTH-producing tumor in another organ. For the test, blood samples are taken from the veins that drain the pituitary gland, called the inferior petrosal sinuses.  
  During the test, you are given medicine through a vein to help you stay calm and comfortable. A thin tube is placed in your groin or neck area and is threaded to the inferior petrosal sinuses to collect a blood sample. Another blood sample is taken from your forearm. You are then given a medicine that causes the tumor to make more ACTH, and blood samples are taken again from the same areas. Levels of ACTH are then compared between the two sample areas.  
  If the ACTH level is higher in the sinus sample, the problem is coming from the pituitary. If the ACTH levels are similar between the sinuses and forearm, the problem is outside of the pituitary gland.

These tests help your health care provider diagnose Cushing syndrome. They also may help rule out other health conditions, such as polycystic ovary syndrome — a hormone problem in people with enlarged ovaries. Depression, eating disorders and alcoholism also can have symptoms similar to Cushing syndrome.

**Treatment**

Treatments for Cushing syndrome are designed to lower the amount of cortisol in the body. The best treatment for you depends on the cause of the syndrome. Options include:

**Reducing glucocorticoid use**

If Cushing syndrome is caused by taking glucocorticoid medicine for a long time, your health care provider may be able to control your symptoms by lowering how much medicine you take. This is done carefully over time, while still managing the condition for which you take it. Don't reduce the dose of glucocorticoid drugs or stop taking them on your own. Do so only with help from your healthcare provider.

Stopping these medicines too quickly can cause you to have too little cortisol in your body. Slowly tapering off the medicine allows your body to make a healthy amount of cortisol.

**Surgery**

If Cushing syndrome is caused by a tumor, your health care provider may recommend removing the tumor with surgery. Pituitary tumors are often removed by a neurosurgeon, who may do the operation through your nose. ACTH-producing tumors in other parts of the body may be removed with regular surgery or using less-invasive approaches with smaller incisions.

If an ACTH-producing tumor isn't found, or if one can't be fully removed and Cushing syndrome continues, your health care provider may recommend removing the adrenal glands. This is called a bilateral adrenalectomy. This procedure immediately stops the body from making too much cortisol. After both adrenal glands are removed, you may need to take medicines to replace cortisol and another adrenal hormone called aldosterone for the rest of your life.

Adrenal gland tumors can be removed through an incision in the midsection or back. Often, adrenal gland tumors that are noncancerous can be removed with a minimally invasive approach.

After Cushing syndrome surgery, your body won't make enough ACTH. You'll need to take a cortisol replacement medicine to give your body the right amount of cortisol. Most of the time, your body starts making enough cortisol again, and your health care provider can taper off the replacement medicine. Your endocrinologist may use blood tests to help decide if you need cortisol medicine and when it may be stopped.

This process can take from six months to a year or more. Sometimes, people with Cushing syndrome need lifelong replacement medicine.

**Radiation therapy**

If the surgeon can't totally remove a pituitary tumor, radiation therapy may be needed along with surgery. Radiation also may be used for people who can't have surgery.

Radiation can be given in small doses over six weeks, or with a single, high dose of radiation. In both cases, your health care provider can plan your procedure in a way that reduces radiation exposure to other tissues.

**Medications**

Medicines can be used to control cortisol levels when surgery and radiation don't work or aren't an option. Medicines also might be used before surgery in people who are very sick with Cushing syndrome. This can improve symptoms of the disease and reduce the risks of surgery. Medical therapy for Cushing syndrome is not a cure and may not completely improve all of the symptoms of too much cortisol.

Medicines to control cortisol production at the adrenal gland include ketoconazole, osilodrostat (Isturisa), mitotane (Lysodren), levoketoconazole (Recorlev), and metyrapone (Metopirone).

Mifepristone (Korlym, Mifeprex) is approved for people with Cushing syndrome who have type 2 diabetes or high blood sugar. Mifepristone does not lower the amount of cortisol the body makes, but it blocks the effect of cortisol on tissues.

Pasireotide (Signifor) is given as a shot two times a day. It works by lowering the amount of ACTH from the tumor, which lowers cortisol levels. Other medicines are being developed.

Side effects from these medicines may include tiredness, upset stomach, vomiting, headaches, muscle aches, high blood pressure, low potassium and swelling. Some have more-serious side effects, such as brain and nervous system side effects and liver damage.

Sometimes, the tumor or its treatment causes the pituitary or adrenal gland to make too little of other hormones. If this happens, your health care provider can recommend hormone replacement.

**Lifestyle and home remedies**

Recovering from Cushing syndrome is usually a slow, gradual process. It can take time before you start to feel better. These tips may help you on your journey back to health.

* **Increase activities slowly.** Work up to a comfortable level of exercise or activity without overdoing it. Don't do activities that could cause you to get hurt, such as high-impact exercise. With patience and consistency, you'll improve little by little over time.
* **Eat sensibly.** Nutritious foods are a good source of fuel for your body during recovery. They also can help you lose any weight you gained from Cushing syndrome. Make sure you're getting enough calcium and vitamin D. Taken together, they help your body absorb calcium, which may strengthen your bones. This can counteract the bone density loss caused by Cushing syndrome.
* **Keep an eye on your mental health.** Depression can be a side effect of Cushing syndrome, but it also can continue or start after treatment begins. Don't ignore depression or wait it out. Seek help quickly from your healthcare provider or a therapist if you're depressed, overwhelmed or having trouble coping during your recovery.
* **Gently soothe aches and pains.** Hot baths, massages and low-impact exercises, such as water aerobics and tai chi, can help reduce some of the muscle and joint pain that happens during Cushing syndrome recovery.

**Complications**

Without treatment, Cushing syndrome can cause complications, including:

* Bone loss, also called osteoporosis, which can lead to broken bones.
* High blood pressure, also called hypertension.
* Type 2 diabetes.
* Serious or multiple infections.
* Loss of muscle mass and strength.

**When to see a doctor**

Call your healthcare provider if you have symptoms of Cushing syndrome, especially if you're taking glucocorticoid medicine to treat a health issue such as asthma, arthritis or inflammatory bowel disease.

**DIFFERENTIAL DIAGNOSIS**

The differential diagnosis for Cushing disease includes Cushing syndrome, ectopic ACTH secretion, exogenous corticosteroid use, pseudo-Cushing syndrome, or physiologic hypercortisolism

**EPIDEMIOLOGY**

Cushing disease is the second most commonly seen cause of Cushing syndrome, the first cause being the exogenous use of steroids. The average incidence of new cases is about 2.4 per million people annually.This disease is often diagnosed 3 to 6 years after the onset of the illness. The peak incidence of Cushing disease is in women between 50 and 60 years old. The prevalence of hypertension and the abnormalities of glucose metabolism are major predictors of morbidity and mortality in untreated cases of the disease. The mortality rate of Cushing disease is estimated to be about 10% to 11%

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**DIABETES INSIPIDUS**

Diabetes insipidus (die-uh-BEE-teze in-SIP-uh-dus) is an uncommon problem that causes the fluids in the body to become out of balance. That prompts the body to make large amounts of urine. It also causes a feeling of being very thirsty even after having something to drink. Diabetes insipidus also is called arginine vasopressin deficiency and arginine vasopressin resistance.

While the terms "diabetes insipidus" and "diabetes mellitus" sound alike, the two conditions are not connected. Diabetes mellitus involves high blood sugar levels. It's a common condition, and it's often called simply diabetes.

There's no cure for diabetes insipidus. But treatment is available that can ease its symptoms. That includes relieving thirst, lowering the amount of urine the body makes and preventing dehydration.

**CAUSES**

Diabetes insipidus happens when the body can't balance its fluid levels in a healthy way.

Fluid in the blood is filtered through the kidneys to remove waste. Afterward, most of that fluid is returned to the bloodstream. The waste and a small amount of fluid leave the kidneys as urine. Urine leaves the body after it's temporarily stored in the bladder.

A hormone known as antidiuretic hormone (ADH) — also called vasopressin — is needed to get the fluid that's filtered by the kidneys back into the bloodstream. ADH is made in a part of the brain called the hypothalamus. It's then stored in the pituitary gland, a small gland found at the base of the brain. Conditions that cause the brain to make too little ADH or disorders that block the effect of ADH cause the body to make too much urine.

In diabetes insipidus, the body can't properly balance fluid levels. The cause of the fluid imbalance depends on the type of diabetes insipidus.

* Central diabetes insipidus. Damage to the pituitary gland or hypothalamus from surgery, a tumor, a head injury or an illness can cause central diabetes insipidus. That damage affects the production, storage and release of ADH. An inherited disorder may cause this condition too. It also can be the result of an autoimmune reaction that causes the body's immune system to damage the cells that make ADH.
* Nephrogenic diabetes insipidus. This happens when there's a problem with the kidneys that makes them unable to properly respond to ADH. That problem may be due to:
  + An inherited disorder.
  + Certain medicines, including lithium and antiviral medicines such as foscarnet (Foscavir).
  + Low levels of potassium in the blood.
  + High levels of calcium in the blood.
  + A blocked urinary tract or a urinary tract infection.
  + A chronic kidney condition.
* Gestational diabetes insipidus. This rare form of diabetes insipidus only happens during pregnancy. It develops when an enzyme made by the placenta destroys ADH in a pregnant person.
* Primary polydipsia. This condition also is called dipsogenic diabetes insipidus. People who have this disorder constantly feel thirsty and drink lots of fluids. It can be caused by damage to the thirst-regulating mechanism in the hypothalamus. It also has been linked to mental illness, such as schizophrenia.

Sometimes no clear cause of diabetes insipidus can be found. In that case, repeated testing over time often is useful. Testing may be able to identify an underlying cause eventually.

**Risk factors**

Anyone can get diabetes insipidus. But those at higher risk include people who:

* Have a family history of the disorder.
* Take certain medicines, such as diuretics, that could lead to kidney problems.
* Have high levels of calcium or low levels of potassium in their blood.
* Have had a serious head injury or brain surgery.

**Complications**

Dehydration

Diabetes insipidus may lead to dehydration. That happens when the body loses too much fluid. Dehydration can cause:

* Dry mouth.
* Thirst.
* Extreme tiredness.
* Dizziness.
* Lightheadedness.
* Fainting.
* Nausea.

Electrolyte imbalance

Diabetes insipidus can change the levels of minerals in the blood that maintain the body's balance of fluids. Those minerals, called electrolytes, include sodium and potassium. Symptoms of an electrolyte imbalance may include:

* Weakness.
* Nausea.
* Vomiting.
* Loss of appetite.
* Confusion.

**Symptoms**

Symptoms of diabetes insipidus in adults include:

* Being very thirsty, often with a preference for cold water.
* Making large amounts of pale urine.
* Getting up to urinate and drink water often during the night.

Adults typically urinate an average of 1 to 3 quarts (about 1 to 3 liters) a day. People who have diabetes insipidus and who drink a lot of fluids may make as much as 20 quarts (about 19 liters) of urine a day.

A baby or young child who has diabetes insipidus may have these symptoms:

* Large amounts of pale urine that result in heavy, wet diapers.
* Bed-wetting.
* Being very thirsty, with a preference for drinking water and cold liquids.
* Weight loss.
* Poor growth.
* Vomiting.
* Irritability.
* Fever.
* Constipation.
* Headache.
* Problems sleeping.
* Vision problems.

**When to see a doctor**

See your health care provider right away if you notice that you're urinating much more than usual and you're very thirsty on a regular basis.

**Diagnosis**

Tests used to diagnose diabetes insipidus include:

* Water deprivation test. For this test, you stop drinking fluids for several hours. During the test, your health care provider measures changes in your body weight, how much urine your body makes, and the concentration of your urine and blood. Your health care provider also may measure the amount of ADH in your blood.  
  During this test, you may receive a manufactured form of ADH. That can help show if your body is making enough ADH and if your kidneys can respond as expected to ADH.
* Urine test. Testing urine to see if it contains too much water can be helpful in identifying diabetes insipidus.
* Blood tests. Checking the levels of certain substances in the blood, such as sodium, potassium and calcium, can help with a diagnosis and may be useful in identifying the type of diabetes insipidus.
* Magnetic resonance imaging (MRI). An MRI can look for problems with the pituitary gland or hypothalamus. This imaging test uses a powerful magnetic field and radio waves to create detailed pictures of the brain.
* Genetic testing. If other people in your family have had problems with too much urination or have been diagnosed with diabetes insipidus, your health care provider may suggest genetic testing.

**Treatment**

If you have mild diabetes insipidus, you may only need to drink more water to avoid dehydration. In other cases, treatment typically is based on the type of diabetes insipidus.

* Central diabetes insipidus. If central diabetes insipidus is caused by a disorder in the pituitary gland or hypothalamus, such as a tumor, that disorder is treated first.  
  When treatment is needed beyond that, a manufactured hormone called desmopressin (DDAVP, Nocdurna) is used. This medication replaces the missing antidiuretic hormone (ADH) and lowers the amount of urine the body makes. Desmopressin is available as a pill, as a nasal spray and as a shot.  
  If you have central diabetes insipidus, it's likely that your body still makes some ADH. But the amount can change from day to day. That means the amount of desmopressin that you need also may change. Taking more desmopressin than you need can cause water retention. In some cases, it may cause potentially serious low sodium levels in the blood. Talk to your health care provider about how and when to adjust your dosage of desmopressin.
* Nephrogenic diabetes insipidus. Because the kidneys don't properly respond to ADH in this form of diabetes insipidus, desmopressin won't help. Instead, your health care provider may advise you to eat a low-salt diet to lower the amount of urine your kidneys make.  
  Treatment with hydrochlorothiazide (Microzide) may ease your symptoms. Although hydrochlorothiazide is a diuretic — a type of medicine that causes the body to make more urine — it can lower urine output for some people with nephrogenic diabetes insipidus.  
  If your symptoms are due to medicines you're taking, stopping those medicines may help. But don't stop taking any medicine without first talking to your health care provider.
* Gestational diabetes insipidus. Treatment for gestational diabetes insipidus involves taking the manufactured hormone desmopressin.
* Primary polydipsia. There is no specific treatment for this form of diabetes insipidus other than lowering the amount of fluids you drink. If the condition is related to a mental illness, treating that may ease symptoms.

**Lifestyle and home remedies**

If you have diabetes insipidus:

* Prevent dehydration. As long as you take your medicine and have easy access to water, you'll likely be able to prevent serious problems from dehydration. Plan ahead by carrying water with you wherever you go. Keep a supply of medicine with you when you're away from home.
* Wear a medical alert bracelet or carry a medical alert card. If you have a medical emergency, the alert provides information that your health care providers need to give you the right care.

**Outlook / Prognosis**

The outlook (prognosis) for AVP-D and AVP-R is generally good. It usually doesn’t cause serious problems as long as you get treatment and drink enough water.

The risk of complications is higher for:

* Infants
* People over 65
* People with certain mental health conditions or developmental disabilities

These groups of people may have difficulty recognizing their thirst or they may not be able to act on it.

**Epidemiology**

DI is uncommon in the United States, with a prevalence of 3 cases per 100,000 population.No significant sex-related differences in central or nephrogenic DI exist, with male and female prevalence being equal. Similarly, no significant differences in prevalence among ethnic groups have been found.

With both central and nephrogenic DI, inherited causes account for approximately 1-2% of all cases. An incidence of about 1 in 20 million births for nephrogenic DI caused by *AQP2 mutations* has been cited.

**Differential Diagnosis**

* Histiocytosis
* Hypercalcemia
* Hypokalemia
* Medullary Cystic Disease
* Pediatric Head Trauma
* Sickle Cell Disease (SCD)
* Type 1 Diabetes Mellitus

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**THYROID NODULES**

Thyroid nodules are solid or fluid-filled lumps that form within your thyroid, a small gland located at the base of your neck, just above your breastbone

Most thyroid nodules aren't serious and don't cause symptoms. Only a small percentage of thyroid nodules are cancerous.

You often won't know you have a thyroid nodule until your doctor discovers it during a routine medical exam. Or your doctor may uncover it during a scan that was done for another health reason. Some thyroid nodules, however, may become large enough to be visible or make it difficult to swallow or breathe.

Treatment options depend on the type of thyroid nodule you have.

**CAUSES**

Several conditions can cause nodules to develop in your thyroid gland, including:

● **Overgrowth of normal thyroid tissue.** An overgrowth of normal thyroid tissue is sometimes referred to as a thyroid adenoma. It's unclear why this occurs, but it's not cancerous and isn't considered serious unless it causes bothersome symptoms from its size.  
 Some thyroid adenomas lead to hyperthyroidism.

● **Thyroid cyst.** Fluid-filled cavities (cysts) in the thyroid most commonly result from degenerating thyroid adenomas. Often, solid components are mixed with fluid in thyroid cysts. Cysts are usually non cancerous, but they occasionally contain cancerous solid components.

● **Chronic inflammation of the thyroid.** Hashimoto's disease, a thyroid disorder, can cause thyroid inflammation and result in enlarged nodules. This often is associated with hypothyroidism.

● **Multinodular goiter.** The term goiter is used to describe any enlargement of the thyroid gland, which can be caused by iodine deficiency or a thyroid disorder. A multinodular goiter contains multiple distinct nodules within the goiter, but its cause is less clear.

● **Thyroid cancer.** The chances that a nodule is cancerous are small. However, a nodule that is large and hard or causes pain or discomfort is more worrisome. You will likely want to have it checked by your doctor.  
 Certain factors increase your risk of thyroid cancer, such as a family history of thyroid or other endocrine cancers and having a history of radiation exposure from medical therapy or from nuclear fallout.

● **Iodine deficiency.** Lack of iodine in your diet can sometimes cause your thyroid gland to develop thyroid nodules. But iodine deficiency is uncommon in the United States, where iodine is routinely added to table salt and other foods.

**RISK FACTOR**

Anyone can have a thyroid nodule, including children and adults. However, they’re about four times more common in females than males.

They also occur more often in people who live in countries where food isn’t fortified with iodine. (Iodine is necessary for your thyroid gland to make hormones.)

Other factors that lead to an increased risk of thyroid nodules include:

● History of thyroid radiation.

● Family history of thyroid nodules or thyroid cancer.

● Increasing age.

● Iron-deficiency anemia.

● Smoking.

● Obesity.

● Metabolic syndrome.

● Alcohol consumption.

● Increased levels of insulin-like growth factor-1 (a hormone).

●     Uterine fibroids.

**SYMPTOMS**

Most thyroid nodules don't cause signs or symptoms. But occasionally some nodules become so large that they can:

● Be felt

● Be seen, often as a swelling at the base of your neck

● Press on your windpipe or esophagus, causing shortness of breath or difficulty swallowing

In some cases, thyroid nodules produce additional thyroxine, a hormone secreted by your thyroid gland. The extra thyroxine can cause symptoms of an overproduction of thyroid hormones (thyr), such as:

● Unexplained weight loss

● Increased sweating

● Tremor

● Nervousness

● Rapid or irregular heartbeat

Only a small number of thyroid nodules are cancerous. But determining which nodules are cancerous can't be done by evaluating your symptoms alone. Most cancerous thyroid nodules are slow growing and may be small when your doctor discovers them. Aggressive thyroid cancers are rare with nodules that may be large, firm, fixed and rapid growing

**DIAGNOSIS AND TEST**

In assessing a lump or nodule in your neck, one of your doctor's main goals is to rule out the possibility of cancer. But your doctor will also want to know if your thyroid is functioning properly. Tests include:

● **Physical exam.** Your doctor will likely ask you to swallow while he or she examines your thyroid because a nodule in your thyroid gland will usually move up and down during swallowing.  
 Your doctor will also look for signs and symptoms of hyperthyroidism, such as tremor, overly active reflexes, and a rapid or irregular heartbeat. He or she will also check for signs and symptoms of hypothyroidism, such as a slow heartbeat, dry skin and facial swelling.

● **Thyroid function tests.** Tests that measure blood levels of thyroid-stimulating hormone (TSH) and hormones produced by your thyroid gland can indicate whether you have hyperthyroidism or hypothyroidism.

● **Ultrasound.** This imaging technique uses high-frequency sound waves to produce images of your thyroid gland. A thyroid ultrasound provides the best information about the shape and structure of nodules. Doctors may use it to distinguish cysts from solid nodules or to determine if multiple nodules are present. Doctors may also use it as a guide in performing a fine-needle aspiration biopsy.

● **Fine-needle aspiration biopsy.** Nodules are often biopsied to make sure no cancer is present. During the procedure, your doctor inserts a very thin needle in the nodule and removes a sample of cells.  
 The procedure is usually done in your doctor's office, takes about 20 minutes and has few risks. Often, your doctor will use ultrasound to help guide the placement of the needle. Your doctor then sends the samples to a laboratory to have them analyzed under a microscope.

● **Thyroid scan.** Your doctor may recommend a thyroid scan to help evaluate thyroid nodules. During this test, an isotope of radioactive iodine is injected into a vein in your arm. You then lie on a table while a special camera produces an image of your thyroid on a computer screen.  
 Nodules that produce excess thyroid hormone — called hot nodules — show up on the scan because they take up more of the isotope than normal thyroid tissue does. Hot nodules are almost always non cancerous.  
 In some cases, nodules that take up less of the isotope — called cold nodules — are cancerous. However, a thyroid scan can't distinguish between cold nodules that are cancerous and those that aren't cancerous.

**TREATMENT**

Treatment depends on the type of thyroid nodule you have.

**Treating benign nodules**

If a thyroid nodule isn't cancerous, treatment options include:

● **Watchful waiting.** If a biopsy shows that you have a noncancerous thyroid nodule, your doctor may suggest simply watching your condition.  
 This usually means having a physical exam and thyroid function tests at regular intervals. It may also include an ultrasound. You're also likely to have another biopsy if the nodule grows larger. If a benign thyroid nodule remains unchanged, you may never need treatment.

● **Thyroid hormone therapy.** If your thyroid function test finds your gland isn't producing enough thyroid hormone, your doctor may recommend thyroid hormone therapy.

● **Surgery.** A noncancerous nodule may sometimes require surgery if it's so large that it makes it hard to breathe or swallow. Doctors may also consider surgery for people with large multinodular goiters, particularly when the goiters constrict airways, the esophagus or blood vessels. Nodules diagnosed as indeterminate or suspicious by a biopsy also need surgical removal, so they can be examined for signs of cancer.

**Treating nodules that cause hyperthyroidism**

If a thyroid nodule is producing thyroid hormones, overloading your thyroid gland's normal hormone production levels, your doctor may recommend treating you for hyperthyroidism. This may include:

● **Radioactive iodine.** Doctors use radioactive iodine to treat hyperthyroidism. Taken as a capsule or in liquid form, radioactive iodine is absorbed by your thyroid gland. This causes the nodules to shrink and signs and symptoms of hyperthyroidism to subside, usually within two to three months.

● **Anti-thyroid medications.** In some cases, your doctor may recommend an anti-thyroid medication such as methimazole (Tapazole) to reduce symptoms of hyperthyroidism. Treatment is generally long term and can have serious side effects on your liver, so it's important to discuss the treatment's risks and benefits with your doctor.

● **Surgery.** If treatment with radioactive iodine or anti-thyroid medications isn't an option, you may be a candidate for surgery to remove the overactive thyroid nodule. You'll likely discuss the risks of surgery with your doctor.

**Treating cancerous nodules**

Treatment for a nodule that's cancerous usually involves surgery.

● **Observation.** Very small cancers have a low risk of growing, so it may be appropriate for your doctor to closely watch cancerous nodules before treating them. This decision is often made with the help of a thyroid specialist. Observation includes ultrasound monitoring and performing blood tests.

● **Surgery.** A common treatment for cancerous nodules is surgical removal. In the past, it was standard to remove a majority of thyroid tissue — a procedure called near-total thyroidectomy. However, today more limited surgery to remove only half of the thyroid may be appropriate for some cancerous nodules. Near-total thyroidectomy may be used depending on the extent of the disease.  
 Risks of thyroid surgery include damage to the nerve that controls your vocal cords and damage to your parathyroid glands — four tiny glands located on the back of your thyroid that help control your body's levels of minerals, such as calcium.  
 After a thyroid surgery, you'll need lifelong treatment with levothyroxine to supply your body with thyroid hormone. Your thyroid specialist will help determine the correct amount to take because it may require more than hormone replacement to manage your cancer risk.

● **Alcohol ablation.** Another option for management of certain small cancerous nodules is alcohol ablation. This technique involves injecting a small amount of alcohol in the cancerous thyroid nodule to destroy it. Multiple treatment sessions are often required.

**COMPLICATION**

Complications associated with some thyroid nodules include:

● **Problems swallowing or breathing.** Large nodules or a multinodular goiter can interfere with swallowing or breathing.

● **Hyperthyroidism.** Problems can occur when a nodule or goiter produces thyroid hormone, leading to an excess amount of the hormone in the body. Hyperthyroidism can result in weight loss, muscle weakness, heat intolerance, and anxiousness or irritability.  
 Potential complications of hyperthyroidism include an irregular heartbeat, weak bones and thyrotoxic crisis, a rare but potentially life-threatening intensification of signs and symptoms that requires immediate medical care.

● **Problems related to thyroid nodule surgery.** If your doctor recommends surgery to remove a nodule, you may need to take thyroid hormone replacement therapy for the rest of your life.

**WHEN TO SEE A DOCTOR**

Although most thyroid nodules are noncancerous and don't cause problems, ask your doctor to evaluate any unusual swelling in your neck, especially if you have trouble breathing or swallowing. It's important to evaluate the possibility of cancer.

Seek medical care if you develop signs and symptoms of hyperthyroidism, such as:

● Sudden weight loss even though your appetite is normal or has increased

● A pounding heart

● Trouble sleeping

● Muscle weakness

● Nervousness or irritability

Also see your doctor if you have signs and symptoms that may mean your thyroid gland isn't making enough thyroid hormone (hypothyroidism), which include:

● Feeling cold

● Feeling tired more easily

● Dry skin

● Memory problems

● Depression

● Constipation

**Prevention**

Since researchers don’t know what causes the majority of thyroid nodules, you can’t prevent them in most cases.

You can, however, try to decrease your risk of developing them by managing certain risk factors. For example, if you have obesity, talk to your healthcare provider about attaining a healthy weight for you. If you smoke cigarettes, try to quit. It’s also important to make sure you get enough iodine in your diet. If you use iodized table salt, you’re likely consuming enough.

Studies have shown that people who take oral birth control and/or statins may have a reduced risk of developing thyroid nodules.

**Outlook / Prognosis**

The prognosis for noncancerous (benign) thyroid nodules is great. They often don’t need treatment, and only about 1% of benign thyroid nodules cause thyroid disease, which is treatable.

The prognosis for cancerous (malignant) thyroid nodules varies greatly depending on several factors, including:

● The type of cancer.

● Your age at diagnosis.

● The size of the nodule/tumor.

● If it’s spread to nearby tissues, such as lymph nodes.

● If it’s spread (metastasized) to distant parts of your body.

If you have thyroid cancer, your healthcare provider will be able to give you a more accurate prognosis.

**Living With**

If you notice a bump on your thyroid, it’s important to see your healthcare provider. Even though the majority of thyroid nodules are benign and cause no other symptoms, it’s still important to have the nodule evaluated in the small chance that it’s cancer.

If you’ve been diagnosed with a thyroid nodule and are taking the “watch and wait” approach, you’ll need to see your provider regularly so that they can monitor the nodule for any changes.

**DIFFERENTIAL DIAGNOSIS**

While most nodules and masses presenting in the anterior neck represent benign thyroid nodules or cysts, malignancy should still be excluded, particularly in patients at risk for thyroid cancer.

Congenital neck masses may present in the anterior neck. These are usually present at birth, but some may present in adulthood. Older age of presentation should raise concern for possible malignancy. Carcinomas of the tongue, tonsil, and thyroid cancer may present as cystic neck masses.

Inflammatory neck masses usually represent enlarged lymph nodes which may be viral or bacterial in etiology. These are commonly located superficial, deep, or posterior to the sternocleidomastoid muscle, and anterior to the trapezius muscle.

Some non-thyroid neoplastic disorders may present as metastatic neck masses; these are most commonly associated with squamous cell carcinoma from the aerodigestive tract

**EPIDEMIOLOGY**

Prevalence depends on the method of screening and the population evaluated. The risk of thyroid nodules is higher with increasing age, female gender, iron deficiency, and history of thyroid radiation. Long-term survivors of hematopoietic stem cell transplantation are at higher risk for secondary thyroid carcinoma with a relative risk of 3.26.

In the adult population, physical examination alone may show a prevalence of 5% to 7% of thyroid nodules. Ultrasound shows a prevalence of 20% to 76% in this same population, which correlates to autopsy findings.

Thyroid nodules are approximately 4 times more common in women than men and occur more often in individuals living in iodine-deficient geographic areas. A 20-year surveillance study estimated a prevalence of 0.8% and 5.3% in men and women, respectively. However, the rate of cancer is twice as high in men as in women (8% versus 4%).

**Thyroid Nodule Guidelines**

A thyroid nodule is a discrete lesion within the thyroid gland that is radiologically distinct from the surrounding thyroid parenchyma. Some palpable lesions may not correspond to distinct radiologic abnormalities . Such abnormalities do not meet the strict definition for thyroid nodules. Nonpalpable nodules detected on US or other anatomic imaging studies are termed incidentally discovered nodules or “incidentalomas.” Nonpalpable nodules have the same risk of malignancy as do sonographically confirmed palpable nodules of the same size . Generally, only nodules >1 cm should be evaluated, since they have a greater potential to be clinically significant cancers. Occasionally, there may be nodules <1 cm that require further evaluation because of clinical symptoms or associated lymphadenopathy. In very rare cases, some nodules <1 cm lack these sonographic and clinical warning signs yet may nonetheless cause future morbidity and mortality. This remains highly unlikely, and given the unfavorable cost/benefit considerations, attempts to diagnose and treat all such small thyroid cancers in an effort to prevent exceedingly rare outcomes is deemed to cause more harm than good. In general, the guiding clinical strategy acknowledges that most thyroid nodules are low risk, and many thyroid cancers pose minimal risk to human health and can be effectively treated.

**What is the appropriate laboratory and imaging evaluation for patients with clinically or incidentally discovered thyroid nodules?**

**Serum thyrotropin measurement**

 RECOMMENDATION 2

 (A) Serum thyrotropin (TSH) should be measured during the initial evaluation of a patient with a thyroid nodule.

 (Strong recommendation, Moderate-quality evidence)

 (B) If the serum TSH is subnormal, a radionuclide (preferably 123I) thyroid scan should be performed. (Strong recommendation, Moderate-quality evidence)

 (C) If the serum TSH is normal or elevated, a radionuclide scan should not be performed as the initial imaging evaluation.

 (Strong recommendation, Moderate-quality evidence)

With the discovery of a thyroid nodule, a complete history and physical examination focusing on the thyroid gland and adjacent cervical lymph nodes should be performed. Pertinent historical factors predicting malignancy include a history of childhood head and neck radiation therapy, total body radiation for bone marrow transplantation, exposure to ionizing radiation from fallout in childhood or adolescence, familial thyroid carcinoma, or thyroid cancer syndrome (e.g., PTEN hamartoma tumor syndrome [Cowden's disease], FAP, Carney complex, Werner syndrome/progeria, or MEN 2, a risk for medullary thyroid cancer [MTC]) in a first-degree relative, rapid nodule growth, and/or hoarseness. Pertinent physical findings suggesting possible malignancy include vocal cord paralysis, cervical lymphadenopathy, and fixation of the nodule to surrounding tissue.

With the discovery of a thyroid nodule >1 cm in any diameter, a serum TSH level should be obtained. If the serum TSH is subnormal, a radionuclide thyroid scan should be obtained to document whether the nodule is hyperfunctioning (“hot,” i.e., tracer uptake is greater than the surrounding normal thyroid), iso functioning (“warm,” i.e., tracer uptake is equal to the surrounding thyroid), or nonfunctioning (“cold,” i.e., has uptake less than the surrounding thyroid tissue). Since hyperfunctioning nodules rarely harbor malignancy, if one is found that corresponds to the nodule in question, no cytologic evaluation is necessary. If overt or subclinical hyperthyroidism is present, additional evaluation is required. A higher serum TSH level, even within the upper part of the reference range, is associated with increased risk of malignancy in a thyroid nodule, as well as more advanced stage thyroid cancer

**Serum thyroglobulin measurement**

■ RECOMMENDATION 3

Routine measurement of serum thyroglobulin (Tg) for initial evaluation of thyroid nodules is not recommended.

(Strong recommendation, Moderate-quality evidence)

Serum Tg levels can be elevated in most thyroid diseases and are an insensitive and nonspecific test for thyroid cancer

**Serum calcitonin measurement**

■ RECOMMENDATION 4

The panel cannot recommend either for or against routine measurement of serum calcitonin in patients with thyroid nodules.

(No recommendation, Insufficient evidence)

The utility of serum calcitonin has been evaluated in a series of prospective, nonrandomized studies. These data suggest that the use of routine serum calcitonin for screening may detect C-cell hyperplasia and MTC at an earlier stage, and overall survival consequently may be improved. However, most studies relied on pentagastrin stimulation testing to increase specificity. This drug is not available in the United States, Canada, and some other countries, and there remain unresolved issues of sensitivity, specificity, assay performance, cut-offs using calcium stimulation, and cost effectiveness. Two retrospective studies have shown improved survival in patients diagnosed with MTC after routine calcitonin testing compared with historical controls, but they were unable to show a decreased number of MTC-related deaths. A cost-effectiveness analysis suggested that calcitonin screening would be cost effective in the United States. However, prevalence estimates of MTC in this analysis included patients with C-cell hyperplasia and microMTC, which have uncertain clinical significance. Based on the retrospective nature of the survival data, unresolved issues of assay performance, lack of availability of pentagastrin in North America, and potential biases in the cost-effective analysis, the task force cannot recommend for or against the routine measurement of serum calcitonin as a screening test in patients with thyroid nodules, although there was not uniform agreement on this recommendation. There was, however, agreement that serum calcitonin may be considered in the subgroup of patients in whom an elevated calcitonin may change the diagnostic or surgical approach (i.e., patients considered for less than total thyroidectomy, patients with suspicious cytology not consistent with PTC). If the unstimulated serum calcitonin determination has been obtained and the level is greater than 50–100 pg/mL, a diagnosis of MTC is common.

There is emerging evidence that a calcitonin measurement from a thyroid nodule fine-needle aspiration (FNA) washout may be helpful in the preoperative evaluation of patients with a modestly elevated basal serum calcitonin (20–100 pg/mL).

**]Fluorodeoxyglucose positron emission tomography scan**

■ RECOMMENDATION 5

(A) Focal [18F]fluorodeoxyglucose positron emission tomography (18FDG-PET) uptake within a sonographically confirmed thyroid nodule conveys an increased risk of thyroid cancer, and FNA is recommended for those nodules ≥1 cm.

(Strong recommendation, Moderate-quality evidence)

B) Diffuse 18FDG-PET uptake, in conjunction with sonographic and clinical evidence of chronic lymphocytic thyroiditis, does not require further imaging or FNA.

(Strong recommendation, Moderate-quality evidence)

FDG-PET is increasingly performed during the evaluation of patients with both malignant and nonmalignant illness. While 18FDG-PET imaging is not recommended for the evaluation of patients with newly detected thyroid nodules or thyroidal illness, the incidental detection of abnormal thyroid uptake may nonetheless be encountered. Importantly, incidental FDG-PET uptake in the thyroid gland can be either focal or diffuse. Focal 18FDG-PET uptake in the thyroid is incidentally detected in 1%–2% of patients, while an additional 2% of patients demonstrate diffuse thyroid uptake

Focal thyroid uptake most often corresponds to a clinically relevant thyroid nodule, and US examination is thus recommended to define thyroid anatomy. Importantly, focal 18FDG-PET uptake increases malignancy risk in an affected nodule, and therefore clinical evaluation and FNA of nodules ≥1 cm is recommended. 18FDG-PET positive thyroid nodules <1 cm that do not meet FNA criteria can be monitored similarly to thyroid nodules with high-risk sonographic patterns that do not meet FNA criteria. A recent meta-analysis confirmed that approximately one in three (∼35%) 18FDG-PET positive thyroid nodules proved to be cancerous, with higher mean maximum standardized uptake value in malignant compared to benign nodules (6.9 vs. 4.8, *p* < 0.001). In contrast, diffuse thyroid uptake most often represents benign disease corresponding to inflammatory uptake in the setting of Hashimoto's disease or other diffuse thyroidal illness. However, if detected, diffuse 18FDG-PET uptake in the thyroid should also prompt sonographic examination to ensure there is no evidence of clinically relevant nodularity. Most patients with diffuse 18FDG-PET uptake demonstrate diffuse heterogeneity on sonographic examination, and no further intervention or FNA is required. It is appropriate to evaluate thyroid function in these patients.

**Thyroid sonography**

■ RECOMMENDATION 6

Thyroid sonography with survey of the cervical lymph nodes should be performed in all patients with known or suspected thyroid nodules.

(Strong recommendation, High-quality evidence)

Diagnostic thyroid/neck US should be performed in all patients with a suspected thyroid nodule, nodular goiter, or radiographic abnormality suggesting a thyroid nodule incidentally detected on another imaging study (e.g., computed tomography [CT] or magnetic resonance imaging [MRI] or thyroidal uptake on 18FDG-PET scan). Thyroid US can answer the following questions: Is there truly a nodule that corresponds to an identified abnormality? How large is the nodule? What is the nodule's pattern of US imaging characteristics? Is suspicious cervical lymphadenopathy present? Is the nodule greater than 50% cystic? Is the nodule located posteriorly in the thyroid gland? These last two features might decrease the accuracy of FNA biopsy performed with palpation.

Ultrasound should evaluate the following: thyroid parenchyma (homogeneous or heterogeneous) and gland size; size, location, zand sonographic characteristics of any nodule(s); the presence or absence of any suspicious cervical lymph nodes in the central or lateral compartments. The US report should convey nodule size (in three dimensions) and location (e.g., right upper lobe) and a description of the nodule's sonographic features including composition (solid, cystic proportion, or spongiform), echogenicity, margins, presence and type of calcifications, and shape if taller than wide, and vascularity. The pattern of sonographic features associated with a nodule confers a risk of malignancy, and combined with nodule size, guides FNA decision-making

In the subset of patients with low serum TSH levels who have undergone radionuclide thyroid scintigraphy suggesting nodularity, US should also be performed to evaluate both the presence of nodules concordant with the hyperfunctioning areas on the scan, which do not require FNA, as well as other non functioning nodules that meet sonographic criteria for FNA .

**US for FNA decision-making**

■ RECOMMENDATION 7

FNA is the procedure of choice in the evaluation of thyroid nodules, when clinically indicated.

(Strong recommendation, High-quality evidence)

FNA is the most accurate and cost-effective method for evaluating thyroid nodules. Retrospective studies have reported lower rates of both nondiagnostic and false-negative cytology from FNA procedures performed using US guidance compared to palpation. Therefore, for nodules with a higher likelihood of either a nondiagnostic cytology (>25%–50% cystic component) or sampling error (difficult to palpate or posteriorly located nodules), US-guided FNA is preferred. If the diagnostic US confirms the presence of a predominantly solid nodule corresponding to what is palpated, the FNA may be performed using palpation or US guidance.

**[A10] Recommendations for diagnostic FNA of a thyroid nodule based on sonographic pattern**

**Recommendations for initial follow-up of nodules with benign FNA cytology**

■ RECOMMENDATION 23

Given the low false-negative rate of US-guided FNA cytology and the higher yield of missed malignancies based upon nodule sonographic pattern rather than growth, the follow-up of thyroid nodules with benign cytology diagnosis should be determined by risk stratification based upon US pattern.

(A) Nodules with high suspicion US pattern: repeat US and US-guided FNA within 12 months.

(Strong recommendation, Moderate-quality evidence)

(B) Nodules with low to intermediate suspicion US pattern: repeat US at 12–24 months. If sonographic evidence of growth (20% increase in at least two nodule dimensions with a minimal increase of 2 mm or more than a 50% change in volume) or development of new suspicious sonographic features, the FNA could be repeated or observation continued with repeat US, with repeat FNA in case of continued growth.

(Weak recommendation, Low-quality evidence)

(C) Nodules with very low suspicion US pattern (including spongiform nodules): the utility of surveillance US and assessment of nodule growth as an indicator for repeat FNA to detect a missed malignancy is limited. If US is repeated, it should be done at ≥24 months.

(Weak recommendation, Low-quality evidence)

**[A25] Recommendation for follow-up of nodules with two benign FNA cytology results**

(D) If a nodule has undergone repeat US-guided FNA with a second benign cytology result, US surveillance for this nodule for continued risk of malignancy is no longer indicated.

(Strong recommendation, Moderate-quality evidence)

Given that there is a low but discrete false-negative rate for nodules with benign FNA cytology results, is there an optimal way to identify these missed malignancies? Although the risk of malignancy after two benign cytology results is virtually zero, routine rebiopsy is not a viable or cost-effective option because of the low false-negative rate of an US-guided FNA benign cytology result. Prior guidelines have recommended repeat FNA for nodules that grow during serial sonographic observation. However, nodule growth can be variably defined. Because of interobserver variation,  a 50% increase in nodule volume was the minimally significant reproducibly recorded change in nodule size, which is equivalent to a 20% increase in two of the three nodule dimensions. If a 50% volume increase cutoff is applied, only 4%–10% of nodules were reported to be larger at a mean of 18 months. However, using cutoffs of a 15% volume increase based upon internally assessed interobserver coefficients of variation, published series report that 32%–50% of nodules increase in size over a 4–5 year period. Because of the stringent methodology of these studies, adoption of a 15% volume increase as statistically significant is not practically applicable.

A recent 5-year prospective multicenter study evaluated outcomes of 1597 nodules from 992 patients with either cytologically or sonographically benign nodules. Nodules 1 cm or larger underwent US-guided FNA and subcentimeter nodules were defined as sonographically benign based upon imaging characteristics equivalent to the ATA low or very low suspicion US patterns. All nodules were followed by annual US exams. The false-negative rate of a benign cytology diagnosis was 1.1%. Of the four missed cancers, on baseline US imaging three were hypoechoic and solid and one was isoechoic with microcalcifications; none was spongiform or mixed cystic solid and noncalcified (ATA very low suspicion pattern). During sonographic surveillance, repeat FNA was prompted by either growth (two nodules) or development of a new suspicious sonographic feature (two nodules). In addition, the shortest time interval to detect change and repeat the FNA was 2 years. Another critical observation from this study was that only one cancer was detected in 5 years among the 852 subcentimeter nodules classified as sonographically benign at baseline. This cancer was identified on the 5-year follow-up US, when its composition changed from mixed cystic/solid to hypoechoic solid with irregular margins prompting FNA. Currently, there are no follow-up studies of nodule growth that extend observation beyond 5 years to help inform decision-making about long-term surveillance. Additional research would be valuable because indefinite follow-up of nodules with benign cytology is costly and may be unnecessary.

Recent investigations of repeat US-guided FNA in nodules with initial benign cytology show higher detection rates for missed malignancy for those nodules with a high suspicion sonographic pattern rather than size increase . a significantly higher malignancy rate of 20.4% in nodules with benign cytology that exhibited either marked hypoechogenicity, irregular borders, microcalcifications, or a taller than wide shape versus a 1.4% risk in those that exhibited a 15% volume increase but lacked these US features. Importantly, the low risk of malignancy did not differ between US negative nodules that grew and those that demonstrated no interval size change (1.4% vs. 0.5%, *p* = 0.18). Similarly,  cancer was detected in 17.4% of nodules with benign cytologic diagnoses and suspicious US features versus 1.3% of those without suspicious characteristics that grew, using criteria of a 50% volume increase. These studies indicate that the use of suspicious US characteristics rather than nodule growth should be the indication for repeat FNA despite an initial benign cytology diagnosis. Repeat US and FNA should be repeated within 12 months as guided by clinical judgement. Given the low false-negative rate of US-guided FNA cytology and the higher yield of missed malignancies based upon nodule sonographic pattern rather than growth, the follow-up of thyroid nodules with benign cytology diagnosis should be determined by risk stratification based upon US pattern as defined in Recommendation 8. If follow-up US for surveillance is performed and the nodule size is stable, the utility of subsequent US imaging for detection of potential malignancy by nodule growth assessment is very low and if performed, the time interval for any additional US exam should be at least as long that between the initial benign FNA cytology result and first follow-up. However, even if a repeat US is not indicated based on a benign cytology, US pattern, or stability in nodule size, larger nodules may require monitoring for growth that could result in symptoms and thus prompt surgical intervention despite benign cytology.

One recent study evaluated the long-term consequences of a false-negative benign cytology. A total of 1369 patients with 2010 cytologically benign thyroid nodules were followed for a mean of 8.5 years. Eighteen false-negative cases were identified, although only a subset of patients underwent repeat FNA or thyroid surgery. Thirty deaths were documented in the entire cohort over this time period and none were attributable to thyroid cancer. These data support that an initial benign cytology conveys an overall excellent prognosis and a conservative follow-up strategy is reasonable.

**Follow-up for nodules that do not meet FNA criteria**

■ RECOMMENDATION 24

Nodules may be detected on US that do not meet criteria for FNA at initial imaging (Recommendation 8). The strategy for sonographic follow-up of these nodules should be based upon the nodule's sonographic pattern.

(A) Nodules with high suspicion US pattern: repeat US in 6–12 months.

(Weak recommendation, Low-quality evidence)

(B) Nodules with low to intermediate suspicion US pattern: consider repeat US at 12–24 months.

(Weak recommendation, Low-quality evidence)

(C) Nodules >1 cm with very low suspicion US pattern (including spongiform nodules) and pure cyst: the utility and time interval of surveillance US for risk of malignancy is not known. If US is repeated, it should be at ≥24 months.

(No recommendation, Insufficient evidence)

(D) Nodules ≤1 cm with very low suspicion US pattern (including spongiform nodules) and pure cysts do not require routine sonographic follow-up.

(Weak recommendation, Low-quality evidence)

Ultrasound studies demonstrate that up to 50% of adults have thyroid nodules. The vast majority of these are subcentimeter, and FNA evaluation is generally not indicated. In addition, based upon both sonographic pattern and size cutoffs (Recommendation 8), many nodules >1 cm may also be followed without FNA. Although no prospective studies address the optimal cost-effective surveillance strategy for these nodules that have not undergone FNA, a recent study  confirms that subcentimeter thyroid nodules corresponding to the ATA very low suspicion risk pattern are highly unlikely to change during 5-year sonographic follow-up, and the risk of malignancy is exceedingly low. The findings from studies correlating sonographic features and malignancy risk in aspirated nodules can be extrapolated to inform a follow-up strategy for this group of nodules that do not meet FNA criteria at the time of their initial detection. For example, the interval for follow-up sonography for a nodule that is hypoechoic and taller than wide should be shorter than that for an isoechoic solid nodule with smooth borders.

US-guided FNA should be performed based upon follow-up US imaging if the nodule subsequently meets criteria based upon Recommendation 8.

**[A27] What is the role of medical or surgical therapy for benign thyroid nodules?**

■ RECOMMENDATION 25

Routine TSH suppression therapy for benign thyroid nodules in iodine sufficient populations is not recommended. Though modest responses to therapy can be detected, the potential harm outweighs benefit for most patients.

(Strong recommendation, High-quality evidence)

■ RECOMMENDATION 26

Individual patients with benign, solid, or mostly solid nodules should have adequate iodine intake. If inadequate dietary intake is found or suspected, a daily supplement (containing 150 μg iodine) is recommended.

(Strong recommendation, Moderate-quality evidence)

■ RECOMMENDATION 27

(A) Surgery may be considered for growing nodules that are benign after repeat FNA if they are large (>4 cm), causing compressive or structural symptoms, or based upon clinical concern.

(Weak recommendation, Low-quality evidence)

(B) Patients with growing nodules that are benign after FNA should be regularly monitored. Most asymptomatic nodules demonstrating modest growth should be followed without intervention.

(Strong recommendation, Low-quality evidence)

■ RECOMMENDATION 28

Recurrent cystic thyroid nodules with benign cytology should be considered for surgical removal or percutaneous ethanol injection (PEI) based on compressive symptoms and cosmetic concerns. Asymptomatic cystic nodules may be followed conservatively.

(Weak recommendation, Low-quality evidence)

■ RECOMMENDATION 29

There are no data to guide recommendations on the use of thyroid hormone therapy in patients with growing nodules that are benign on cytology.

(No recommendation, Insufficient evidence)

Evidence from multiple prospective, RCTs, and from three meta-analyses suggest that thyroid hormone supplementation in doses that suppress the serum TSH to subnormal levels may result in a decrease in nodule size and may prevent the appearance of new nodules in regions of the world with borderline low iodine intake. However, the effect is modest, with most studies suggesting an average 5%–15% reduction in nodule volume when treated with suppressive levothyroxine (LT4) therapy for 6–18 months. Two high-quality meta-analyses confirm that six to eight patients will require suppressive LT4 therapy to achieve one successful treatment response. The extent of TSH suppression achieved in high-quality studies is variable, though the majority suppressed TSH to <0.2 mIU/L, with many to <0.1 mIU/L. Hyperthyroidism to this degree has been significantly associated with an increased risk of cardiac arrhythmias and osteoporosis, as well as adverse symptomatology. Together, these data confirm that LT4 suppressive therapy demonstrates modest (though usually clinically insignificant) efficacy in nodule volume reduction, but increases the risk of adverse consequences related to iatrogenic thyrotoxicosis. One large prospective, randomized trial demonstrated that sufficient dietary iodine intake (150 μg daily) also reduced nodule size slightly more than placebo. The consumption of adequate dietary iodine is recommended for all adults and is without harm when not excessive. Data supporting LT4 therapy in non–TSH-suppressive doses for prevention of thyroid nodule growth are incomplete. One recent cohort analysis suggested non suppressive doses of LT4 therapy conferred protection from nodule growth over time. However, the non blinded, nonrandomized nature of the trial precludes broad translation of the data, and the efficacy of non suppressive LT4 remains unproven.

Cystic nodules that are cytologically benign can be monitored for recurrence (fluid reaccumulation), which can be seen in 60%–90% of patients. For those patients with subsequent recurrent symptomatic cystic fluid accumulation, surgical removal, generally by hemithyroidectomy, or PEI are both reasonable strategies. Four controlled studies demonstrated a 75%–85% success rate after PEI compared with a 7%–38% success rate in controls treated by simple cyst evacuation or saline injection. Success was achieved after an average of two PEI treatments. Complications included mild to moderate local pain, flushing, dizziness, and dysphonia. Surgery may be considered for growing solid nodules that are benign on repeat cytology if they are large (>4 cm), causing compressive or structural symptoms, or based upon clinical concern.

**[A28] How should thyroid nodules in pregnant women be managed?**

**[A29] FNA for thyroid nodules discovered during pregnancy**

■ RECOMMENDATION 30

(A) FNA of clinically relevant thyroid nodules (refer to section [A10]) should be performed in euthyroid and hypothyroid pregnant women.

(Strong recommendation, Moderate-quality evidence)

(B) For women with suppressed serum TSH levels that persist beyond 16 weeks gestation, FNA may be deferred until after pregnancy and cessation of lactation. At that time, a radionuclide scan can be performed to evaluate nodule function if the serum TSH remains suppressed.

(Strong recommendation, Moderate-quality evidence)

It is uncertain if thyroid nodules discovered in pregnant women are more likely to be malignant than those found in nonpregnant women, since there are no population-based studies to address this question. Pregnancy does not appear to modify microscopic cellular appearance, thus standard diagnostic criteria should be applied for cytologic evaluation. Serial evaluation of nodules throughout pregnancy has demonstrated that thyroid nodules will enlarge slightly throughout gestation, though this does not imply malignant transformation. The recommended evaluation of a clinically relevant nodule in a pregnant patient is thus the same as for a nonpregnant patient, with the exception that a radionuclide scan is contraindicated. In addition, for patients with nodules diagnosed as DTC by FNA during pregnancy, delaying surgery until after delivery does not affect outcome. Surgery performed during pregnancy is associated with greater risk of complications, longer hospital stays, and higher costs.

**[A30] Approaches to pregnant patients with malignant or indeterminate cytology**

■ RECOMMENDATION 31

PTC discovered by cytology in early pregnancy should be monitored sonographically. If it grows substantially (as defined in section [A24]) before 24–26 weeks gestation, or if US reveals cervical lymph nodes that are suspicious for metastatic disease, surgery should be considered during pregnancy. However, if the disease remains stable by midgestation, or if it is diagnosed in the second half of pregnancy, surgery may be deferred until after delivery.

(Weak recommendation, Low-quality evidence)

If FNA cytology is consistent with PTC, surgery is generally recommended. However, the decision to perform such surgery either during pregnancy or after delivery must be individualized. If surgery is not performed, the utility of thyroid hormone therapy targeted to lower serum TSH levels to improve the prognosis of thyroid cancer diagnosed during gestation is not known. Because higher serum TSH levels may be correlated with a more advanced stage of cancer at surgery, if the patient's serum TSH is >2 mU/L, it may be reasonable to initiate thyroid hormone therapy to maintain the TSH between 0.3 to 2.0 mU/L for the remainder of gestation.

Most data confirm that the prognosis of women with well-differentiated thyroid cancer identified but not treated during pregnancy is similar to that of nonpregnant patients. Because of this, surgery in most pregnant patients is deferred until postpartum, and no further testing is required. However, some studies differ from these findings. Two Italian cohort studies have investigated women diagnosed with DTC in relation to the timing of pregnancy. a statistically higher rate of persistence/recurrence when DTC was diagnosed during pregnancy or within 2 years postpartum. However, the stimulated Tg was found to be >10 ng/mL during 131I ablation in many cases, suggesting the extent of thyroidectomy and/or tumor resection may have been limited in this cohort and therefore contributed to biochemical persistence of disease.  followed a small cohort of 10 patients with DTC during pregnancy or within 1 year postpartum, again noting a large rate of persistent disease (60%) compared to nonpregnant controls (4.2%–13.1%). Similarly, the majority of cases with persistent disease were attributable to biochemical elevations in Tg or anti-Tg antibodies, again raising the question of whether the extent of initial resection was limited in comparison to nonpregnant controls. Given the likelihood that biochemical persistence could be attributable to an increased size of remnant tissue or incomplete surgical resection in both studies, these data should not refute previous, larger analyses showing no increased recurrence rates when DTC is diagnosed during pregnancy.

Theoretically, molecular marker analysis could be helpful in the evaluation of DTC or clinically relevant, cytologically indeterminate thyroid nodules detected during pregnancy. However, the application of molecular testing in pregnant women with indeterminate cytology remains uncertain. There are no published data validating the performance of any molecular marker in this population. Therefore, the committee cannot recommend for or against their use in pregnant women. However, it is theoretically possible that changes in a Nodule's RNA expression may occur during gestation altering performance of the 167 GEC while the seven-gene mutational panel (*BRAF*, *RAS*, *PAX8/PPARγ*, *RET/PTC*) would be more likely to demonstrate similar performance to that of a nonpregnant population.

When surgery is advised during pregnancy, it is most often because of high-risk clinical or sonographic findings, nodule growth, or change over short duration follow-up or it is based upon physician judgement. To minimize the risk of miscarriage, surgery during pregnancy should be done in the second trimester before 24 weeks gestation. However, PTC discovered during pregnancy does not behave more aggressively than that diagnosed in a similar-aged group of nonpregnant women. A retrospective study of pregnant women with DTC found no difference in either recurrence or survival rates between women operated during or after pregnancy. Further, retrospective data suggest that treatment delays of <1 year from the time of thyroid cancer discovery do not adversely affect patient outcome. A separate study reported a higher rate of complications in pregnant women undergoing thyroid surgery compared with nonpregnant women. If FNA cytology is indeterminate, monitoring may be considered with further evaluation and may be delayed until after delivery. Some experts recommend thyroid hormone suppression therapy for pregnant women with FNA suspicious for or diagnostic of PTC, if surgery is deferred until the postpartum period

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**HYPERTHYROIDISM**

Hyperthyroidism happens when the thyroid gland makes too much thyroid hormone. 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 amount 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.

**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.

**RISK FACTOR**

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.

**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.

**DIAGNOSIS**

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**

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 make 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 REMEDY**

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.

**COMPLICATION**

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.

**WHEN TO SEE A DOCTOR**

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.

**EPIDEMIOLOGY**

The prevalence of hyperthyroidism varies worldwide, based on dietary iodine content. Hyperthyroidism is more common in women compared to men. Other risk factors associated with the development of hyperthyroidism include smoking, iodine deficiency, iodine excess, selenium deficiency, genetic factors, and the use of certain drugs. Graves disease is typically seen in younger patients and is the most common cause of hyperthyroidism in this demographic. The incidence of Graves disease is highest between the age group of 30 to 50 years. Toxic multifocal goiter is typically seen in older individuals and is the most common cause of hyperthyroidism in this demographic. Graves disease and toxic multifocal goiter have a female predilection and are typically seen in patients with pertinent family and personal medical histories. Thyroid nodular disease is also more common in women than men by 5- to 15-fold. Autoimmune thyroid disorders like Graves disease are more common in iodine-replete areas, and nodular thyroid diseases are more common in iodine-deficient areas.

The Whickham Survey demonstrated a prevalence of hyperthyroidism in women, approximately 10 times more than that of men (2.7% versus 0.23%). An incidence of 80 cases per 100,000 women was seen at the 20-year follow-up of the Whickham cohort. The prevalence of hyperthyroidism in the United States was 1.3% in the general population, with 0.5% cases of overt hyperthyroidism and 0.7% cases of subclinical hyperthyroidism. A meta-analysis found the prevalence of hyperthyroidism in Europe to be 0.75%. The prevalence of overt hyperthyroidism is similar in China at 0.78%. Amiodarone-induced thyrotoxicosis (AIT) is seen in about 6% of the individuals taking the medication in iodine-sufficient areas and about 10% in individuals taking the medication from iodine-deficient areas.

**DIFFERENTIAL DIAGNOSIS**

Hyperthyroidism presents with relatively nonspecific signs and symptoms such as palpitations, increased frequency of bowel movements, and weight loss, among others. Therefore, other pathologies should be ruled out as possible explanations for the patient’s symptomatology. For etiologies of hyperthyroidism, differential diagnoses can be made based on the physical findings of the thyroid gland. Palpation of a normal thyroid gland in the context of hyperthyroidism can be due to Graves disease, painless thyroiditis, or factitious hyperthyroidism (thyrotoxicosis factitia). Graves disease can also present as a non-tender, enlarged thyroid. Palpation of a tender enlarged thyroid may indicate De Quervain thyroiditis (subacute thyroiditis). Palpation of a single thyroid nodule is likely indicative of thyroid adenoma, and palpation of multiple thyroid nodules strongly indicates toxic multinodular goiter. Other differential diagnoses include euthyroid hyperthy

**PROGNOSIS**

Hyperthyroidism secondary to Graves disease or toxic multinodular goiter has overall good outcomes due to high success rates of definitive treatment and efficacy of symptom management. However, as with any disease, the prognosis of a particular disease pathology is patient-oriented and reflects management, response to therapy, and compliance with prescribed treatments.

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**HYPERPARATHYROIDISM**

**Hyperparathyroidism** is when your parathyroid glands create high amounts of parathyroid hormone in the bloodstream. These glands, located behind the thyroid at the bottom of your neck, are about the size of a grain of rice.

The parathyroid hormone produced by the thyroid glands helps maintain the right balance of calcium in the bloodstream and in tissues that depend on calcium for proper functioning. This is especially important for nerve and muscle function, as well as bone health.

There are two types of hyperparathyroidism. In primary hyperparathyroidism, an enlargement of one or more of the parathyroid glands causes overproduction of parathyroid hormone. This causes high calcium levels in the blood, which can cause a variety of health problems. Surgery is the most common treatment for primary hyperparathyroidism.

Secondary hyperparathyroidism occurs due to another disease that first causes low calcium levels in the body. Over time, increased parathyroid hormone levels occur as the body fights to keep the calcium level up in the standard range. This is common in kidney disease and after certain intestinal surgeries or diseases.

**Causes**

Hyperparathyroidism is caused by factors that increase the production of parathyroid hormone.

The parathyroid glands keep proper levels of both calcium and phosphorus in your body by turning the release of parathyroid hormone off or on. This is similar to how a thermostat controls a heating system to maintain a constant air temperature. Vitamin D also is involved in controlling the amount of calcium in your blood.

Normally, this balancing act works well.

* **When calcium levels in your blood fall too low,** your parathyroid glands release enough parathyroid hormone to restore the balance. This hormone raises calcium levels by releasing calcium from your bones, increasing the amount of calcium absorbed from your small intestine and decreasing the amount of calcium lost in urine.
* **When blood-calcium levels are too high,** the parathyroid glands produce less parathyroid hormone.

Calcium is best known for its role in keeping your teeth and bones healthy. But calcium also aids in the transmission of signals in nerve cells. And it's involved in muscle contraction. Phosphorus, another mineral, works along with calcium in these areas.

Sometimes one or more of the parathyroid glands produce high amounts of parathyroid hormone. These high hormone levels can be the body responding appropriately to keep the calcium in the standard range, or they may be inappropriately elevating the calcium in the blood. Which one depends on the underlying problem.

Hyperparathyroidism may occur because of primary hyperparathyroidism or secondary hyperparathyroidism.

**Primary hyperparathyroidism**

Primary hyperparathyroidism occurs because of a problem with one or more of the four parathyroid glands:

* A noncancerous growth (adenoma) on a gland is the most common cause.
* Enlargement (hyperplasia) of two or more parathyroid glands accounts for most other cases.
* A cancerous tumor is a very rare cause of primary hyperparathyroidism.

One or more of the parathyroid glands produces high amounts of parathyroid hormone. This leads to high calcium levels and low phosphorus levels in your blood. Primary hyperparathyroidism usually occurs randomly. But some people inherit a gene that causes the disorder.

**Secondary hyperparathyroidism**

Secondary hyperparathyroidism is the result of another condition that lowers the blood calcium, which then affects the gland's function. This causes your parathyroid glands to overwork and produce high amounts of parathyroid hormone to maintain or restore the calcium level to the standard range. Factors that may result in secondary hyperparathyroidism include:

* **Severe calcium deficiency.** Your body may not get enough calcium from your diet, often because your digestive system doesn't absorb the calcium from food. This is common after intestinal surgery, including weight loss surgery.
* **Severe vitamin D deficiency.** Vitamin D helps maintain appropriate calcium levels in the blood. It also helps your digestive system absorb calcium from your food.

Your body produces vitamin D when your skin is exposed to sunlight. You also get some vitamin D in food. If you don't get enough vitamin D, then calcium levels may drop.

* **Chronic kidney failure.** Your kidneys convert vitamin D into a form that your body can use. If your kidneys work poorly, usable vitamin D may decrease and calcium levels drop. This causes parathyroid hormone levels to go up. Chronic kidney failure is the most common cause of secondary hyperparathyroidism.

In some people with long-term secondary hyperparathyroidism, usually from end-stage kidney disease, the parathyroid glands enlarge. They begin to release parathyroid hormone on their own. The hormone level doesn't go down with medical treatment and the blood calcium becomes too high. This is called tertiary hyperparathyroidism, and people with this condition may require surgery to remove parathyroid tissue.

**Risk factors**

You may be at an increased risk of primary hyperparathyroidism if you:

* Are a woman who has gone through menopause
* Have had prolonged, severe calcium or vitamin D deficiency
* Have a rare, inherited disorder, such as multiple endocrine neoplasia, type 1, which usually affects multiple glands
* Have had radiation treatment for cancer that has exposed your neck to radiation
* Have taken lithium, a drug most often used to treat bipolar disorder

**Symptoms**

Primary hyperparathyroidism is often diagnosed before signs or symptoms of the disorder occur. This is usually because an elevated level of calcium is found on routine blood tests. When symptoms do occur, they're the result of damage or dysfunction in other organs or tissues. This damage or dysfunction is due to high calcium levels in the blood and urine or too little calcium in bones.

Symptoms may be so mild and nonspecific that they don't seem related to parathyroid function, or they may be severe. The range of signs and symptoms include:

* Weak bones that break easily (osteoporosis)
* Kidney stones
* Excessive urination
* Stomach (abdominal) pain
* Tiring easily or weakness
* Depression or forgetfulness
* Bone and joint pain
* Frequent complaints of illness with no clear cause
* Nausea, vomiting or loss of appetite

**Complications**

Complications of hyperparathyroidism are mainly related to the long-term effect of too little calcium in your bones and too much calcium in your bloodstream. Common complications include:

* **Osteoporosis.** The loss of calcium from bones often results in weak, brittle bones that break easily (osteoporosis).
* **Kidney stones.** Too much calcium in your blood may lead to too much calcium in your urine. This can cause small, hard deposits of calcium and other substances to form in your kidneys (kidney stone). A kidney stone usually causes major pain as it passes from the kidneys through the urinary tract.
* **Cardiovascular disease.** Although the exact cause-and-effect link is unclear, high calcium levels are associated with heart and blood vessel (cardiovascular) conditions, such as high blood pressure and certain types of heart disease.
* **Neonatal hypoparathyroidism.** Severe, untreated hyperparathyroidism in pregnant women may cause dangerously low levels of calcium in newborns. Primary hyperparathyroidism is not common in women of childbearing age.

**Diagnosis**

In most cases, elevated calcium is found by blood tests ordered for other reasons. For example, routine blood work or testing to figure out the cause of symptoms of another condition. Your provider may diagnose hyperparathyroidism by ordering:

**Blood tests**

If blood test results show that you have high calcium levels in your blood, your health care provider will likely repeat the test. This repeated test can confirm the results after you haven't eaten for a period of time.

Many conditions can raise calcium levels. But your health care provider can diagnose hyperparathyroidism if blood tests show you also have high levels of parathyroid hormone.

**Additional tests**

After diagnosing primary hyperparathyroidism, your health care provider will likely order more tests. These can rule out possible conditions causing hyperparathyroidism, identify possible complications and determine the severity of the condition. These tests include:

* **Bone mineral density test.** This test is done to see if you have developed osteoporosis. The most common test to measure bone mineral density is dual-energy X-ray absorptiometry (DEXA).

This test uses special X-ray devices to measure how many grams of calcium and other bone minerals are packed into a bone segment.

* **Urine test.** A 24-hour collection of urine can provide information on how well your kidneys work and how much calcium is passed in your urine.

This test may help your provider determine the severity of hyperparathyroidism or diagnose a kidney disorder causing hyperparathyroidism. If a very low calcium level is found in the urine, this may mean it's a condition that doesn't need treatment.

* **Imaging tests of kidneys.** Your provider may order an X-ray or other imaging tests of your abdomen to determine if you have kidney stones or other kidney problems.

**Imaging tests before surgery**

If your health care provider recommends surgery, one of these imaging tests may be used to locate the parathyroid gland or glands that are causing problems:

* **Sestamibi parathyroid scan.** Sestamibi is a radioactive compound that is absorbed by overactive parathyroid glands. It can be detected by a scanner that detects radioactivity.

A healthy thyroid gland also absorbs sestamibi. To keep the thyroid absorption from blocking the view of the absorption in a parathyroid tumor (adenoma), you're also given radioactive iodine. This is only absorbed by the thyroid. Using this process, the thyroid image is digitally removed so it can't be seen.

Computerized tomography (CT) scanning may be combined with the sestamibi scan to improve detection of any problems with the parathyroid glands.

* **Ultrasound.** Ultrasound uses sound waves to create images of your parathyroid glands and surrounding tissue.

A small device held against your skin (transducer) sends out high-pitched sound waves and records the sound wave echoes as they reflect off internal structures. A computer converts the echoes into images on a monitor.

**Treatment**

Treatment options for primary hyperparathyroidism can include watchful waiting, surgery and medications.

**Watchful waiting**

Your health care provider may recommend no treatment and regular monitoring if:

* Your calcium levels are only slightly elevated
* Your kidneys are working well, and you have no kidney stones
* Your bone density is within the standard range or only slightly below the range
* You have no other symptoms that may improve with treatment

If you choose this watch-and-wait approach, you'll likely need regularly scheduled tests to monitor your blood-calcium levels and bone density.

**Surgery**

Surgery is the most common treatment for primary hyperparathyroidism and provides a cure in most cases. A surgeon will remove only those glands that are enlarged or have a tumor.

If all four glands are affected, a surgeon will likely remove only three glands and perhaps a portion of the fourth — leaving some functioning parathyroid tissue.

Surgery may be done as an outpatient procedure, allowing you to go home the same day. In such cases, the surgery can be done through very small cuts (incisions) in the neck. You receive only local anesthetics to numb the area.

Complications from surgery aren't common. Risks include:

* Damage to nerves controlling the vocal cords.
* Long-term low calcium levels requiring the use of calcium and vitamin D supplements due to removal or damage to all parathyroid glands. This means the body cannot produce enough parathyroid hormone to keep the calcium in the standard range.

**Medications**

Medications to treat hyperparathyroidism include the following:

* **Calcimimetics.** A calcimimetic is a drug that mimics calcium circulating in the blood. The drug may trick the parathyroid glands into releasing less parathyroid hormone. This drug is sold as cinacalcet (Sensipar).

Cinacalcet may be an option to treat primary hyperparathyroidism, particularly if surgery hasn't successfully cured the disorder or a person isn't a good surgery candidate.

Cinacalcet and vitamin D analogs (prescription forms of vitamin D) are used to manage secondary hyperparathyroidism in chronic kidney disease. These medications help keep the balance of calcium and phosphorus minerals so that the parathyroid glands don't have to work hard.

The most commonly reported side effects of cinacalcet are joint and muscle pain, diarrhea, nausea, and respiratory infection.

* **Hormone replacement therapy.** For women who have gone through menopause and have signs of osteoporosis, hormone replacement therapy may help bones keep calcium. However, this treatment doesn't address the underlying problems with the parathyroid glands.

Prolonged use of hormone replacement therapy can increase the risk of blood clots and breast cancer. Work with your health care provider to evaluate the risks and benefits to help you decide what's best for you.

Some common side effects of hormone replacement therapy include breast pain and tenderness, dizziness, and headaches.

* **Bisphosphonates.** Bisphosphonates also prevent the loss of calcium from bones and may lessen osteoporosis caused by hyperparathyroidism. Some side effects associated with bisphosphonates include low blood pressure, a fever and vomiting. This treatment doesn't address the underlying problems with the parathyroid glands, and the blood calcium level remains above the standard range.

**Self care**

If you and your health care provider have chosen to monitor, rather than treat, your primary hyperparathyroidism, the following suggestions can help prevent complications:

* **Monitor how much calcium and vitamin D you get in your diet.** Restricting how much calcium you eat or drink is not recommended for people with hyperparathyroidism.

The daily recommended amount of calcium for adults ages 19 to 50 and men ages 51 to 70 is 1,000 milligrams (mg) of calcium a day. That calcium recommendation increases to 1,200 mg a day for women age 51 and older and men age 71 and older.

The daily recommended amount of vitamin D is 600 international units (IUs) of vitamin D a day for people ages 1 to 70 and 800 IUs a day for adults age 71 and older. Talk to your provider about dietary guidelines that are right for you.

* **Drink plenty of fluids.** Drink enough fluids, mostly water, to produce nearly clear urine to lessen the risk of kidney stones.
* **Exercise regularly.** Regular exercise, including strength training, helps maintain strong bones. Talk to your provider about what type of exercise program is best for you.
* **Don't smoke.** Smoking may increase bone loss as well as increase your risk of several serious health problems. Talk to your provider about the best ways to quit.
* **Avoid calcium-raising medications.** Certain medications, including some diuretics and lithium, can raise calcium levels. If you take such medications, ask your provider whether another medication may be appropriate for you.

**Outlook / Prognosis**

If you have hyperparathyroidism and don’t have surgery, you’ll need to monitor your symptoms. You might also need to make changes to what you eat or take medications or supplements. Once or twice per year, your provider will test your:

* Blood calcium levels.
* Blood pressure.
* Kidney function.
* Bone density.

**How effective is surgery for hyperparathyroidism?**

For people with primary hyperparathyroidism, parathyroidectomy is very effective at bringing calcium levels back to normal, and at improving bone density and symptoms. Studies suggest that, after surgery, over 80% of people (4 out of 5) saw symptom improvement, and over 90% (9 out of 10) had calcium levels return to normal and bone density improve.

Kidney transplant improves secondary hyperparathyroidism in about 40% of people within a year.

**How long can you live with hyperparathyroidism?**

Many people live with primary hyperparathyroidism for years without it affecting their health. But eventually, you may need surgery to treat it. Studies suggest that, of people who don’t have symptoms of primary hyperparathyroidism at the time of their diagnosis, about 25% (1 out of 4) will eventually need surgery.

**Prevention**

Managing underlying conditions, like chronic kidney disease, can reduce your risk of secondary hyperparathyroidism. There aren’t specific ways to reduce your risk of primary hyperparathyroidism.

**Living With**

If you have hyperparathyroidism, the following tips can help you take care of yourself:

* Drink plenty of water to stay hydrated.
* Stay active and exercise to keep your bones strong.
* If your provider recommends limiting foods with phosphorus in them, avoid foods with ingredients that include “-phos” (like calcium **phos**phate or **phos**phoric acid).

**Should you take vitamin D if you have hyperparathyroidism?**

For some people with hyperparathyroidism and low vitamin D levels, it might make sense to take vitamin D supplements. Always ask your provider what kinds of foods, beverages and supplements you should be looking for — and what you should avoid.

**When to see a doctor**

See your healthcare provider if you have any signs or symptoms of hyperparathyroidism. These symptoms could be caused by many disorders, including some with serious complications. It's important to get a prompt, accurate diagnosis and the right treatment.

**Epidemiology**

Primary hyperparathyroidism is more common in women, the incidence being 66 per 100,000 person-years in females, and 25 per 100,000 person-years in males. In a large study of 3.5 million enrollees in Kaiser Permanente of southern California, the incidence fluctuated over time but was not seen to decrease substantially . On the contrary, the prevalence of primary hyperparathyroidism saw a substantial increase in this population. The mean age at diagnosis has remained between 52 and 56 years.

However, primary hyperparathyroidism is underdiagnosed, so the incidence and prevalence are likely much higher. Two large studies, both from academic centers, showed that hypercalcemia led to measurement of parathyroid hormone in under one third of patients.

Vitamin D deficiency has been estimated to affect approximately 40% of US adults, according to data from the National Health and Nutrition Examination Survey (NHANES).. Deficiency of the vitamin in adults has been attributed to decreases in sun exposure, changes in dietary intake, gastrointestinal disorders such as malabsorption syndromes and pancreatic insufficiency, and liver failure with decreased hydroxylation. In CKD, secondary hyperparathyroidism is common and varies based on the eGFR. In milder forms of CKD, elevations in parathyroid hormone levels occur in about 10% of patients, with the prevalence increasing to 90% of individuals with severe CKD who are approaching the need for dialysis therapy

**Differential Diagnosis of Hyperparathyroidism**

1. Primary Hyperparathyroidism
   1. Parathyroid adenoma (most common)
   2. Parathyroid hyperplasia
   3. Parathyroid carcinoma (rare)
2. Secondary Hyperparathyroidism
   1. Chronic kidney disease (CKD)
   2. Vitamin D deficiency
   3. Malabsorption syndromes (e.g., celiac disease, Crohn’s disease)
   4. Hypocalcemia from other causes
3. Tertiary Hyperparathyroidism
   1. Autonomous parathyroid hyperfunction following prolonged secondary hyperparathyroidism, usually in CKD patients (often post-renal transplant)
4. Other Conditions Causing Hypercalcemia with PTH Changes
   1. Familial hypocalciuric hypercalcemia (FHH) — benign inherited condition with low urinary calcium
   2. Malignancy-associated hypercalcemia (PTH suppressed)
   3. Granulomatous diseases (e.g., sarcoidosis) — increased calcitriol, PTH suppressed
   4. Endocrine disorders causing hypercalcemia (e.g., hyperthyroidism)

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**Hypoparathyroidism**

Hypoparathyroidism is a rare, treatable condition that happens when you have low levels of parathyroid hormone in your blood, which causes you to have low levels of calcium (hypocalcemia) and high levels of phosphorus in your blood.

Hypoparathyroidism is usually a chronic (lifelong) condition, but it can be temporary.

Most people have four pea-sized parathyroid glands located behind their thyroid gland — the butterfly-shaped gland in your neck. Like your thyroid, your parathyroid glands are part of your endocrine system. Sometimes your parathyroid glands are located along your esophagus or in your chest. These are known as ectopic (in an abnormal place) parathyroid glands.

Your parathyroid glands are in charge of controlling the amount of calcium in your blood by producing parathyroid hormone (PTH). Too little PTH results in low amounts of calcium in your blood (hypocalcemia), and too much PTH causes high amounts of calcium in your blood (hypercalcemia). PTH also helps control the levels of phosphorus and vitamin D in your blood and bones.

Calcium is one of the most important and common minerals in your body. Most of your calcium is stored in your bones, but you have and need it in your blood as well. The calcium in your blood has many important roles, including helping:

* Your nerves work.
* Make your muscles squeeze together so you can move.
* Your blood clot if you’re bleeding.
* Your heart works properly.

A low level of calcium in your blood (hypocalcemia), which is caused by hypoparathyroidism, can affect your body’s ability to perform these important functions. Your body also needs calcium in your bones to make them strong. Hypocalcemia happens when there are low levels of calcium in your blood, not in your bones.

Calcium and phosphorus are both electrolytes. Hypoparathyroidism can lead to electrolyte imbalance since it causes low levels of calcium and high levels of phosphorus in your blood.

Electrolytes are essential minerals in your body that have an electric charge. They’re key to many important functions in your body. Because of this, it’s important to treat hypoparathyroidism to return your blood calcium and phosphorus levels to normal.

Low levels of magnesium, another important electrolyte, can also cause hypoparathyroidism because your parathyroid glands need magnesium to function properly.

In the medical world, the prefix “hyper-” means “too much” or “high.” The prefix “hypo-” means “not enough” or “low.” Hypoparathyroidism happens when your parathyroid glands don’t release enough parathyroid hormone (PTH), and hyperparathyroidism happens when your parathyroid glands make too much PTH.

Since your parathyroid glands are in charge of controlling the amount of calcium in your blood, too much PTH causes too much calcium in your blood, and too little PTH causes not enough calcium.

Both adults and children can get hypoparathyroidism, though it’s a rare condition. Adults are more likely to get hypoparathyroidism from accidental damage to their parathyroid glands from neck or thyroid surgery. Children are more likely to have hypoparathyroidism due to a genetic condition called DiGeorge syndrome.

Hypoparathyroidism is a rare condition. It affects fewer than 200,000 people in the United States.

**Causes**

Causes of hypoparathyroidism include:

* **Damage to your parathyroid glands**: Approximately 75% of hypoparathyroidism cases are from accidental damage to your parathyroid glands from neck or thyroid surgery. Hypoparathyroidism can occur years to decades after you’ve had thyroid or neck surgery, but it’s more likely to develop soon after surgery. Most of these cases of hypoparathyroidism are temporary, but some are chronic. Your parathyroid glands can also be damaged from radiation therapy, though this is rare.
* **Certain genetic conditions**: Genetic causes of hypoparathyroidism represent fewer than 10% of cases. The most common genetic cause is DiGeorge syndrome, a chromosomal genetic condition. A baby born with DiGeorge syndrome doesn’t have parathyroid glands. Without parathyroid glands, your body can’t make parathyroid hormone, so people with DiGeorge syndrome have chronic hypoparathyroidism. Approximately 60% of children who have hypoparathyroidism have DiGeorge syndrome. Other genetic syndromes that are associated with deafness and kidney disease can also cause hypoparathyroidism.
* **Certain autoimmune diseases**: A disease called type 1 autoimmune polyglandular syndrome causes your immune system to attack your parathyroid glands, which causes chronic hypoparathyroidism. Addison’s disease and pernicious anemia can also cause hypoparathyroidism.
* **Infiltrative disorders**: Your parathyroid glands can be infiltrated (invaded) by iron (hemochromatosis), copper (Wilson disease) and certain cancer metastases. Each of these situations can cause hypoparathyroidism.
* **Low levels of magnesium**: Your parathyroid glands need magnesium, a type of electrolyte in your blood, to function properly. Because of this, low levels of magnesium (hypomagnesemia) can cause hypoparathyroidism. This is often called functional hypoparathyroidism because the hypoparathyroidism goes away when appropriate levels of magnesium are restored.

**signs and symptoms of hypoparathyroidism**

In most cases, hypoparathyroidism progresses very gradually, and symptoms can be mild. Many people have symptoms for years before they’re diagnosed.

Signs and symptoms of hypoparathyroidism include:

* Tingling in your lips, fingers and toes.
* Muscle cramps.
* Muscle spasms (tetany).
* Abdominal pain.
* “Brain fog” or confusion.
* Abnormal heart rhythm (arrhythmia).
* Brittle nails.
* Dry hair and dry, scaly skin.
* Cataracts.
* Weakened tooth enamel (in children).

**Diagnosis and Tests**

Hypoparathyroidism is generally diagnosed when a person has low levels of calcium and parathyroid hormone in their blood.

Since symptoms are often mild, healthcare providers sometimes “accidentally” find hypoparathyroidism when a routine blood screening shows the person has low levels of blood calcium.

A person is considered to have chronic hypoparathyroidism if they have low blood levels of parathyroid hormone and calcium at least twice within six months.

TESTS

If you’re experiencing symptoms of hypoparathyroidism, your healthcare provider will perform a physical exam and ask questions about your symptoms and medical history.

They may have you undergo one or more of the following tests, which can help diagnose hypoparathyroidism:

* Parathyroid hormone (PTH) blood test.
* Calcium blood test.
* Phosphorus blood test.
* Magnesium blood test.
* 24-hour urine test.

Your healthcare provider may have you undergo other tests to check for more serious side effects of hypoparathyroidism, including:

* An electrocardiogram (ECG or EKG) to check for an abnormal heart rhythm.
* A computed tomography (CT) scan to check for calcium deposits in your brain.

**Management and Treatment**

The goal of treatment for hypoparathyroidism is to minimize symptoms and correct the amount of calcium and minerals in your body.

Treatment can include:

* **Taking calcium carbonate and vitamin D supplements**: Most people with hypoparathyroidism have to take calcium and vitamin D supplements for life. It’s the go-to treatment option for hypoparathyroidism. Your body needs vitamin D to absorb and use calcium, so if you have hypoparathyroidism, you need to take both supplements.
* **Eating a high-calcium and low-phosphorus diet**: People with hypoparathyroidism likely won’t get enough calcium that they need from diet alone, but your healthcare provider may recommend eating a diet high in calcium and low in phosphorus if you have hypoparathyroidism.
* **Getting parathyroid hormone (PTH) injections**: If taking calcium and vitamin D supplements isn’t working to treat your hypoparathyroidism, your provider might have you take parathyroid hormone injections.

**Are there any side effects to hypoparathyroidism treatment?**

If a person with hypoparathyroidism has too much vitamin D and calcium as a part of their treatment, it can cause a high level of blood calcium (hypercalcemia), which can be harmful to your health. Because of this, you’ll have to have your blood monitored frequently to make sure your hypoparathyroidism treatment is working properly.

Long-term use of parathyroid hormone injections may cause osteosarcoma, a type of bone cancer. For this reason, healthcare providers don’t generally prescribe it to treat hypoparathyroidism unless it’s necessary.

**Outlook / Prognosis**

The prognosis for hypoparathyroidism is generally good, especially if it’s diagnosed early.

However, if a person has cataracts, brain calcifications and/or dental changes from hypoparathyroidism, they can’t be reversed.

Most cases of hypoparathyroidism are chronic (life-long), though it can sometimes be temporary.

**complications of hypoparathyroidism**

Long-term complications of hypoparathyroidism can include:

* Issues with kidney function.
* Kidney stones.
* Cataracts.
* Calcium deposits in your brain.

For children specifically, complications from hypoparathyroidism can include:

* Poor growth.
* Dental issues.
* Slow mental development.

Complications of untreated hypoparathyroidism due to sudden and severe (acute) hypocalcemia include seizures and larynx spasms, which can make it difficult to breathe. If you’re experiencing these symptoms, get to the nearest hospital as soon as possible.

**Prevention**

Risk factors for hypoparathyroidism include:

* Having recent neck or thyroid surgery.
* Having a family history of parathyroid conditions.
* Having certain autoimmune diseases that affect your endocrine system, such as Addison’s disease.

**Living With**

If you experience symptoms of hypoparathyroidism, contact your healthcare provider.

If you’ve already been diagnosed with hypoparathyroidism, you’ll need to see your provider regularly to monitor your blood calcium levels to make sure your treatment is working.

If you have symptoms of acute hypocalcemia, such as painful muscle cramps or seizures, get to the nearest hospital as soon as possible.

**Epidemiology**

Hypoparathyroidism has an estimated prevalence in the United States of 37 per 100,000 person-years. In Denmark, it is estimated to be 22 per 100,000 person-years.

Age-related demographics

A study by Powers et al found 74% of US hypo parathyroid patients to be aged 45 years or older.

Sex-related demographics

In the United States, 75% of hypoparathyroidism cases are in females and 25% in males. Similarly, in an Italian study, Cipriani et al found the rate of hospitalizations for hypoparathyroidism in women and men to be 72.2% and 27.8%, respectively.

**Differential Diagnosis of Hypoparathyroidism**

1. Iatrogenic Causes (Most Common)
   1. Post-surgical hypoparathyroidism (thyroidectomy, parathyroidectomy, neck surgery)
   2. Radiation-induced parathyroid damage (neck/chest radiotherapy, I-131 therapy)
2. Congenital and Genetic Disorders
   1. DiGeorge syndrome (22q11.2 deletion) – abnormal parathyroid development, thymic hypoplasia, cardiac defects
   2. Genetic mutations affecting PTH gene or calcium-sensing receptor (CaSR) gene
   3. Hypoparathyroidism-deafness-renal dysplasia (HDR) syndrome
   4. Sanjad-Sakati and Kenney-Caffey syndromes (hypoparathyroidism with dysmorphism)
   5. Autoimmune polyendocrine syndrome type 1 (APS-1/APECED) caused by AIRE gene mutation
3. Autoimmune Hypoparathyroidism
   1. Isolated autoimmune hypoparathyroidism
   2. Part of autoimmune polyglandular syndromes (APS-1 and APS-2)
4. Autoantibodies against CaSR causing functional inhibition of PTH secretion
5. Infiltrative and Metabolic Causes
   1. Hemochromatosis (iron overload damaging parathyroids)
   2. Wilson disease (copper deposition)
   3. Malignant infiltration/metastasis to parathyroid glands
   4. Magnesium imbalance:
      1. Hypomagnesemia causing impaired PTH secretion
      2. Hypermagnesemia inhibiting PTH release (e.g., magnesium therapy in preterm labor)
6. Pseudohypoparathyroidism
   1. End-organ resistance to PTH (normal or elevated PTH with hypocalcemia)
   2. Associated with characteristic somatic features (short stature, brachydactyly)
7. Other Causes
   1. Idiopathic hypoparathyroidism (sporadic or familial)
   2. Functional hypoparathyroidism due to severe illness or transient causes
   3. Chronic kidney disease causing secondary hyperparathyroidism (differential diagnosis)

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**Precocious puberty**

Precocious puberty means early puberty. It’s the term for puberty that begins much earlier than usual — before age 8 in girls and before age 9 in boys.

Puberty is the process during which your child has a growth spurt and develops the sexual and physical features of an adult. In your child’s brain, their hypothalamus releases chemicals (hormones) that cause their pituitary gland to release hormones called gonadotropins. Gonadotropins stimulate the growth of the sex glands (gonads). In male children, their gonads are their testicles, which release testosterone. In females, their gonads are their ovaries, which release estrogen.

Puberty usually starts between the ages of 8 and 13 in female children and between the ages of 9 and 14 years in male children. Children affected by precocious puberty undergo this process much earlier.

**Types of precocious puberty**

There are two main types of precocious puberty: central precocious puberty and peripheral precocious puberty.

**Central precocious puberty**

Central precocious puberty is the more common type. It occurs when your child’s brain releases gonadotropin-releasing hormone (GnRH) too early. This causes their testes or ovaries to release sex hormones (androgens) too early.

**Peripheral precocious puberty**

Peripheral precocious puberty occurs as a result of problems with your child’s reproductive organs (ovaries or testicles) or adrenal glands. Sometimes it results from hormone exposure from their environment. Other names for peripheral precocious puberty include gonadotropin-independent precocious puberty and peripheral precocity.

Any child can develop precocious puberty. The condition happens more often in females than males.

Early puberty affects about 20 out of every 10,000 children. It affects fewer than 5 in every 10,000 male children.

**Causes of precocious puberty**

Precocious puberty has different causes depending on the type.

**Central precocious puberty**

Central precocious puberty occurs when your child’s brain releases GnRH too early, in turn causing their testes or ovaries to release androgens too early. In most cases, the cause of this — especially in female children — is unknown. Causes may include:

* Brain trauma
* Brain tumors
* Brain infections
* Brain abnormalities
* Radiation treatment

**Peripheral precocious puberty**

Issues with your child’s reproductive organs or adrenal glands cause peripheral precocious puberty. Causes may include:

* Ovary, testes or adrenal gland tumors
* Tumors that release human chorionic gonadotropin (HCG)
* Genetic conditions, such as McCune-Albright syndrome
* Severe hypothyroidism
* Adrenal gland disorders, like congenital adrenal hyperplasia

Sometimes, exposure to hormones from sources outside your child’s body causes peripheral precocious puberty. For example, exposure to products like creams, medications or supplements containing estrogen, testosterone or androgen.

**Signs of precocious puberty**

The signs and symptoms of precocious puberty in both sexes include acne, body odor and a growth spurt. Precocious puberty also causes sexual characteristics to develop early. In females, these include:

* Breast development
* Menstruation
* Pubic and underarm hair

Early puberty in males may cause:

* A deepening voice
* Facial, pubic and underarm hair
* Enlargement of the penis and testicles
* Muscle development

**Risk factors for this condition**

Precocious puberty tends to affect certain groups more often. Children who are at a higher risk of developing the condition include:

* Females
* Children with overweight or obesity
* Black children

**Complications associated with precocious puberty**

Early puberty may cause a growth spurt in a child, but when puberty ends, the child stops growing. Therefore, they may be shorter than other children of the same age. Precocious puberty may also be embarrassing for children who are developing more quickly than other children.

These issues can lead to behavioral, emotional and social issues. Children may have trouble with anxiety and depression. They may be at a higher risk of developing substance use disorders and engaging in high-risk behaviors.

**Diagnosis and Tests**

Your child’s healthcare provider will perform a physical examination and ask questions about your child’s medical history.

They may order an X-ray of your child’s hand and wrist to check their bone age. If your child’s body overproduces reproductive hormones, their bones mature earlier than normal, which suggests precocious puberty.

Your child’s provider may also order blood tests to measure your child’s hormone levels. These tests will check your child’s pituitary hormones — luteinizing hormone (LH) and follicle-stimulating hormone (FSH). These hormones control puberty. They’ll also check the levels of your child’s sex hormones.

Your child’s provider may recommend a brain MRI (magnetic resonance imaging). This test can help rule out issues in your child’s brain like tumors.

Your child’s provider may order a pelvic ultrasound if they suspect your child has peripheral precocious puberty. This test checks for ovarian or adrenal tumors in your child’s pelvis and adrenal glands. These growths sometimes cause early puberty in female children.

Based on their findings, your child’s provider may refer you to a pediatric endocrinologist.

**Management and Treatment**

Precocious puberty treatment depends on the type.

**Central precocious puberty**

Turning off the pituitary gland’s production of LH and FSH is the main goal of central precocious puberty treatment. Turning off production will slow down the signs of puberty and delay menstruation. Treatment typically includes a GnRH agonist (puberty blocker), a synthetic (human-made) hormone that works by halting the production of reproductive or growth hormones. Your child’s provider will give your child an injection of the medication at regular intervals until it’s safe for puberty to begin.

**Peripheral precocious puberty**

Eliminating the source of reproductive hormones is the treatment for peripheral precocious puberty. Some children need surgery to remove a tumor or another mass that’s causing the symptoms of early puberty. Others may need medication like a steroid called a glucocorticoid. Removing an outside source of reproductive hormones, like estrogen creams, may be enough to stop early puberty.

**Outlook / Prognosis**

Your child’s outcome will depend on several factors, including:

* Bone age
* Age of onset (how old they were when precocious puberty started)
* How quickly precocious puberty developed
* Your child’s treatment plan

Early treatment with medications or surgery usually stops precocious puberty. This treatment allows a child to develop and grow into adulthood at a more normal rate.

**Prevention**

You can’t prevent most early puberty cases. Limiting your child’s exposure to reproductive hormones from outside sources may prevent it. These sources may include estrogen or testosterone creams, lotions or other medications.

**Living With**

Call your child’s healthcare provider if they’re showing any signs of precocious puberty, especially if they’re younger than 8 years old.

**Epidemiology**

Frequency

The frequency of findings suggestive of precocious puberty in girls and boys depends on whether one is looking at genital hair or breast development, as well as the age at which the condition is considered precocious. The prevalence also depends on whether one is doing population-based screening or assessing the number of patients who are referred to specialists for evaluation. One of the very few studies looking at the prevalence and incidence of precocious puberty based on a national patient register was a Danish report covering the period 1993-2001. The investigators estimated the prevalence at about 0.2% of girls (0.8% for girls ages 5-9 years) and less than 0.05% of boys.This is far lower than indicated in the studies noted below, which are based on the examination of larger groups of children.

*United States*

In 1969, Marshall and Tanner published the results of their study of 192 White British girls, stating that the average age of the larch was 11 years and defining precocious puberty in girls as commencing before age 8 years.No studies that looked at the age of appearance of breast and pubic hair in normal children were performed in the United States during that time.

**DIFFERENTIAL DIAGNOSIS**

Precocious puberty requires differentiation from the benign forms of puberty.These include

* Premature Thelarche: It is the premature unilateral or bilateral development of the breast tissue in girls between the age of 12 to 24 months. There are no other associated pubertal changes. Bone age, growth velocity, and biochemical testing are normal. It is usually a diagnosis of exclusion. Frequent clinical follow up to monitor growth, and pubertal progression is required.
* Premature Adrenarche: The early production of adrenal androgens characterizes this benign condition. It presents with pubic or axillary hair, body odor, or acne before the age of 8 years.  There is no breast development in females and no testicular enlargement in males. Bone age is usually not advanced. It is essential to rule out exposure to androgen sources such as creams or gels, adrenal tumors, and late-onset CAH.
* Premature Menarche: Isolated premature menarche is the onset of vaginal bleeding in girls less than 7 years of age. They may present with either a single episode or few cycles (less than 3) of bleeding and have normal progression to puberty. Recent studies have suggested no effect on adult height. Sexual abuse, vaginal foreign body, and infections of the vulva and vagina need to be ruled out.

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**Hirsutism**

Hirsutism (HUR-soot-iz-um) is a condition in women that results in excessive growth of dark or coarse hair in a male-like pattern — face, chest and back.

With hirsutism, extra hair growth often arises from excess male hormones (androgens), primarily testosterone.

Self-care methods and effective treatment options are available for women who wish to treat hirsutism.

**Causes**

Hirsutism may be caused by:

* **Polycystic ovary syndrome (PCOS).** This condition, which often begins with puberty, causes an imbalance of sex hormones. Over years, PCOS may slowly result in excess hair growth, irregular periods, obesity, infertility and sometimes multiple cysts on the ovaries.
* **Cushing syndrome.** This occurs when your body is exposed to high levels of the hormone cortisol. It can develop from your adrenal glands making too much cortisol or from taking medications such as prednisone over a long period.
* **Congenital adrenal hyperplasia.** This inherited condition is characterized by abnormal production of steroid hormones, including cortisol and androgen, by your adrenal glands.
* **Tumors.** Rarely, an androgen-secreting tumor in the ovaries or adrenal glands can cause hirsutism.
* **Medications.** Some medications can cause hirsutism. These include minoxidil (Minoxidil, Rogaine); danazol, which is used to treat women with endometriosis; testosterone (Androgel, Testim); and dehydroepiandrosterone (DHEA). If your partner uses topical products containing androgens, you can be affected as well, through skin-to-skin contact.

Often hirsutism occurs with no identifiable cause.

**Risk factors**

Several factors can influence your likelihood of developing hirsutism, including:

* **Family history.** Several conditions that cause hirsutism, including congenital adrenal hyperplasia and polycystic ovary syndrome, run in families.
* **Ancestry.** Women of Mediterranean, Middle Eastern and South Asian ancestry are more likely to have more body hair with no identifiable cause than are other women.
* **Obesity.** Being obese causes increased androgen production, which can worsen hirsutism.

**Symptoms**

Hirsutism is stiff or dark body hair, appearing on the body where women don't commonly have hair — primarily the face, chest, lower abdomen, inner thighs and back. People have widely varying opinions on what's considered excessive.

When high androgen levels cause hirsutism, other signs might develop over time, a process called virilization. Signs of virilization might include:

* Deepening voice
* Balding
* Acne
* Decreased breast size
* Increased muscle mass
* Enlargement of the clitoris

**Complications**

Hirsutism can be emotionally distressing. Some women feel self-conscious about having unwanted hair. Some develop depression. Also, although hirsutism doesn't cause physical complications, the underlying cause of a hormonal imbalance can.

If you have hirsutism and irregular periods, you might have polycystic ovary syndrome, which can inhibit fertility. Women who take certain medications to treat hirsutism should avoid pregnancy because of the risk of birth defects.

**Prevention**

Hirsutism generally isn't preventable. But losing weight if you're overweight might help reduce hirsutism, particularly if you have polycystic ovary syndrome.

**Diagnosis**

Tests that measure the amount of certain hormones in your blood, including testosterone or testosterone-like hormones, might help determine whether elevated androgen levels are causing your hirsutism.

Your doctor might also examine your abdomen and do a pelvic exam to look for masses that could indicate a tumor.

**Treatment**

Treatment of hirsutism with no sign of endocrine disorder is not necessary. For women who do need or seek treatment, it may involve treating any underlying disorder, developing a self-care routine for unwanted hair, and trying various therapies and medications.

**Medications**

If cosmetic or self-care methods of hair removal haven't worked for you, talk with your doctor about drugs that treat hirsutism. With these medications it usually takes up to six months, the average life cycle of a hair follicle, before you see a significant difference in hair growth. Options include:

* **Oral contraceptives.** Birth control pills or other hormonal contraceptives, which contain estrogen and progestin, treat hirsutism caused by androgen production. Oral contraceptives are a common treatment for hirsutism in women who don't want to become pregnant. Possible side effects include nausea and headache.
* **Anti-androgens.** These types of drugs block androgens from attaching to their receptors in your body. They're sometimes prescribed after six months on oral contraceptives if the oral contraceptives aren't effective enough.  
  The most commonly used anti-androgen for treating hirsutism is spironolactone (Aldactone, CaroSpir). The results are modest and take at least six months to be noticeable. Possible side effects include menstrual irregularity. Because these drugs can cause birth defects, it's important to use contraception while taking them.
* **Topical cream.** Eflornithine (Vaniqa) is a prescription cream specifically for excessive facial hair in women. It's applied directly to the affected area of your face twice a day. It helps slow new hair growth but doesn't get rid of existing hair. It can be used with laser therapy to enhance the response.

**Procedures**

Hair removal methods whose results may last longer than self-care methods — and which may be combined with medical therapy — include:

* **Laser therapy.** A beam of highly concentrated light (laser) is passed over your skin to damage hair follicles and prevent hair from growing (photoepilation). You might need multiple treatments. For people whose unwanted hair is black, brown or auburn, photoepilation is usually a better option than electrolysis.  
  Talk with your doctor about the risks and benefits of the various lasers used for this hair removal method. People with tanned or darkly pigmented skin are at increased risk of side effects from certain lasers, including a darkening or lightening of their usual skin tones, blistering, and inflammation.
* **Electrolysis.** This treatment involves inserting a tiny needle into each hair follicle. The needle emits a pulse of electric current to damage and eventually destroy the follicle. You might need multiple treatments. For people with naturally blond or white hair, electrolysis is a better option than laser therapy.  
  Electrolysis is effective but can be painful. A numbing cream spread on your skin before treatment might reduce discomfort.

**Self care**

Self-care methods such as the following temporarily remove or reduce the visibility of unwanted facial and body hair. There is no evidence that self-removal of hair leads to heavier hair growth.

* **Plucking.** Plucking is a good method to remove a few stray hairs, but is not useful for removing a large area of hair. Plucked hair usually regrows. This hair removal method may be done with tweezers, thin threads (threading) or other devices designed for this purpose.
* **Shaving.** Shaving is quick and inexpensive, but it needs to be repeated regularly.
* **Waxing.** Waxing involves applying warm wax on your skin where the unwanted hair grows. Once the wax hardens, you pull it from your skin to remove hair. Waxing removes hair from a large area quickly, but it may sting temporarily and sometimes causes skin irritation and redness.
* **Depilation.** Chemical depilatories are applied to the affected skin, where they dissolve hair. These products are available in a variety of forms, such as gel, cream or lotion. They may irritate the skin and cause dermatitis. You'll need to repeat depilation regularly to maintain the effect.
* **Bleaching.** Bleaching lightens hair color, making it less noticeable on people with light skin. Hair-bleaching products, which usually contain hydrogen peroxide, may cause skin irritation. Test any product you use on a small area of skin first.

**Epidemiology**

Frequency

*United States*

Hirsutism affects approximately 10% of women in the United States.

*International*

The prevalence rates of hirsutism in northern Europe are similar to those in the United States; in other places, rates are not known with certainty.

Mortality/Morbidity

The mortality and morbidity of hirsutism are determined by the underlying cause. Most women with idiopathic hirsutism have no associated mortality or morbidity. On the other extreme, a small number of women may have malignant disease with a grave prognosis.

A study by Comim et al suggested that premenopausal hirsutism and/or oligomenorrhea are risk factors for postmenopausal fractures, especially in the humerus and lower leg. The study included 1057 postmenopausal women aged over 55 years. However, another study, by Rubin et al, suggested that polycystic ovary syndrome (PCOS) reduces fracture risk, although the report dealt with a younger group of patients than did the Comim study and indicated that the risk reduction was greater in women who were under age 30 years when diagnosed.

A prospective study by Robinson et al indicated that an association exists between maternal hirsutism and behavioral problems in offspring. The investigators reported that children born to mothers with hirsutism had a greater risk of borderline emotional symptoms (adjusted risk ratio [aRR] = 2.61), conduct disorder (aRR = 2.54), attention deficit hyperactivity disorder (aRR = 2.33), conduct problems (aRR = 2.22), and peer relationship difficulties (aRR = 1.92).

**Differential Diagnosis**

* Androgen-Secreting Adrenal Tumors
* Androgen-Secreting Ovarian Tumors
* Congenital Adrenal Hyperplasia
* Exogenous Androgens
* Iatrogenic Cushing Syndrome
* Idiopathic Hirsutism
* Polycystic Ovary Syndrome (PCOS) Imaging

**Endocrine Society guidelines**

The guidelines suggest testing for elevated androgen levels in all women with an abnormal hirsutism score. However, they recommend against testing for elevated androgen levels in eumenorrheic women with unwanted local hair growth (ie, in the absence of an abnormal hirsutism score) because of the low likelihood of identifying a medical disorder that would change management or outcome.

For most women with patient-important hirsutism despite cosmetic measures (shaving, plucking, waxing), the Endocrine Society recommends starting with pharmacologic therapy and adding direct hair removal methods (electrolysis, photoepilation) for those who desire additional cosmetic benefit. For women with mild hirsutism and no evidence of an endocrine disorder, either pharmacologic therapy or direct hair removal methods are suggested.

For pharmacologic therapy, oral combined estrogen-progestin contraceptives are suggested for the majority of women, with the addition of an antiandrogen agent after 6 months if the response is suboptimal. The guidelines recommend against antiandrogen monotherapy unless adequate contraception is used. In addition, they recommend against using insulin-lowering drugs solely for treating hirsutism.

For women who choose hair removal therapy, the guidelines suggest photoepilation for those whose unwanted hair is auburn, brown, or black and electrolysis for those with white or blonde hair.

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**Pseudohypoparathyroidism**

Pseudohypoparathyroidism (PHP) is a rare genetic disorder where your body doesn’t process parathyroid hormone (PTH), even though your parathyroid glands produce normal amounts of it.

Parathyroid hormone helps maintain calcium, phosphorus and vitamin D levels in your blood. PHP disrupts your body’s ability to use the hormones your parathyroid gland makes (parathyroid hormone resistance). As a result, the calcium levels in your blood drop and the phosphorus levels rise. This imbalance can lead to problems like muscle cramps, numbness, seizures and dental issues.

PHP is different from hypoparathyroidism. People with hypoparathyroidism don’t produce enough PTH to begin with.

**Types of PHP**

The different types are:

* **PHP-1**. This is the most common type. In addition to PTH resistance, PHP-1 causes skeletal abnormalities like a round face, short stature, short neck and shortened hand and foot bones. Healthcare providers call this set of symptoms **Albright hereditary osteodystrophy (AHO)**. People with PHP-1 inherit the *GNAS* gene variant (change) from one of their biological parents.
* **PPHP (pseudopseudohypoparathyroidism)**. This is a limited form of PHP-1. People with PPHP have physical symptoms of AHO but don’t have PTH resistance.
* **PHP-2**. People with PHP-2 have PTH resistance but lack the physical symptoms of AHO. Researchers don’t yet know which genetic abnormality causes PHP-2.

**Symptoms of pseudohypoparathyroidism**

Pseudohypoparathyroidism symptoms vary from person to person and may include:

* Muscle spasms
* Muscle cramps
* Numbness or tingling in your hands or feet
* Seizures
* Teeth that grow in later than expected
* Weakened tooth enamel
* Low blood pressure
* Brittle hair and nails
* Anxiety
* Brittle hair and nails
* Depression

People with PHP-1 also have Albright hereditary osteodystrophy (AHO). AHO and PHP features may include:

* Round face
* Short stature
* Short neck
* Shortened bones in your hands and feet
* Obesity
* Vision issues like cataracts, blurred vision or light sensitivity
* Bony bumps under your skin
* Developmental delays

**Pseudohypoparathyroidism causes**

Variations (changes) in your *GNAS* gene cause the disease. Some people inherit it from a biological parent. Others develop it for no known reason. PHP usually develops during infancy or childhood. But adults can get it, too.

**Complications of pseudohypoparathyroidism**

If you have PHP, you’re more likely to develop other endocrine system disorders. These hormonal issues can cause symptoms like low energy and low sex drive.

Some people with PHP are also more likely to develop:

* Parkinsonism
* Difficulty with fine motor skills
* Carpal tunnel syndrome (in people with PHP-1)
* Spinal stenosis
* Sleep apnea (in children)

**Diagnosis and Tests**

A healthcare provider will do a physical examination and review your family history. If they suspect the disease, they’ll likely run tests to confirm a diagnosis. These tests may include:

* **Blood tests** to measure hormone levels
* **Urine tests** (pee tests) to measure calcium and phosphorus levels
* **Genetic testing** for the *GNAS* gene
* **Electrocardiogram (EKG**) to check for an abnormal heart rhythm
* **Hand X-rays** to check for shortened bones
* **CT (computed tomography) scan** to look for differences in your brain

**Management and Treatment**

Treatment aims to restore and maintain proper levels of calcium and phosphorus in your blood. Managing these levels can help reduce your symptoms.

There’s no cure for the disease, but you can manage it with ongoing, lifelong treatment. Treatments may include:

* Calcium and vitamin D supplements
* Calcitriol capsules (a medication that increases calcium in your body)
* Calcitriol injections
* Growth or thyroid hormone replacement
* A high-calcium, low-phosphorus diet

**When should I see my healthcare provider?**

If you have PHP, see your healthcare provider regularly so they can monitor your calcium and phosphorus levels. Routine appointments can help things stay on track.

Call 911 or head to your nearest emergency room if you develop severe symptoms like difficulty breathing, painful muscle cramps or seizures.

**Outlook / Prognosis**

If you have pseudohypoparathyroidism, you’ll receive ongoing care with your primary care physician. Because PHP can affect several parts of your body, you may also need to see specialists who can help manage your specific symptoms. Your healthcare team could include:

* Endocrinologists
* Orthopaedic surgeons
* Pediatricians
* Neurologists
* Physical therapists
* Occupational therapists
* Nutritionists
* Dentists
* Geneticists
* Pain management specialists

You’ll likely need to take supplements for the rest of your life.

Developmental and intellectual abilities vary significantly depending on the type and severity of the disease. In most cases, people with PHP have a normal life expectancy compared to people without PHP. Your healthcare provider can tell you what to expect.

**Differential Diagnoses of Pseudohypoparathyroidism (PHP)**

1. Secondary Hyperparathyroidism
   1. Due to vitamin D deficiency, chronic kidney disease, or malabsorption causing hypocalcemia and compensatory elevated PTH
   2. Distinguished by underlying cause of hypocalcemia and normal PTH responsiveness
2. Autoimmune Polyglandular Syndromes
   1. May present with hypocalcemia and endocrine abnormalities
   2. Usually associated with other autoimmune endocrinopathies
3. Severe Vitamin D Deficiency
   1. Can mimic PTH resistance with hypocalcemia, hyperphosphatemia, and elevated PTH
   2. Corrected by vitamin D supplementation
4. Hypomagnesemia
   1. Causes functional PTH resistance and hypocalcemia
   2. Magnesium correction improves calcium levels
5. Albright Hereditary Osteodystrophy (AHO) Phenocopies
   1. Other syndromes with similar skeletal features such as Turner syndrome, tricho-rhino-phalangeal syndrome
   2. Distinguished by genetic testing and clinical features
6. Fibrodysplasia Ossificans Progressiva (FOP)
   1. Ectopic ossifications resembling those seen in some PHP variants
   2. Progressive heterotopic bone formation with distinct clinical course
7. Renal Disease (Chronic or Acute)
   1. Can cause secondary hyperparathyroidism and biochemical abnormalities similar to PHP
8. Other Genetic Disorders Affecting GNAS or Related Pathways
   1. Variants within PHP subtypes (PHP1A, PHP1B, PHP1C) and related disorders
   2. Confirmed by molecular genetic analysis

**Epidemiology**

The estimated prevalence of PHP type 1a, type 1b, and PPHP is 1 per 150,000 in Italy.In Japan, the estimated prevalence of PHP type 1a and type 1b is 1 per 295,000.PHP occurs approximately twice as frequently in females as in males. Onset of endocrine symptoms occurs during childhood, although cases with severe hypothyroidism at neonatal screening have been reported.

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**OSTEOPOROSIS**

Osteoporosis causes bones to become weak and brittle — so brittle that a fall or even mild stresses such as bending over or coughing can cause a break. Osteoporosis-related breaks most commonly occur in the hip, wrist or spine.

Bone is living tissue that is constantly being broken down and replaced. Osteoporosis occurs when the creation of new bone doesn't keep up with the loss of old bone.

Osteoporosis affects men and women of all races. But white and Asian women, especially older women who are past menopause, are at highest risk. Medicines, healthy diet and weight-bearing exercise can help prevent bone loss or strengthen already weak bones.

**Causes**

Your bones are in a constant state of renewal — new bone is made and old bone is broken down. When you're young, your body makes new bone faster than it breaks down old bone and your bone mass increases. After the early 20s this process slows, and most people reach their peak bone mass by age 30. As people age, bone mass is lost faster than it's created.

How likely you are to develop osteoporosis depends partly on how much bone mass you attained in your youth. Peak bone mass is partly inherited and varies also by ethnic group. The higher your peak bone mass, the more bone you have "in the bank" and the less likely you are to develop osteoporosis as you age.

**Risk factors**

Several factors can increase the likelihood that you'll develop osteoporosis — including your age, race, lifestyle choices, and medical conditions and treatments.

**Unchangeable risks**

Some risk factors for osteoporosis are out of your control, including:

* **Your sex.** Women are much more likely to develop osteoporosis than are men.
* **Age.** The older you get, the greater your risk of osteoporosis.
* **Race.** You're at greatest risk of osteoporosis if you're white or of Asian descent.
* **Family history.** Having a parent or sibling with osteoporosis puts you at greater risk, especially if your mother or father fractured a hip.
* **Body frame size.** Men and women who have small body frames tend to have a higher risk because they might have less bone mass to draw from as they age.

**Hormone levels**

Osteoporosis is more common in people who have too much or too little of certain hormones in their bodies. Examples include:

* **Sex hormones.** Lowered sex hormone levels tend to weaken bone. The fall in estrogen levels in women at menopause is one of the strongest risk factors for developing osteoporosis. Treatments for prostate cancer that reduce testosterone levels in men and treatments for breast cancer that reduce estrogen levels in women are likely to accelerate bone loss.
* **Thyroid problems.** Too much thyroid hormone can cause bone loss. This can occur if your thyroid is overactive or if you take too much thyroid hormone medicine to treat an underactive thyroid.
* **Other glands.** Osteoporosis has also been associated with overactive parathyroid and adrenal glands.

**Dietary factors**

Osteoporosis is more likely to occur in people who have:

* **Low calcium intake.** A lifelong lack of calcium plays a role in the development of osteoporosis. Low calcium intake contributes to diminished bone density, early bone loss and an increased risk of fractures.
* **Eating disorders.** Severely restricting food intake and being underweight weakens bone in both men and women.
* **Gastrointestinal surgery.** Surgery to reduce the size of your stomach or to remove part of the intestine limits the amount of surface area available to absorb nutrients, including calcium. These surgeries include those to help you lose weight and for other gastrointestinal disorders.

**Steroids and other medicines**

Long-term use of oral or injected corticosteroid medicines, such as prednisone and cortisone, interferes with the bone-rebuilding process. Osteoporosis has also been associated with medications used to combat or prevent:

* Seizures.
* Gastric reflux.
* Cancer.
* Transplant rejection.

**Medical problems**

The risk of osteoporosis is higher in people who have certain medical problems, including:

* Celiac disease.
* Inflammatory bowel disease.
* Kidney or liver disease.
* Cancer.
* Multiple myeloma.
* Rheumatoid arthritis.

**Lifestyle choices**

Some bad habits can increase your risk of osteoporosis. Examples include:

* **Sedentary lifestyle.** People who spend a lot of time sitting have a higher risk of osteoporosis than do those who are more active. Any weight-bearing exercise and activities that promote balance and good posture are good for your bones, but walking, running, jumping, dancing and weightlifting seem particularly helpful.
* **Excessive alcohol consumption.** Regular consumption of more than two alcoholic drinks a day increases the risk of osteoporosis.
* **Tobacco use.** The exact role tobacco plays in osteoporosis isn't clear, but it has been shown that tobacco use contributes to weak bones.

**Symptoms**

There typically are no symptoms in the early stages of bone loss. But once your bones have been weakened by osteoporosis, you might have signs and symptoms that include:

* Back pain, caused by a broken or collapsed bone in the spine.
* Loss of height over time.
* A stooped posture.
* A bone that breaks much more easily than expected.

**Prevention**

Good nutrition and regular exercise are essential for keeping your bones healthy throughout your life.

**Calcium**

Men and women between the ages of 18 and 50 need 1,000 milligrams of calcium a day. This daily amount increases to 1,200 milligrams when women turn 50 and men turn 70.

Good sources of calcium include:

* Low-fat dairy products.
* Dark green leafy vegetables.
* Canned salmon or sardines with bones.
* Soy products, such as tofu.
* Calcium-fortified cereals and orange juice.

If you find it difficult to get enough calcium from your diet, consider taking calcium supplements. However, too much calcium has been linked to kidney stones. Although yet unclear, some experts suggest that too much calcium, especially in supplements, can increase the risk of heart disease.

The Health and Medicine Division of the National Academies of Sciences, Engineering, and Medicine recommends that total calcium intake, from supplements and diet combined, should be no more than 2,000 milligrams daily for people older than 50.

**Vitamin D**

Vitamin D improves the body's ability to absorb calcium and improves bone health in other ways. People can get some of their vitamin D from sunlight, but this might not be a good source if you live in a high latitude, if you're housebound, or if you regularly use sunscreen or avoid the sun because of the risk of skin cancer.

Dietary sources of vitamin D include cod liver oil, trout and salmon. Many types of milk and cereal have been fortified with vitamin D.

Most people need at least 600 international units (IU) of vitamin D a day. That recommendation increases to 800 IU a day after age 70.

People without other sources of vitamin D and especially with limited sun exposure might need a supplement. Most multivitamin products contain between 600 and 800 IU of vitamin D. Up to 4,000 IU of vitamin D a day is safe for most people.

**Exercise**

Exercise can help you build strong bones and slow bone loss. Exercise will benefit your bones no matter when you start, but you'll gain the most benefits if you start exercising regularly when you're young and continue to exercise throughout your life.

Combine strength training exercises with weight-bearing and balance exercises. Strength training helps strengthen muscles and bones in your arms and upper spine. Weight-bearing exercises — such as walking, jogging, running, stair climbing, skipping rope, skiing and impact-producing sports — affect mainly the bones in your legs, hips and lower spine. Balance exercises such as tai chi can reduce your risk of falling especially as you get older.

**Complications**

Bone breaks, particularly in the spine or hip, are the most serious complications of osteoporosis. Hip fractures often are caused by a fall and can result in disability and even an increased risk of death within the first year after the injury.

In some cases, broken bones in the spine can occur even if you haven't fallen. The bones that make up your spine, called vertebrae, can weaken to the point of collapsing, which can result in back pain, lost height and a hunched-forward posture.

**Diagnosis**

Your bone density can be measured by a machine that uses low levels of X-rays to determine the proportion of minerals in your bones. During this painless test, you lie on a padded table as a scanner passes over your body. In most cases, only certain bones are checked — usually in the hip and spine.

**Treatment**

Treatment recommendations are often based on an estimate of your risk of breaking a bone in the next 10 years using information such as the bone density test. If your risk isn't high, treatment might not include medication and might focus instead on modifying risk factors for bone loss and falls.

**Bisphosphonates**

For both men and women at increased risk of broken bones, the most widely prescribed osteoporosis medications are bisphosphonates. Examples include:

* Alendronate (Binosto, Fosamax).
* Risedronate (Actonel, Atelvia).
* Ibandronate.
* Zoledronic acid (Reclast, Zometa).

Side effects include nausea, abdominal pain and heartburn-like symptoms. These are less likely to occur if the medicine is taken properly. Intravenous forms of bisphosphonates don't cause stomach upset but can cause fever, headache and muscle aches.

A very rare complication of bisphosphonates is a break or crack in the middle of the thigh bone. A second rare complication is delayed healing of the jawbone, called osteonecrosis of the jaw. This can occur after an invasive dental procedure, such as removing a tooth.

**Denosumab**

Compared with bisphosphonates, denosumab (Prolia, Xgeva) produces similar or better bone density results and reduces the chance of all types of breaks. Denosumab is delivered via a shot under the skin every six months.

Similar to bisphosphonates, denosumab has the same rare complication of causing breaks or cracks in the middle of the thighbone and osteonecrosis of the jaw. If you take denosumab, you might need to continue to do so indefinitely. Recent research indicates there could be a high risk of spinal column fractures after stopping the drug.

**Hormone-related therapy**

Estrogen, especially when started soon after menopause, can help maintain bone density. However, estrogen therapy can increase the risk of breast cancer and blood clots, which can cause strokes. Therefore, estrogen is typically used for bone health in younger women or in women whose menopausal symptoms also require treatment.

Raloxifene (Evista) mimics estrogen's beneficial effects on bone density in postmenopausal women, without some of the risks associated with estrogen. Taking this drug can reduce the risk of some types of breast cancer. Hot flashes are a possible side effect. Raloxifene also may increase your risk of blood clots.

In men, osteoporosis might be linked with a gradual age-related decline in testosterone levels. Testosterone replacement therapy can help improve symptoms of low testosterone, but osteoporosis medications have been better studied in men to treat osteoporosis and thus are recommended alone or in addition to testosterone.

**Bone-building medicines**

If you have severe osteoporosis or if the more common treatments for osteoporosis don't work well enough, your doctor might suggest trying:

* **Teriparatide (Bonsity, Forteo).** This powerful drug is similar to parathyroid hormone and stimulates new bone growth. It's given by daily injection under the skin for up to two years.
* **Abaloparatide (Tymlos)** is another drug similar to parathyroid hormone. This drug can be taken for only two years.
* **Romosozumab (Evenity).** This is the newest bone-building medicine to treat osteoporosis. It is given as an injection every month at your doctor's office and is limited to one year of treatment.

After you stop taking any of these bone-building medications, you generally will need to take another osteoporosis drug to maintain the new bone growth.

**Lifestyle and home remedies**

These suggestions might help reduce your risk of developing osteoporosis or breaking bones:

* **Don't smoke.** Smoking increases rates of bone loss and the chance of fracture.
* **Limit alcohol.** Consuming more than two alcoholic drinks a day may decrease bone formation. Being under the influence of alcohol also can increase your risk of falling.
* **Prevent falls.** Wear low-heeled shoes with nonslip soles and check your house for electrical cords, area rugs and slippery surfaces that might cause you to fall. Keep rooms brightly lit, install grab bars just inside and outside your shower door, and make sure you can get into and out of your bed easily.

**Epidemiology**

In 2017–2018, the age-adjusted prevalence of osteoporosis at either the femur neck or lumbar spine or both among adults aged 50 and over was 12.6%, and the prevalence of low bone mass at either skeletal site was 43.1%. Osteoporosis prevalence was higher in women than men and higher among adults aged 65 and over than adults aged 50–64. From 2007–2008 through 2017–2018, the age-adjusted prevalence of osteoporosis in women increased from 14.0% to 19.6%, but no significant change was seen among men. No significant change was seen in low bone mass prevalence for men or women from 2007–2008 through 2017–2018. Monitoring the prevalence of osteoporosis and low bone mass may inform public health programs that focus on reducing or preventing osteoporosis and its consequences. Healthy People 2020 has a goal of 5.3% or less for the prevalence of osteoporosis at the femur neck for adults aged 50 and over. In the United States, the prevalence of osteoporosis among adults aged 50 and over at the femur neck only was 6.3% and has not met the 2020 goal

**Diagnostic Considerations**

The differential diagnosis of osteoporosis is very extensive. When dealing with reduced bone density, always rule out the other possible causes before treating the patient for osteoporosis. Many patients have a coexisting cause of bone loss.

The differential diagnosis of an atraumatic compression fracture may include osteomalacia, tumor, osteonecrosis, infection, and other bone-softening metabolic disorders. Metastatic bone disease should always be ruled out when a patient incurs multiple fractures.

Osteoporosis may be confused with osteomalacia, but in osteoporosis the bones are porous and brittle, whereas in osteomalacia the bones are soft. This difference in bone consistency is related to the ratio of mineral to organic material (principally, collagen). In osteoporosis, the mineral-to-collagen ratio is within the reference range, whereas in osteomalacia, the proportion of mineral composition is reduced relative to organic matrix content.

Sometimes a patient's first fracture is the sentinel event that alerts the clinician to an underlying disorder leading to osteoporosis.

Other conditions to be considered include the following:

* Leukemia
* Lymphoma
* Fractures secondary to bone metastases from cancer
* Pediatric osteogenesis imperfecta
* Renal osteodystrophy

**Differential Diagnoses**

* Homocystinuria/Homocysteinemia
* Hyperparathyroidism
* Osteomalacia and Renal Osteodystrophy Imaging
* Mastocytosis
* Multiple Myeloma

**GUIDELINES**

guidelines recommend evaluation of all women age 50 or older for osteoporosis risk. The initial evaluation should include a detailed history, physical exam, and clinical fracture risk assessment with the Fracture Risk Assessment (FRAX) tool or other fracture risk assessment tool.

BMD measurement should be considered, based on the patient's clinical fracture risk profile. For BMD measurement, axial dual-energy x-ray absorptiometry (DXA)(lumbar spine and hip; 1/3 radius if indicated) is recommended.

The AACE recommends BMD testing in the following patients:

* Women age 65 or older
* Postmenopausal women with a history of fracture(s) without major trauma, with osteopenia identified radiographically, or starting long-term systemic glucocorticoid therapy (≥3 months)
* Perimenopausal or postmenopausal women with risk factors for osteoporosis if willing to consider pharmacologic interventions, with low body weight (< 127 lb or body mass index <

This guideline summary addresses the assessment, diagnosis and current treatments for osteoporosis, including recommendations to prevent fragility fractures. It applies to postmenopausal women, and to men age 50 years or older.

*Concerning assessment of fracture risk in postmenopausal women, and men age ≥50:*

1. Conduct a FRAX assessment in people with a clinical risk factor for fragility fracture.
2. Measure BMD in people with intermediate fracture risk by FRAX (amber) to refine the estimate of 10-year risk.
3. Measure BMD in people with high and very high fracture risk by FRAX (red) to guide drug choice and provide a baseline for BMD monitoring.
4. Consider imaging to look for a vertebral fracture in people with acute onset back pain who have risk factors for osteoporosis , and/or in people with a history of ≥4cm height loss, kyphosis, recent or current long-term oral glucocorticoid therapy, or a BMD T-score ≤-2.5.
5. Assess falls risk in patients with osteoporosis and/or fragility fractures and offer those at risk an exercise programme to improve balance and muscle strength.

*Regarding drug treatment to prevent fractures in postmenopausal women, and men age ≥50:*

1. Offer drug treatment to people at high and very high risk of fracture.
2. Consider, particularly in older people, drug treatment in those with a prior and/or recent fragility fracture.

*When selecting drug treatments to prevent fractures in postmenopausal women, and men age ≥50:*

1. Consider the level of fracture risk, any additional clinical risk factors, patient choice, and the cost-effectiveness of treatment, when deciding on a particular drug treatment.
2. Start treatment promptly following a fragility fracture, because risk of re-fracture is highest immediately after a fracture and risk remains elevated.
3. Consider referral of very high risk patients to an osteoporosis specialist in secondary care, for assessment and consideration of parenteral treatment ( some may need first-line anabolic drug treatment, especially if multiple vertebral fractures). Indications of very high risk include the presence of important risk factors, including a recent vertebral fracture [within the last 2 years], ≥2 vertebral fractures [whenever they have occurred], BMD T-Score ≤-3.5, treatment with high dose glucocorticoids [≥7.5 mg/day of prednisolone or equivalent over 3 months]; the presence of multiple clinical risk factors, particularly with a recent fragility fracture indicating high imminent risk of re-fracture; or other indicators of very high fracture risk, including as defined by FRAX.
4. In other patients for whom treatment is indicated, offer antiresorptive therapy with oral bisphosphonates (alendronate or risedronate) or intravenous zoledronate, or in postmenopausal women age ≤60 years hormone replacement therapy.
5. Consider alternative treatment options if these first-line bisphosphonates are unsuitable or not tolerated; denosumab, ibandronate, raloxifene, strontium ranelate, teriparatide, abaloparatide or romosozumab.
6. Following treatment with an anabolic agent ( teriparatide, abaloparatide or romosozumab), start alendronate, zoledronate or denosumab without delay.

*When postmenopausal women, and men age ≥50, have started drug treatment:*

1. Regularly review patients' tolerance of, and adherence to, oral drug treatments.
2. Remember long-term treatment is often required, because osteoporosis is a long-term condition for which there is currently no cure.
3. Plan to prescribe oral bisphosphonates for at least 5 years, or intravenous bisphosphonates for at least 3 years and then re-assess fracture risk. Longer durations of treatment will be needed in those who are older (age ≥70 years), have had a hip or vertebral fracture, are on high-dose oral glucocorticoids [≥7.5 mg/day of prednisolone or equivalent over 3 months], or have a further fragility fracture during osteoporosis treatment. In lower risk patients, a temporary treatment pause of 18 to 36 months can be considered after 5 years’ oral bisphosphonate or 3 years’ intravenous bisphosphonate
4. Before starting denosumab, ensure the long-term treatment plan considers the potential need to stop denosumab and how this would be managed.
5. Do not stop denosumab treatment without a plan for subsequent anti-resorptive therapy, where renal function permits.
6. Repeat fracture risk assessment after any new fracture, regardless of when this occurs.
7. Reassess fracture risk 18 months to 3 years after pausing drug treatment.

*When postmenopausal women, and men age ≥50, are treated with oral glucocorticoids:*

1. If starting ≥7.5 mg/day prednisolone or equivalent for the next 3 months, start bone protective treatment at the same time (without waiting for a DXA scan, which can follow later).
2. Offer antiresorptive therapy with oral bisphosphonates (alendronate or risedronate) or intravenous zoledronate, and in those at very high risk of vertebral fracture refer for consideration of anabolic therapy.
3. Consider denosumab as an alternative treatment option.

*When advising on lifestyle and dietary measures:*

1. Recommend a healthy, balanced diet, moderation of alcohol consumption and avoidance of smoking.
2. Ensure a sufficient dietary calcium and vitamin D intake and supplement these as necessary.
3. Encourage a combination of regular weight-**bearing and muscle strengthening exercise.**

***Regarding fracture prevention services:***

1. **Patients who sustain a fragility fracture should have access to a multidisciplinary, coordinator-based Fracture Liaison Service (FLS)** which enables timely fracture and falls risk assessment, investigation, treatment, and monitoring.
2. **Ensure that diagnostic imaging services routinely evaluate the spine in all imaging** of postmenopausal women, and men age ≥50 years, in which the spine is visualized, and report vertebral fractures using standardized methods.

***When a postmenopausal woman, or a man age ≥50 has a symptomatic osteoporotic vertebral fracture:***

1. **Consider referral to an exercise programme** which provides progressive muscle strengthening activity, including back extensor muscle strengthening and/or endurance exercise.
2. **Investigate for underlying causes of fragility fracture.**
3. **Start treatment promptly** to reduce the risk of further fractures.

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**Osteomalacia**

Osteomalacia is a condition in which your bones soften and weaken, causing them to break more easily.

It most often affects adults due to a lack of vitamin D. Your body needs vitamin D to absorb calcium and phosphorus. These minerals help your bones maintain their strength and hardness. Without enough vitamin D, your bones don’t mineralize as they usually would. This leads to bone fragility.

In children, inadequate concentrations of vitamin D may cause a similar condition called rickets.

You may not notice osteomalacia at first. But over time, it can cause bone pain, usually in the lower half of your body. Eventually, you may feel pain all over your body. Simple movements may hurt. Know that you don’t have to live with this pain. Reach out to a healthcare provider. They can help find the cause and offer treatment options.

**symptoms of osteomalacia**

The main symptom of osteomalacia is bone pain. It most commonly affects your hips, pelvis and legs.

Other osteomalacia symptoms may include:

* Bones that break more easily
* Muscle pain, stiffness and weakness, especially after being active
* Difficulty walking or a change in your gait
* Muscle spasms or cramps, especially in your hands and feet
* “Pins-and-needles” feeling (paresthesia) in your arms and legs
* More frequent falls

**Causes of osteomalacia**

Osteomalacia develops most commonly due to a vitamin D deficiency. This is often from not getting enough sunlight. But it may also be from not getting enough vitamin D from the foods you eat. Vitamin D is essential for calcium absorption and for maintaining bone health.

Other osteomalacia causes may include:

* A digestive condition that leads to malabsorption
* Kidney failure
* Liver disease
* Anti seizure medications
* Certain rare genetic conditions

**Risk factors for osteomalacia**

When you’re in sunlight, your skin naturally produces vitamin D. Your skin may not produce enough vitamin D if you:

* Live in a cold, dark climate
* Work inside all day
* Wear clothing that covers most of your skin
* Have darker skin pigmentation

You may not be getting enough vitamin D from the foods you eat if you:

* Don’t consume any milk products
* Follow a vegetarian or vegan diet
* Have a condition that causes malabsorption, like Crohn’s disease or celiac disease
* Have recently had bariatric surgery, like gastric bypass surgery

Other people who have a higher risk of osteomalacia include those who:

* Have obesity
* Are age 65 and older
* Are pregnant or breastfeeding

**Diagnosis and Tests**

Your healthcare provider will do a physical examination and ask about your family and medical history. They’ll also ask questions about your nutrition and activity level.

Your provider will recommend blood tests to check your levels of vitamin D, calcium and phosphorus. The most significant sign of osteomalacia is low levels of vitamin D. But low calcium or phosphorus levels may also point to osteomalacia.

To confirm a diagnosis, your provider may also check your levels of:

* Creatinine
* Electrolytes
* Alkaline phosphatase
* Parathyroid hormone

Other tests may include:

* 24-hour urine test to check the amount of calcium in your urine
* X-rays to look for any signs of bone weakening or fractures
* Bone mineral density scan to assess your bone density and monitor for bone loss
* Bone biopsy to see if you have bone softening

**Management and Treatment**

Osteomalacia treatment includes the use of vitamin D, calcium and/or phosphorus supplements. Your healthcare provider will tell you how much of each of these you need to take. If you have malabsorption issues or recently had bariatric surgery, you may need to take larger doses of vitamin D and calcium.

While supplements should help treat osteomalacia, your symptoms may take several months to improve. Depending on the severity of osteomalacia, you may need to continue taking vitamin D for a long time. If you stop taking it, osteomalacia may return.

People with conditions like liver or kidney failure will need additional treatment and support. Your provider will want to monitor your blood levels regularly. You may need a special form of vitamin D.

Other treatments to relieve or correct osteomalacia symptoms may include:

* Getting enough sunlight exposure
* Eating more foods with vitamin D and calcium
* Wearing braces to reduce or prevent bone irregularities
* Surgery to correct bone deformities (in severe cases)

**Outlook / Prognosis**

With early diagnosis and treatment (dietary supplements), most people will start to recover from osteomalacia within a few weeks. But it can still take up to six months for your bones to heal and strengthen again.

**Prevention**

Yes, you can usually prevent osteomalacia by:

* Getting enough sunlight
* Getting enough vitamin D and calcium from the foods you eat

Depending on where you live and the time of year, you may be able to get enough vitamin D from sunlight alone. People with lighter skin typically need to expose themselves to 10 to 15 minutes of sunshine two to three times per week. People with darker skin usually need more time in the sun. This must be direct sunlight — not through windows or clothing.

Be careful not to spend too much time in the sun without sunscreen. Too much sun exposure can increase your risk for skin cancer. Ask your healthcare provider about how much time you should spend in the sun.

You won’t be able to get all the vitamin D you need through food alone, but it can help. Some foods naturally contain vitamin D. These include:

* Fatty fish like tuna, salmon, sardines and mackerel
* Rainbow trout
* Red meat
* Beef liver
* Mushrooms
* Egg yolks
* Cod liver oil

Other foods are fortified with vitamin D. Talk to your healthcare provider about which sources are best for you. As with anything, you have to weigh the pros and cons of various foods.

If you’re still not getting enough vitamin D through sunlight and food, your provider may recommend a supplement.

**Living With**

As we age, taking care of our bones becomes even more important. To help maintain your bone health:

* Eat an adequate amount of food containing vitamin D and calcium.
* Expose yourself to an adequate amount of sunlight.
* Maintain a healthy weight for you.
* Get regular physical activity.
* Don’t smoke.
* If you drink beverages containing alcohol, do so in moderation.

**When should I see my healthcare provider?**

If you have bone pain or any of the other osteomalacia symptoms, reach out to a healthcare provider. They can test your blood levels and determine if this condition is affecting you.

**Differential Diagnosis of Osteomalacia**

Symptoms of osteomalacia — particularly low-trauma fracture — are nonspecific and can be seen in other bone disorders. Diseases that should be considered in the differential diagnosis include osteoporosis, Paget’s disease of the bone, malignant diseases (especially multiple myeloma), primary hyperparathyroidism, and renal osteodystrophy, all of which are associated with low-trauma fractures.

The clinical presentation of osteoporosis is similar to that of osteomalacia, but the physical exam and laboratory findings (normal calcium, phosphate, and alkaline phosphatase levels in osteoporosis) can distinguish osteoporosis from osteomalacia. Bone histomorphometry on trans-iliac bone biopsy provides definite differentiation of osteomalacia from osteoporosis.

Paget’s disease differs from osteomalacia in radiographic findings. The cortical thickening, coarse trabeculae, and areas of radiolucency and sclerosis seen in Paget’s disease are absent in osteomalacia.

The signs and symptoms of malignant diseases, such as multiple myeloma, can be similar to those of osteomalacia. However, multiple myeloma shows lytic lesion on radiographs and anemia, hypercalcemia, and elevated creatinine due to the impaired renal function.

Primary hyperparathyroidism presents with symptoms similar to those of osteomalacia. The presence of hypercalcemia, which is typically rare in osteomalacia, is the basis for the differential diagnosis. The presence of hyperphosphatemia, instead of hypophosphatemia, can be used to differentiate renal osteodystrophy from osteomalacia.

**Epidemiology**

Globally, vitamin D deficiency is the most common cause of osteomalacia. Osteomalacia caused by vitamin D deficiency (nutritional osteomalacia) occurs almost exclusively in parts of the world where vitamin D deficiency is endemic. The prevalence of nutritional osteomalacia is hard to determine because the condition is often asymptomatic, especially in older adults, or goes unrecognized. In parts of the world where vitamin D deficiency is rare, hypophosphatemia is the most common cause of osteomalacia.

**Guideline Recommendations:**

1. Diagnosis:

* Osteomalacia is characterized by impaired bone matrix mineralization after growth plate closure.
* Most common cause: Vitamin D deficiency.
* Diagnostic clues: low serum vitamin D, low/normal calcium, elevated parathyroid hormone (PTH), bone pain, muscle weakness, fractures.
* Laboratory evaluation: serum calcium, phosphate, alkaline phosphatase, 25-hydroxyvitamin D, PTH levels.
* Imaging may show Looser’s zones (pseudo fractures).

2. Treatment Principles:

* Address underlying cause: e.g., malabsorption, renal disease, tumor-induced osteomalacia.
* Vitamin D supplementation:
  + Typical regimens: 800–1200 IU daily or 50,000 IU weekly for 8–12 weeks followed by maintenance doses.
  + Higher doses (up to 10,000–50,000 IU) may be needed in malabsorption or severe deficiency.
  + Vitamin D metabolites (calcifediol or calcitriol) may be used in renal failure or malabsorption.
* Calcium supplementation:
  + Usually 1000 mg elemental calcium daily; higher doses (2000–3000 mg) in malabsorption or post-bariatric surgery.
* Phosphate supplementation: for hypophosphatemic or tumor-induced osteomalacia.
* Surgical resection: of tumors causing oncogenic osteomalacia when identified.

3. Monitoring and Follow-up:

* Monitor serum calcium, phosphate, alkaline phosphatase, and vitamin D levels.
* Clinical improvement usually begins within weeks; full recovery may take several months.
* Watch for secondary hyperparathyroidism and rare progression to tertiary hyperparathyroidism.
* Long-term maintenance therapy is often required to prevent relapse.

4. Prevention:

* Adequate sunlight exposure tailored to skin type and geographic location.
* Dietary vitamin D and calcium intake optimization.
* Address risk factors such as malabsorption syndromes, chronic kidney disease, and certain medications.

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**RICKETS**

**DEFINITION AND DESCRIPTION**

Rickets is the softening and weakening of bones in children, often because of an extreme and prolonged vitamin D or calcium deficiency. Rare inherited problems also can cause rickets.

Vitamin D helps a child's body absorb calcium and phosphorus from food. Not enough vitamin D makes it hard to maintain proper calcium and phosphorus levels in bones, which can cause rickets.

Adding vitamin D or calcium to the diet generally corrects the bone problems associated with rickets. When rickets is due to another underlying medical problem, your child may need additional medicines or other treatment. Some skeletal deformities caused by rickets may require corrective surgery.

Rare inherited disorders related to low levels of phosphorus, the other mineral component in bone, may require other medicines.

**Causes**

Your child's body needs vitamin D to absorb calcium and phosphorus from food. Rickets can occur if your child's body doesn't get enough vitamin D or has problems using vitamin D properly. Occasionally, not getting enough calcium or lack of calcium and vitamin D can cause rickets.

**Lack of vitamin D**

Children who don't get enough vitamin D from these two sources can develop a deficiency:

* **Sunlight.** Your child's skin produces vitamin D when it's exposed to sunlight. But children in developed countries tend to spend less time outdoors. They also are more likely to use sunscreen, which blocks the sun's rays that trigger the skin's production of vitamin D.
* **Food.** Fish oil, egg yolks and fatty fish such as salmon and mackerel contain vitamin D. Vitamin D also has been added to some foods and beverages, such as milk, cereal and some fruit juices.

**Problems with absorption**

Some children are born with or develop medical problems that affect the way their bodies absorb vitamin D. Some examples include:

* Celiac disease.
* Inflammatory bowel disease.
* Cystic fibrosis.
* Kidney problems.

**Risk factors**

Factors that can increase a child's risk of rickets include:

* **Darker skin pigmentation.** Brown or Black skin has more of the pigment melanin, which lowers the skin's ability to produce vitamin D from sunlight.
* **Mother's vitamin D deficiency during pregnancy.** A baby born to a mother with serious vitamin D deficiency can be born with symptoms of rickets or develop them within a few months after birth.
* **Northern latitudes.** Children who live in geographical locations where there is less sunshine are at higher risk of rickets.
* **Premature birth.** Babies born before their due dates tend to have lower levels of vitamin D because they had less time to receive the vitamin from their mothers in the womb.
* **Medicines.** Certain types of anti-seizure medicines and antiretroviral medicines, used to treat HIV infections, appear to interfere with the body's ability to use vitamin D.
* **Exclusive breastfeeding.** Breast milk doesn't contain enough vitamin D to prevent rickets. Babies who are exclusively breastfed typically receive vitamin D drops.

**Complications**

If not treated, rickets can lead to:

* Failure to grow.
* Bone deformities.
* Dental defects.
* Seizures.

**Prevention**

Exposure to sunlight provides the best source of vitamin D. During most seasons, 10 to 15 minutes of exposure to the sun near midday is enough. But if you have brown or Black skin, if it's winter, or if you live in northern latitudes, you might not be able to get enough vitamin D from sun exposure.

In addition, because of skin cancer concerns, infants and young children, especially, are warned to avoid direct sun or to wear sunscreen and protective clothing.

To prevent rickets, make sure your child eats foods that contain vitamin D naturally — fatty fish such as salmon and tuna, fish oil, and egg yolks — or that have been fortified with vitamin D, such as:

* Infant formula.
* Cereal.
* Bread.
* Milk, but not foods made from milk, such as some yogurts and cheese.
* Orange juice.

Check labels to determine the vitamin D content of fortified foods.

If you're pregnant, ask your healthcare professional about taking vitamin D supplements.

Guidelines recommend that all infants should receive 400 international units (IU) a day of vitamin D. Because human milk contains only a small amount of vitamin D, infants who are exclusively breastfed should receive supplemental vitamin D daily. Some bottle-fed infants also may need vitamin D supplements if they aren't receiving enough from their formula.

**Symptoms**

Symptoms of rickets can include:

* Delayed growth.
* Delayed motor skills.
* Pain in the spine, pelvis and legs.
* Muscle weakness.

In infants, symptoms of rickets may be harder to identify because bone and muscle complaints are often not detected until a child starts to walk. Symptoms of rickets in infants caused by low blood calcium levels may include:

* Tight muscle tone.
* Breathing sounds that are not regular.

Because rickets softens the areas of growing tissue at the ends of a child's bones, known as growth plates, it can cause skeletal deformities such as:

* Bowed legs or knock-knees.
* Thickened wrists and ankles.
* Breastbone projection.

**Diagnosis**

During the exam, the healthcare professional typically will gently press on your child's bones, checking for irregularities. They may pay specific attention to the following:

* **Skull.** Babies who have rickets often have softer skull bones and might have a delay in the closure of the soft spots, called fontanels.
* **Legs.** While even healthy toddlers are a little bowlegged, an exaggerated bowing of the legs is common with rickets.
* **Chest.** Some children with rickets develop changes in their rib cages, which can flatten and cause their breastbones to protrude.
* **Wrists and ankles.** Children who have rickets often have larger or thicker wrists and ankles.

Diagnosing rickets in babies can be challenging. Rickets may be harder to identify as bone and muscle changes often are not detected until a child starts to walk. Your healthcare professional likely will pay attention to if your baby is growing well, has regular breathing sounds and has typical muscle tone.

For children of all ages, X-rays of the affected bones can reveal bone deformities. Blood and urine tests can confirm a diagnosis of rickets and also monitor the progress of treatment.

**Treatment**

Most cases of rickets can be treated with vitamin D and calcium supplements. Follow the directions as to dosage. Too much vitamin D can be harmful.

Your child's healthcare team may check your child's progress with X-rays and blood tests.

If your child has a rare inherited disorder that causes low amounts of phosphorus, supplements and medicines may be prescribed.

For some cases of bowleg or spinal deformities, your healthcare professional might suggest special bracing to position your child's body properly as the bones grow. More-serious skeletal deformities might require surgery.

**Differential diagnosis**

The differential for leg bowing in children includes:

* developmental or congenital bowing
* Blount disease
* osteogenesis imperfecta
* many others that are not usually a consideration (see leg bowing in children)

The differential for a widening of the growth plate includes:

* Schmid-type metaphyseal chondrodysplasia
* hypovitaminosis C (scurvy)
* delayed maturation due to illness
* endocrine disturbances
  + growth hormone excess
  + hyperparathyroidism
  + hypothyroidism

The differential for flaring of the metaphysis includes:

* anemias
* fibrous dysplasia
* storage diseases
* chronic lead poisoning
* bone dysplasias

**Epidemiology of Rickets**

* Global Prevalence:  
  Rickets remains a significant global health issue, particularly in infants and children. Prevalence rates vary widely by region, with 10% to 70% reported in African, Middle Eastern, and Asian countries. Nutritional rickets is the most common form worldwide
* Incidence:  
  Nutritional rickets has an estimated annual incidence of approximately 1.39 per 100,000 children under 5 years in some populations[6](https://www.dynamed.com/condition/rickets). However, incidence is likely underreported in low-resource settings.
* Geographic Distribution:  
  Despite abundant sunshine, the Middle East and Africa have some of the highest rates of rickets globally, largely due to cultural practices, nutritional deficiencies, and socioeconomic factors. Asia Pacific, particularly India and China, also report high burdens due to malnutrition and vitamin D deficiency.
* Risk Factors:
  + Vitamin D deficiency due to limited sun exposure, skin pigmentation, or dietary insufficiency
  + Calcium deficiency, especially in low-income regions
  + Malabsorption syndromes and chronic illnesses
  + Exclusive breastfeeding without supplementation
* Trends:  
  Although rickets incidence declined in many developed countries with vitamin D fortification programs, recent reports indicate a resurgence or persistence of nutritional rickets even in Western countries, linked to lifestyle changes and migration.
* Public Health Impact:  
  Rickets contribute to significant morbidity including bone deformities, growth retardation, and increased fracture risk. It remains a preventable cause of childhood morbidity and mortality worldwide.
* Market and Healthcare Access:  
  The global rickets treatment market was valued at approximately USD 1.15 billion in 2023, expected to grow due to increasing awareness, improved diagnostics, and expanding healthcare infrastructure, especially in Asia Pacific and developing regions

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**PAGET DISEASE OF BONE**

Paget's (PAJ-its) disease of bone interferes with your body's normal recycling process, in which new bone tissue gradually replaces old bone tissue. Over time, bones can become fragile and misshapen. The pelvis, skull, spine and legs are most commonly affected.

The risk of Paget's disease of bone increases with age and if family members have the disorder. However, for reasons unknown to doctors, the disease has become less common over the past several years and is less severe when it does develop. Complications can include broken bones, hearing loss and pinched nerves in your spine.

Bisphosphonates — the medications used to strengthen bones weakened by osteoporosis — are the mainstay of treatment. Surgery may be necessary if complications occur.

**Causes**

The cause of Paget's bone disease is unknown. Scientists suspect a combination of environmental and genetic factors contribute to the disease. Several genes appear to be linked to getting the disease.

Some scientists believe Paget's disease of bone is related to a viral infection in your bone cells, but this theory is controversial.

**Risk factors**

Factors that can increase your risk of Paget's disease of bone include:

* **Age.** People older than 50 are most likely to develop the disease.
* **Sex.** Men are more commonly affected than are women.
* **National origin.** Paget's disease of bone is more common in England, Scotland, central Europe and Greece — as well as countries settled by European immigrants. It's uncommon in Scandinavia and Asia.
* **Family history.** If you have a relative who has Paget's disease of bone, you're more likely to develop the condition.

**Complications**

In most cases, Paget's disease of bone progresses slowly. The disease can be managed effectively in nearly all people. Possible complications include:

* **Fractures and deformities.** Affected bones break more easily, and extra blood vessels in these deformed bones cause them to bleed more during repair surgeries. Leg bones can bow, which can affect your ability to walk.
* **Osteoarthritis.** Misshapen bones can increase the amount of stress on nearby joints, which can cause osteoarthritis.
* **Neurological problems.** When Paget's disease of bone occurs in an area where nerves pass through the bone, such as the spine and skull, the overgrowth of bone can compress and damage the nerve, causing pain, weakness or tingling in an arm or leg or hearing loss.
* **Heart failure.** In severe cases, your heart may have to work harder to pump blood to the affected areas of your body. Sometimes, this increased workload can lead to heart failure.
* **Bone cancer.** Bone cancer occurs in up to 1% of people with Paget's disease of bone.

**Symptoms**

Most people who have Paget's disease of bone have no symptoms. When symptoms occur, the most common complaint is bone pain.

Because this disease causes your body to generate new bone faster than normal, the rapid remodeling produces bone that's less organized and weaker than normal bone, which can lead to bone pain, deformities and fractures.

The disease might affect only one or two areas of your body or might be widespread. Your signs and symptoms, if any, will depend on the affected part of your body.

* **Pelvis.** Paget's disease of bone in the pelvis can cause hip pain.
* **Skull.** An overgrowth of bone in the skull can cause hearing loss or headaches.
* **Spine.** If your spine is affected, nerve roots can become compressed. This can cause pain, tingling and numbness in an arm or leg.
* **Leg.** As the bones weaken, they may bend — causing you to become bow legged. Enlarged and misshapen bones in your legs can put extra stress on nearby joints, which may cause osteoarthritis in your knee or hip.

**Diagnosis**

During the physical exam, your doctor will examine areas of your body that are causing you pain. He or she may also order X-rays and blood tests that can help confirm the diagnosis of Paget's disease of bone.

**Imaging tests**

Bone changes can be revealed by:

* **X-rays.** The first indication of Paget's disease of bone is often abnormalities found on X-rays done for other reasons. X-ray images of your bones can show areas of bone breakdown, enlargement of the bone and deformities that are characteristic of the disease, such as bowing of your long bones.
* **Bone scan.** In a bone scan, radioactive material is injected into your body. This material travels to the spots on your bones most affected, and they light up on the scan images.

**Lab tests**

People who have Paget's disease of bone usually have elevated levels of alkaline phosphatase in their blood, which can be revealed by a blood test.

**Treatment**

If you don't have symptoms, you might not need treatment. However, if the disease is active — indicated by an elevated alkaline phosphatase level — and is affecting high-risk sites in your body, such as your skull or spine, your doctor might recommend treatment to prevent complications, even if you don't have symptoms.

**Medications**

Osteoporosis drugs (bisphosphonates) are the most common treatment for Paget's disease of bone. Bisphosphonates are typically given by injection into a vein, but they can also be taken by mouth. When taken orally, bisphosphonates are generally well tolerated but can irritate the stomach.

Bisphosphonates that are given intravenously include:

* Zoledronic acid (Zometa, Reclast)
* Pamidronate (Aredia)
* Ibandronate (Boniva)

Oral bisphosphonates include:

* Alendronate (Fosamax, Binosto)
* Risedronate (Actonel, Atelvia)

Rarely, bisphosphonate therapy has been linked to severe muscle, joint or bone pain, which might not resolve when the medication is discontinued. Bisphosphonates can also increase the risk of a rare condition in which a section of jawbone dies and deteriorates, usually associated with active dental disease or oral surgery.

If you can't tolerate bisphosphonates, your doctor might prescribe calcitonin (Miacalcin), a naturally occurring hormone involved in calcium regulation and bone metabolism. Calcitonin is a drug that you administer to yourself by injection or nasal spray. Side effects may include nausea, facial flushing and irritation at the injection site.

**Surgery**

In rare cases, surgery might be required to:

* Help fractures heal
* Replace joints damaged by severe arthritis
* Realign deformed bones
* Reduce pressure on nerves

Paget's disease of bone often causes the body to produce too many blood vessels in the affected bones, increasing the risk of serious blood loss during an operation.

If you're scheduled for surgery that involves bones affected by Paget's disease of bone, your doctor might prescribe medications to reduce the activity of the disease, which may help reduce blood loss during surgery.

**Self-care**

To reduce your risk of complications associated with Paget's disease of bone, try these tips:

* **Prevent falls.** Paget's disease of bone puts you at high risk of bone fractures. Ask your doctor for advice on preventing falls. He or she may recommend that you use a cane or a walker.
* **Fall-proof your home.** Remove slippery floor coverings, use nonskid mats in your bathtub or shower, tuck away cords, and install handrails on stairways and grab bars in your bathroom.
* **Eat well.** Be sure your diet includes adequate levels of calcium and vitamin D, which helps bones absorb calcium. This is especially important if you're taking a bisphosphonate. Review your diet with your doctor and ask if you should take vitamin and calcium supplements.
* **Exercise regularly.** Regular exercise is essential for maintaining joint mobility and bone strength. Talk to your doctor before beginning an exercise program to determine the right type, duration and intensity of exercise for you. Some activities may place too much stress on your affected bones.

**When to see a doctor**

Talk to your doctor if you have:

* Pain in your bones and joints
* Tingling and weakness in an extremity
* Bone deformities
* Unexplained hearing loss, especially if it's only on one side

**Outlook / Prognosis**

The prognosis (outlook) for Paget’s disease of the bone is excellent if it's diagnosed and treated early in the course of the disease before complications such as arthritis, fractures and hearing loss have occurred.

**DIFFERENTIAL DIAGNOSIS**

The differential diagnosis of Paget disease includes the following:

* Osteomalacia
* Osteoporosis
* Malignancy of the bone, primary or metastatic
* Renal osteodystrophy
* Osteoarthritis
* Osteopenia
* Fibrous dysplasia

**EPIDEMIOLOGY**

Paget disease is usually seen in individuals older than 50 years of age. Around the world, it is reported that the prevalence of the disease has decreased during the past 2 decades, currently estimated between 1.5% to 8.3%.It is common in Caucasians of northern European descent. Paget disease is equally common in males and females. In the US, it is said to affect 1 to 3 million people, but most of the patients are asymptomatic. The disorder is slightly more common in white males. The disorder usually presents in the fourth to fifth decade of life, but the diagnosis is often made a decade later.

**Guidelines Summary**

Current endocrine guidelines for Paget disease:

* Obtain plain x-rays of the affected body part.
* Determine the extent of bone involvement with a radionuclide scan.
* Measure levels of serum ALP to evaluate bone formation/resorption and also assess response to treatment or follow untreated patients.
* Patients at risk for complications like fractures should be started on bisphosphonates, with alendronate 40 mg daily being the first choice in the oral category.
* Another straightforward treatment option is a single 5 mg dose of intravenous zoledronic acid if there are no contraindications.
* If a patient has normal ALP levels, monitor the disease with a specific marker for bone formation.
* One can follow patients with serial bone scans to assess the disease if bone markers are all normal.
* The use of bisphosphonates is effective in slowing down the progression of disease and/or the hearing loss.
* If patients with Paget disease need surgery, one should consider pretreatment with bisphosphonates

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**HYPOGONADISM**

Male hypogonadism is a condition in which the body doesn't produce enough of the hormone that plays a key role in masculine growth and development during puberty (testosterone) or enough sperm or both.

You can be born with male hypogonadism, or it can develop later in life, often from injury or infection. The effects — and what you can do about them — depend on the cause and at what point in your life male hypogonadism occurs. Some types of male hypogonadism can be treated with testosterone replacement therapy.

**Causes**

Male hypogonadism means the testicles don't produce enough of the male sex hormone testosterone. There are two basic types of hypogonadism:

* **Primary.** This type of hypogonadism — also known as primary testicular failure — originates from a problem in the testicles.
* **Secondary.** This type of hypogonadism indicates a problem in the hypothalamus or the pituitary gland — parts of the brain that signal the testicles to produce testosterone. The hypothalamus produces gonadotropin-releasing hormone, which signals the pituitary gland to make follicle-stimulating hormone (follicle-stimulating hormone (FSH)) and luteinizing hormone (luteinizing hormone (LH)). Luteinizing hormone then signals the testes to produce testosterone.

Either type of hypogonadism can be caused by an inherited (congenital) trait or something that happens later in life (acquired), such as an injury or an infection. At times, primary and secondary hypogonadism occur together.

**Primary hypogonadism**

Common causes of primary hypogonadism include:

* **Klinefelter syndrome.** This condition results from a congenital abnormality of the sex chromosomes, X and Y. A male normally has one X and one Y chromosome. In Klinefelter syndrome, two or more X chromosomes are present in addition to one Y chromosome.

The Y chromosome contains the genetic material that determines the sex of a child and related development. The extra X chromosome that occurs in Klinefelter syndrome causes abnormal development of the testicles, which in turn results in underproduction of testosterone.

* **Undescended testicles.** Before birth, the testicles develop inside the abdomen and normally move down into their permanent place in the scrotum. Sometimes one or both of the testicles aren't descended at birth.

This condition often corrects itself within the first few years of life without treatment. If not corrected in early childhood, it can lead to malfunction of the testicles and reduced production of testosterone.

* **Mumps orchitis.** A mumps infection involving the testicles that occurs during adolescence or adulthood can damage the testicles, affecting the function of the testicles and testosterone production.
* **Hemochromatosis.** Too much iron in the blood can cause testicular failure or pituitary gland dysfunction, affecting testosterone production.
* **Injury to the testicles.** Because they're outside the abdomen, the testicles are prone to injury. Damage to both testicles can cause hypogonadism. Damage to one testicle might not impair total testosterone production.
* **Cancer treatment.** Chemotherapy or radiation therapy for the treatment of cancer can interfere with testosterone and sperm production. The effects of both treatments often are temporary, but permanent infertility may occur.

Although many men regain their fertility within a few months after treatment, preserving sperm before starting cancer therapy is an option for men.

**Secondary hypogonadism**

In secondary hypogonadism, the testicles are normal but don't function properly due to a problem with the pituitary or hypothalamus. A number of conditions can cause secondary hypogonadism, including:

* **Kallmann's syndrome.** This is an abnormal development of the area of the brain that controls the secretion of pituitary hormones (hypothalamus). This abnormality can also affect the ability to smell (anosmia) and cause red-green color blindness.
* **Pituitary disorders.** An abnormality in the pituitary gland can impair the release of hormones from the pituitary gland to the testicles, affecting normal testosterone production. A pituitary tumor or other type of brain tumor located near the pituitary gland may cause testosterone or other hormone deficiencies.

Also, treatment for a brain tumor, such as surgery or radiation therapy, can affect the pituitary gland and cause hypogonadism.

* **Inflammatory disease.** Certain inflammatory diseases, such as sarcoidosis, histiocytosis and tuberculosis, involve the hypothalamus and pituitary gland and can affect testosterone production.
* **HIV/AIDS.** HIV/AIDS can cause low levels of testosterone by affecting the hypothalamus, the pituitary and the testes.
* **Medications.** The use of certain drugs, such as opiate pain medications and some hormones, can affect testosterone production.
* **Obesity.** Being significantly overweight at any age might be linked to hypogonadism.
* **Aging.** As men age, there's a slow, progressive decrease in testosterone production. The rate varies greatly.

**Risk factors**

Risk factors for hypogonadism include:

* Human immunodeficiency virus (HIV) / acquired immunodeficiency syndrome (AIDS)
* Previous chemotherapy or radiation therapy
* Aging
* Obesity
* Malnutrition

Hypogonadism can be inherited. If any of these risk factors are in your family health history, tell your doctor.

**Complications**

The complications of untreated hypogonadism differ depending on when it develops — during fetal development, puberty or adulthood.

Complications might include:

* Abnormal genitalia
* Enlarged male breasts (gynecomastia)
* Infertility
* Erectile dysfunction
* Osteoporosis
* Poor self-image

**Symptoms**

Hypogonadism can begin during fetal development, before puberty or during adulthood. Signs and symptoms depend on when the condition develops.

**Fetal development**

If the body doesn't produce enough testosterone during fetal development, the result may be impaired growth of the external sex organs. Depending on when hypogonadism develops and how much testosterone is present, a child who is genetically male may be born with:

* Female genitals
* Genitals that are neither clearly male nor clearly female (ambiguous genitals)
* Underdeveloped male genitals

**Puberty**

Male hypogonadism can delay puberty or cause incomplete or lack of normal development. It can hamper:

* Development of muscle mass
* Voice deepening
* Growth of body and facial hair
* Growth of the penis and testicles

And it can cause:

* Excessive growth of the arms and legs in relation to the trunk of the body
* Development of breast tissue (gynecomastia)

**Adulthood**

In adult males, hypogonadism can alter certain masculine physical characteristics and impair normal reproductive function. Early signs and symptoms might include:

* Decreased sex drive
* Decreased energy
* Depression

Over time, men with hypogonadism can develop:

* Erectile dysfunction
* Infertility
* Decrease in hair growth on the face and body
* Decrease in muscle mass
* Development of breast tissue (gynecomastia)
* Loss of bone mass (osteoporosis)

Severe hypogonadism can also cause mental and emotional changes. As testosterone decreases, some men have symptoms similar to those of menopause in women. These can include:

* Difficulty concentrating
* Hot flashes

**When to seek help**

See your healthcare provider if you have symptoms of male hypogonadism. Finding the cause of hypogonadism is an important first step to getting appropriate treatment.

**Diagnosis**

Early detection in boys can help prevent problems from delayed puberty. Early diagnosis and treatment in men offer better protection against osteoporosis and other related conditions.

Your health care provider will conduct a physical exam and note whether your sexual development, such as your pubic hair, muscle mass and size of your testes, is consistent with your age.

Your provider will test your blood level of testosterone if you have signs or symptoms of hypogonadism. Because testosterone levels vary and are generally highest in the morning, blood testing is usually done early in the day, before 10 a.m., possibly on more than one day.

If tests confirm that you have low testosterone, further testing can determine if a testicular disorder or a pituitary abnormality is the cause. These studies might include:

* Hormone testing
* Semen analysis
* Pituitary imaging
* Genetic studies
* Testicular biopsy

**Treatment**

**Adults**

Testosterone replacement can raise testosterone levels and help ease the symptoms of male hypogonadism. These include less desire for sex, less energy, less facial and body hair, and loss of muscle mass and bone mass.

For older adults who have low testosterone and symptoms of hypogonadism due to aging, it's less clear how well testosterone replacement works.

Anyone taking testosterone replacement should have a medical checkup and blood tests several times during the first year of treatment and yearly after that. This is to see how well the treatment works and to watch for side effects.

**Types of testosterone replacement therapy**

Testosterone taken by mouth, also called oral, isn't often used for treatment of hypogonadism. Oral testosterone can cause serious liver problems. And it doesn't keep testosterone levels even.

The U.S. Food and Drug Administration has approved one oral testosterone replacement, testosterone undecanoate (Jatenzo, Tlando, Kyzatrex). The lymph system absorbs it, so it might not cause the liver problems seen with other oral forms of testosterone. It's not used to treat hypogonadism caused by aging.

Other forms you might choose can depend on how easy they are to get and use, how much they cost, and whether insurance covers them. They include:

* **Gels.** There are several available with different ways of applying them. Depending on the brand, you rub the testosterone into your skin on your upper arm or shoulder (AndroGel, Testim, Vogelxo) or apply it to the front and inner thigh (Fortesta).

The body soaks in testosterone through the skin. Don't shower or bathe for several hours after using a gel to give it time to soak in.

Side effects include skin irritation and, if someone touches you, having the medicine get on someone else. Don't let your skin touch anyone until the gel is fully dry. Or cover the area after putting on the gel.

* **Shot.** Testosterone cypionate (Depo-Testosterone) and testosterone enanthate (Xyosted) are given in a muscle or under the skin. Symptoms might vary between doses depending on how often you get the shots.

You or a family member can learn to give testosterone shots at home. If you're not OK with giving yourself shots, a member of your care team can do it for you.

The shot form of testosterone undecanoate (Aveed) goes deep into a muscle, typically every 10 weeks. A member of your medical team must give it. It can have serious side effects.

* **Patch.** A patch containing testosterone is put on an arm or the torso each night. Possible side effects are mild or severe skin problems.
* **Gum and cheek, also called buccal cavity.** Small and puttylike, gum-and-cheek testosterone replacement sends testosterone through the area above the top teeth where the gum meets the upper lip, called the buccal cavity.

This product, taken three times a day, sticks to the gumline and sends testosterone into the bloodstream. It can irritate the gum.

* **Nasal.** This testosterone gel (Natesto) can be pumped into the nostrils. This option reduces the risk that medicine will get on someone else through skin contact. This type of testosterone is put into each nostril three times a day. This might make it less easy to use than other methods.
* **Pellets put under the skin, called Implants.** Testosterone-containing pellets (Testopel) are surgically put under the skin every 3 to 6 months.

Testosterone therapy carries risks, including:

* Making too many red blood cells.
* Acne.
* Bigger breasts.
* Sleep problems.
* Growth of the prostate.
* Not making as much sperm.

Risks from testosterone therapy are most often due to doses that are too high. Many of these side effects go away when the dose is lowered. That's why it's so important to have regular follow-up visits with a health care professional, who will monitor the testosterone levels in your blood.

**Treatment of infertility due to hypogonadism**

If a pituitary problem is the cause, pituitary hormones can be given to help the body make more sperm and restore fertility. A pituitary tumor may need treatment with surgery, medicine, radiation or replacement of other hormones.

There's often no way to help men with primary hypogonadism make sperm. But there are ways to help couples who haven't been able to have children. Assisted reproductive technology offers ways to help.

**Treatment for boys**

Treatment of delayed puberty in boys depends on the cause. Three to six months of testosterone shots can help start puberty. The testosterone can help increase muscle mass, beard and pubic hair growth, and growth of the penis. This treatment is given only if the bones have matured enough.

**Outlook / Prognosis**

There’s no one-time fix for low testosterone. However, consistent hormone replacement therapy helps improve sex drive, ease symptoms of depression and increase energy levels for those experiencing low testosterone. Treatment may also boost muscle mass and bone density.

The mortality of men with testosterone deficiency is significantly higher than among men with normal testosterone levels. But, it is unclear whether replacing testosterone to a normal level reduces that increased mortality. Treatment is largely focused on the treatment of symptoms, not the specific testosterone level.

For congenital hypogonadism, testosterone replacement therapy often helps prevent problems related to delayed puberty.

**Prevention**

Healthcare providers and medical researchers don’t know how to prevent low testosterone from genetic conditions or damage to your testicles, hypothalamus or pituitary gland.

Lifestyle habits that may help keep testosterone levels normal include:

* Eating a healthy diet.
* Exercise.
* Weight management.
* Avoiding excessive use of alcohol and drugs.

**Epidemiology of Hypogonadism**

* Prevalence:  
  Hypogonadism affects approximately 2.1% to 12.8% of adult men in the general population, with prevalence increasing with age. By 2025, it is estimated that about 6.5 million men in the United States will have hypogonadism
* Age-related Increase:  
  The prevalence rises significantly in older men. For example, the Baltimore Longitudinal Study reports low testosterone in about 10% of men in their 50s, 20% in their 60s, and 30% in their 70s
* Types and Genetic Causes:
  + Klinefelter syndrome (hypergonadotropic hypogonadism): Occurs in about 1 in 500 to 1,000 male live births
  + Other causes include Kallmann syndrome and pituitary disorders.
* Market and Awareness Trends:  
  The global male hypogonadism market was valued at approximately USD 4 billion in 2024, expected to grow to USD 6.7 billion by 2034 at a CAGR of around 5.2–6.3%, driven by aging populations, increased diagnosis, and awareness  
  Growth is also fueled by lifestyle factors, chronic illnesses, and expanded healthcare accessibility including telemedicine
* Geographic Distribution:  
  North America is the largest market, with the U.S. accounting for the majority of cases and revenue. Asia-Pacific is the fastest-growing region due to increasing healthcare infrastructure and awareness
* Associated Morbidity:  
  Hypogonadism contributes to sexual dysfunction, infertility, psychological symptoms, and metabolic disturbances, increasing the demand for diagnosis and treatment.

**Differential Diagnosis of Hypogonadism**

1. Primary Hypogonadism (Hypergonadotropic Hypogonadism)

* Klinefelter syndrome (most common genetic cause)
* Cryptorchidism (undescended testes)
* Testicular injury or trauma
* Testicular infection (e.g., mumps orchitis)
* Chemotherapy or radiation therapy affecting testes
* Testicular tumors or gonadectomy
* Enzymatic defects in testosterone synthesis (e.g., 17β-hydroxysteroid dehydrogenase deficiency)
* Sertoli-cell-only syndrome
* Gonadal dysgenesis (e.g., Turner syndrome in females)
* LH receptor resistance

2. Secondary Hypogonadism (Hypogonadotropic Hypogonadism)

* Kallmann syndrome (idiopathic hypogonadotropic hypogonadism with anosmia)
* Pituitary or hypothalamic tumors
* Hypopituitarism due to infarction, infiltration, trauma, or surgery
* Infections (e.g., HIV, tuberculosis, sarcoidosis)
* Genetic disorders (e.g., Prader-Willi syndrome, Laurence-Moon syndrome)
* Medications (opioids, steroids, estrogens, psychoactive drugs)
* Obesity, metabolic syndrome, type 2 diabetes
* Hemochromatosis (iron overload affecting pituitary)
* Acute systemic illness or chronic diseases (liver failure, uremia)

3. Mixed Hypogonadism

* Aging-related decline in testosterone
* Systemic diseases (HIV, sickle cell disease)
* Medications causing combined primary and secondary effects

4. Other Conditions to Differentiate From Hypogonadism

* Constitutional delay of puberty (most common cause of delayed puberty, not true hypogonadism)
* Eugonadotropic hypogonadism causes (normal gonadotropins but low testosterone), e.g.:
  + Hyperprolactinemia
  + Polycystic ovary syndrome (PCOS) in females
  + Delayed menarche in females
* Testicular torsion or orchitis (acute causes of testicular dysfunction)
* Female-specific conditions causing hypogonadism-like symptoms:
  + Pelvic inflammatory disease
  + Endometriosis

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**KLINEFELTER SYNDROME**

Klinefelter syndrome is a common condition that results when a person assigned male at birth has an extra copy of the X sex chromosome instead of the typical XY. Klinefelter syndrome is a genetic condition that occurs before birth, but it often isn't diagnosed until adulthood.

Klinefelter syndrome may affect testicular growth. This results in smaller testicles, which can lead to making less of the hormone testosterone. The syndrome also may cause smaller muscle mass, less body and facial hair, and extra breast tissue. The effects of Klinefelter syndrome vary, and not everyone has the same symptoms.

Most people with Klinefelter syndrome produce little or no sperm but assisted reproductive procedures may make it possible for some people with Klinefelter syndrome to have biological children.

**Symptoms**

Symptoms of Klinefelter syndrome vary widely. Many children with Klinefelter syndrome show few or only mild symptoms. Most often the condition isn't diagnosed until puberty or adulthood, or it may never be diagnosed. For others, the condition has a noticeable effect on growth or appearance. Klinefelter syndrome may affect development, physical appearance, sexual development and mental health.

**Development**

* Slow motor development, such as taking longer than average to sit up, crawl and walk.
* Speaking later than other babies of the same age.
* Learning and language problems, such as trouble with reading, writing, spelling or math.

**Physical appearance**

* Taller than average height.
* Longer legs, shorter body, narrower shoulders, broader hips and extra belly fat compared with other children and adults assigned male at birth.
* After puberty, less muscle mass and less facial and body hair compared with other teens and adults assigned male at birth.
* Extra breast tissue, called gynecomastia.
* Low energy levels.

**Sexual development**

* Small, firm testicles and a small penis. Babies may be born with testicles that haven't moved from the belly into the scrotum, a condition called undescended testicles.
* Puberty changes that are delayed, that only include some changes or that don't happen at all.
* Low sperm count or no sperm.
* Low sex drive.

**Mental health**

* Difficulty expressing thoughts and feelings.
* Having a hard time engaging in social activities.

**When to see a doctor**

Talk to your healthcare professional if you notice:

* **Slow development during infancy or childhood.** Delays in growth and development can be the first sign of several conditions that need treatment, including Klinefelter syndrome. Though some differences in physical and mental development are expected among children, check with a healthcare professional if you have any concerns.
* **Problems with fertility.** Problems with fertility aren't often diagnosed in people with Klinefelter syndrome until they realize they're not able to have a biological child.

**Causes**

Klinefelter syndrome occurs because of a random change in the egg or the sperm that causes a baby assigned male at birth to be born with an extra X sex chromosome. The condition is not passed down in families.

Klinefelter syndrome can be caused by:

* One extra copy of the X sex chromosome in each cell (XXY), the most common cause.
* An extra X sex chromosome in some of the cells. This is called mosaic Klinefelter syndrome and may result in fewer symptoms.
* More than one extra copy of the X sex chromosome, which is rare and results in a severe form of the syndrome.

In people assigned male at birth, extra copies of genes on the X sex chromosome can interfere with sexual development and fertility.

**Risk factors**

Klinefelter syndrome occurs because of a random genetic change in the sperm or the egg. The risk of Klinefelter syndrome is not raised by anything parents do or don't do. For people carrying a pregnancy after age 35, the risk is higher but only slightly.

**Complications**

Klinefelter syndrome may raise the risk of:

* Anxiety and depression.
* Social, emotional and behavioral problems, such as low self-esteem.
* Problem with fertility and sexual function.
* Thin and brittle bones, a condition called osteoporosis.
* Heart and blood vessel disease.
* Breast cancer and some other cancers.
* Lung disease.
* Metabolic syndrome, which includes type 2 diabetes, high blood pressure, and high cholesterol and triglycerides.
* Being overweight.
* Autoimmune disorders such as lupus and rheumatoid arthritis.
* Tooth and mouth problems that make dental cavities more likely.
* Autism spectrum disorder.

Some complications caused by Klinefelter syndrome are the result of low testosterone, also called hypogonadism. Hormone therapy lessens the risk of certain health problems, especially when therapy is started at the beginning of puberty.

**Diagnosis**

To diagnose Klinefelter syndrome, a healthcare professional does a physical exam and asks questions about symptoms and health. This may include looking at the genital area and chest and talking about development and functioning.

Main tests used to diagnose Klinefelter syndrome are:

* **Hormone testing.** Blood tests can show hormone level changes that are a sign of Klinefelter syndrome.
* **Chromosome analysis.** Also called a karyotype, this test can confirm a diagnosis of Klinefelter syndrome. A blood sample is sent to the lab to check the shape and number of chromosomes.

Healthcare professionals sometimes diagnose Klinefelter syndrome before birth when testing is done for another reason. The syndrome can be found in pregnancy during a procedure to look at fetal cells taken from the fluid around the baby or from the placenta. These tests may be done for pregnant people who are older than age 35 or have a family history of genetic conditions.

Klinefelter syndrome may be suspected during a noninvasive prenatal screening blood test. This test looks at cell-free DNA in the pregnant person's blood sample. To confirm the diagnosis, more-invasive prenatal testing is needed.

**Treatment**

If you or your child is diagnosed with Klinefelter syndrome, your healthcare team may include a doctor called an endocrinologist who specializes in conditions involving the body's glands and hormones. Your team also may include a speech therapist, a pediatrician, a physical therapist, a genetic counselor, a reproductive medicine or infertility specialist, and a counselor or psychologist.

Although there's no way to repair the sex chromosome changes due to Klinefelter syndrome, treatments can help lessen its effects. The earlier the condition is diagnosed and treatment is started, the greater the benefits. But it's never too late to get help.

Treatment for Klinefelter syndrome is based on symptoms and may include:

* **Testosterone therapy.** Starting at the time of the usual onset of puberty, testosterone therapy can be given to help stimulate changes that typically occur at puberty. These changes include a deeper voice, facial and body hair, bigger muscle mass, and sexual desire. Testosterone therapy also can help bone density. It may help mood, focus and attention too. Testosterone therapy does not help with fertility problems.
* **Breast tissue removal.** If extra breast tissues develops, the tissue can be removed by a plastic surgeon, if desired.
* **Therapy.** Speech and language therapy can help if there are speech or language problems. Physical therapy can help with motor skills and muscle strength. Occupational therapy can help with social skills and job skills.
* **Educational evaluation and support.** If learning and socializing are a problem, extra services may help. Talk to your child's teacher, school counselor or school nurse about what kind of support is available.
* **Fertility treatment.** Most people with Klinefelter syndrome cannot have biological children because few or no sperm are made in the testicles. For some people who make a small amount of sperm, a procedure called intracytoplasmic sperm injection (ICSI) may help. During ICSI, sperm is taken from the testicle with a biopsy needle and injected directly into the egg.
* **Mental health support.** Having Klinefelter syndrome can be a challenge, especially during puberty and young adulthood. Coping with infertility also can be a challenge. A family therapist, counselor or psychologist can help work through emotional concerns.

**Outlook / Prognosis**

If you or your child has Klinefelter syndrome, it’s important to meet with a genetic counselor as soon as you receive a diagnosis. An endocrinologist can also discuss the timing of initiating testosterone replacement. Because symptoms vary so much from person to person, your treatment might not be the same as another person with the condition. But with help from your healthcare provider, you can come up with a plan that works for you.

**How long can a person live with Klinefelter syndrome?**

People who have Klinefelter syndrome have a normal life expectancy. Treatment can help people with this condition live full, happy, healthy lives.

**Prevention**

You can’t prevent Klinefelter syndrome because it’s a random change in your genetic code — and it happens before birth. You can’t pass this condition down to your child. And there’s nothing a parent can do to keep their child from developing Klinefelter syndrome.

**DIFFERENTIAL DIAGNOSIS**

The differential diagnosis for Klinefelter syndrome includes a range of conditions with overlapping clinical features. These clinical entities include both genetic syndromes and endocrinological disorders that can mimic or coexist with the phenotype of Klinefelter syndrome.

* Acromegaly
* Adrenogenital and gonadal-secreting tumors
* Azoospermia
* Beckwith-Wiedemann syndrome
* Constitutional gigantism
* Diabetes mellitus
* Fragile X syndrome
* Hyperprolactinemia
* Hypogonadism
* Male infertility
* Marfan syndrome
* Mosaicism
* Neurofibromatosis
* Primary testicular failure
* Sanfilippo syndrome
* Simpson-Rosan-Golabi syndrome

Accurate diagnosis requires careful consideration of these differential conditions through a comprehensive clinical evaluation, genetic testing, and appropriate screening. Early identification ensures effective management and intervention, improving outcomes for individuals affected by these syndromes.

**EPIDEMIOLOGY**

Klinefelter syndrome is the most common form of aneuploidy, characterized by an abnormal number of chromosomes in the affected individual's cells. The estimated prevalence is between 1 in 500 and 1 in 1000 males.Diagnosis often occurs in adulthood, as many cases remain unidentified until later in life. Recognition often begins during evaluation for specific clinical features across different life stages, such as in the following:

* Prenatal testing or observation of genital abnormalities in a newborn with hypotonia
* Documentation of learning or behavioral difficulties in an adolescent
* Evaluation for tall stature, small testicular size, or incomplete puberty in an adolescent
* Evaluation for infertility (3% of men evaluated for infertility have Klinefelter syndrome) or hypogonadism in a male adult

Up to two-thirds of individuals with Klinefelter syndrome remain undiagnosed.Comparative studies suggest that Klinefelter syndrome may occur more frequently with advancing parental age, environmentally derived errors in meiosis I, or a decrease in elective terminations for prenatally diagnosed cases. Underdiagnosis is likely due to the variable phenotype, with many cases presenting with only subtle features.

An estimated quarter of individuals with Klinefelter syndrome show no discernible diagnostic features based on history or examination. With the increased use of noninvasive prenatal testing, the frequency of prenatal diagnosis is expected to rise, enabling early management by pediatricians.

Fewer than 10% of cases are detected before puberty, and only 26% to 37% are identified overall, with most remaining undiagnosed. The average age of diagnosis is 30 years, and the median lifespan is reduced by 5 or 6 years compared to the general male population.

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**TURNER SYNDROME**

Turner syndrome, a condition that affects only females, results when one of the X chromosomes (sex chromosomes) is missing or partially missing. Turner syndrome can cause a variety of medical and developmental problems, including short height, failure of the ovaries to develop and heart defects.

Turner syndrome may be diagnosed before birth (prenatally), during infancy or in early childhood. Occasionally, in females with mild signs and symptoms of Turner syndrome, the diagnosis is delayed until the teen or young adult years.

Girls and women with Turner syndrome need ongoing medical care from a variety of specialists. Regular checkups and appropriate care can help most girls and women lead healthy, independent lives.

**Symptoms**

Signs and symptoms of Turner syndrome may vary among girls and women with the disorder. For some girls, the presence of Turner syndrome may not be readily apparent, but in other girls, several physical features are apparent early. Signs and symptoms can be subtle, developing slowly over time, or significant, such as heart defects.

**Before birth**

Turner syndrome may be suspected prenatally based on prenatal cell-free DNA screening — a method to screen for certain chromosomal abnormalities in a developing baby using a blood sample from the mother — or prenatal ultrasound. Prenatal ultrasound of a baby with Turner syndrome may show:

* Large fluid collection on the back of the neck or other abnormal fluid collections (edema)
* Heart abnormalities
* Abnormal kidneys

**At birth or during infancy**

Signs of Turner syndrome at birth or during infancy may include:

* Wide or weblike neck
* Low-set ears
* Broad chest with widely spaced nipples
* High, narrow roof of the mouth (palate)
* Arms that turn outward at the elbows
* Fingernails and toenails that are narrow and turned upward
* Swelling of the hands and feet, especially at birth
* Slightly smaller than average height at birth
* Slowed growth
* Cardiac defects
* Low hairline at the back of the head
* Receding or small lower jaw
* Short fingers and toes

**In childhood, teens and adulthood**

The most common signs in almost all girls, teenagers and young women with Turner syndrome are short stature and ovarian insufficiency due to ovarian failure. Failure of the ovaries to develop may occur at birth or gradually during childhood, the teen years or young adulthood. Signs and symptoms of these include:

* Slowed growth
* No growth spurts at expected times in childhood
* Adult height significantly less than might be expected for a female member of the family
* Failure to begin sexual changes expected during puberty
* Sexual development that "stalls" during teenage years
* Early end to menstrual cycles not due to pregnancy
* For most females with Turner syndrome, inability to conceive a child without fertility treatment

**When to see a doctor**

Sometimes it's difficult to distinguish the signs and symptoms of Turner syndrome from other disorders. It's important to get a prompt, accurate diagnosis and appropriate care. See your doctor if there are concerns about the possibility of Turner syndrome. Your doctor may refer you to a physician who specializes in genetics (geneticist) or in hormone disorders (endocrinologist) for further evaluation.

**Causes**

Most people are born with two sex chromosomes. Males inherit the X chromosome from their mothers and the Y chromosome from their fathers. Females inherit one X chromosome from each parent. In females who have Turner syndrome, one copy of the X chromosome is missing, partially missing or changed.

The genetic changes of Turner syndrome may be one of the following:

* **Monosomy.** The complete absence of an X chromosome generally occurs because of an error in the father's sperm or in the mother's egg. This results in every cell in the body having only one X chromosome.
* **Mosaicism.** In some cases, an error occurs in cell division during early stages of fetal development. This results in some cells in the body having two complete copies of the X chromosome. Other cells have only one copy of the X chromosome.
* **X chromosome changes.** Changed or missing parts of one of the X chromosomes can occur. Cells have one complete and one altered copy. This error can occur in the sperm or egg with all cells having one complete and one altered copy. Or the error can occur in cell division in early fetal development so that only some cells contain the changed or missing parts of one of the X chromosomes (mosaicism).
* **Y chromosome material.** In a small percentage of Turner syndrome cases, some cells have one copy of the X chromosome and other cells have one copy of the X chromosome and some Y chromosome material. These individuals develop biologically as female, but the presence of Y chromosome material increases the risk of developing a type of cancer called gonadoblastoma.

**Effects of the missing or changed chromosome**

The missing or changed X chromosome of Turner syndrome causes problems during fetal development and other developmental problems after birth — for example, short stature, ovarian insufficiency and heart defects. Physical characteristics and health complications that arise from these chromosomal issues vary greatly.

**Risk factors**

The loss or alteration of the X chromosome occurs randomly. Sometimes, it's because of a problem with the sperm or the egg, and other times, the loss or alteration of the X chromosome happens early in fetal development.

Family history doesn't seem to be a risk factor, so it's unlikely that parents of one child with Turner syndrome will have another child with the disorder.

**Complications**

Turner syndrome can affect the proper development of several body systems, but this varies greatly among individuals with the syndrome. Complications that can occur include:

* **Heart problems.** Many infants with Turner syndrome are born with heart defects or even slight abnormalities in heart structure that increase their risk of serious complications. Heart defects often include problems with the aorta, the large blood vessel that branches off the heart and delivers oxygen-rich blood to the body.
* **High blood pressure.** Turner syndrome can increase the risk of high blood pressure — a condition that increases the risk of developing diseases of the heart and blood vessels.
* **Hearing loss.** Hearing loss is common with Turner syndrome. In some cases, this is due to the gradual loss of nerve function. An increased risk of frequent middle ear infections can also result in hearing loss.
* **Vision problems.** An increased risk of weak muscle control of eye movements (strabismus), nearsightedness and other vision problems can occur with Turner syndrome.
* **Kidney problems.** Turner syndrome may be associated with malformations of the kidneys. Although these abnormalities generally don't cause medical problems, they may increase the risk of urinary tract infections.
* **Autoimmune disorders.** Turner syndrome can increase the risk of an underactive thyroid (hypothyroidism) due to the autoimmune disorder Hashimoto's thyroiditis. There is also an increased risk of diabetes. Sometimes Turner syndrome is associated with gluten intolerance (celiac disease) or inflammatory bowel disease.
* **Skeletal problems.** Problems with the growth and development of bones increase the risk of abnormal curvature of the spine (scoliosis) and forward rounding of the upper back (kyphosis). Turner syndrome can also increase the risk of developing weak, brittle bones (osteoporosis).
* **Learning disabilities.** Girls and women with Turner syndrome usually have normal intelligence. However, there is increased risk of learning disabilities, particularly with learning that involves spatial concepts, math, memory and attention.
* **Mental health issues.** Girls and women with Turner syndrome may have challenges functioning in social situations, may experience anxiety and depression, and may have an increased risk of attention-deficit/hyperactivity disorder (ADHD).
* **Infertility.** Most females with Turner syndrome are infertile. However, a very small number may become pregnant spontaneously, and some can become pregnant with fertility treatment.
* **Pregnancy complications.** Because women with Turner syndrome are at increased risk of complications during pregnancy, such as high blood pressure and aortic dissection, they should be evaluated by a heart specialist (cardiologist) and a high-risk pregnancy doctor (maternal-fetal medicine specialist) before pregnancy.

**Diagnosis**

If, based on signs and symptoms, the doctor suspects that your child has Turner syndrome, a lab test will be done to analyze your child's chromosomes. The test involves a blood sample. Occasionally, your doctor may also request a cheek scraping (buccal smear) or skin sample. The chromosome analysis determines whether or not there is a missing X chromosome or a change in one of the X chromosomes.

**Prenatal diagnosis**

A diagnosis is sometimes made during fetal development. Certain features on an ultrasound image may raise suspicion that your baby has Turner syndrome or another genetic condition affecting development in the womb.

Prenatal screening tests that evaluate the baby's DNA in the mother's blood (prenatal cell-free fetal DNA screening or noninvasive prenatal screening) may also indicate an increased risk of Turner syndrome. However, doing a karyotype during pregnancy or after delivery is recommended to confirm the diagnosis.

If Turner syndrome is suspected before birth (prenatally), your pregnancy and childbirth specialist (obstetrician) may ask if you're interested in additional tests to make a diagnosis before your baby is born. One of two procedures can be performed to test prenatally for Turner syndrome:

* **Chorionic villus sampling.** This involves taking a small piece of tissue from the developing placenta. The placenta contains the same genetic material as the baby. The chorionic villus cells can be sent to the genetics lab for chromosome studies. This is usually done between 11 and 14 weeks of pregnancy.
* **Amniocentesis.** In this test, a sample of the amniotic fluid is taken from the uterus. The baby sheds cells into the amniotic fluid. The fluid can be sent to the genetics lab for study of the baby's chromosomes in these cells. This is typically done after 14 weeks of pregnancy.

Discuss the benefits and risks of prenatal testing with your doctor.

**Treatment**

Because symptoms and complications vary, treatments are tailored to address the individual's specific problems. Evaluation and monitoring for medical or mental health issues associated with Turner syndrome throughout life can help to address problems early.

The primary treatments for nearly all girls and women with Turner syndrome include hormone therapies:

* **Growth hormone.** Growth hormone therapy — usually given daily as an injection of recombinant human growth hormone — is typically recommended to increase height as much as possible at appropriate times during early childhood until the early teen years. Starting treatment early can improve height and bone growth.
* **Estrogen therapy.** Most girls with Turner syndrome need to start estrogen and related hormone therapy in order to begin puberty. Often, estrogen therapy is started around age 11 or 12 years. Estrogen helps to promote breast development and improve the size (volume) of the uterus. Estrogen helps with bone mineralization, and when used with growth hormone, may also help with height. Estrogen replacement therapy usually continues throughout life, until the average age of menopause is reached.

Other treatments are tailored to address particular problems as needed. Regular checkups have shown substantial improvements in the health and quality of life for girls and women with Turner syndrome.

It's important to help your child prepare for the transition from care with your pediatrician to adult medical and mental health care. A primary care doctor can help to continue coordination of care among a number of specialists throughout life.

**Health care team**

Because Turner syndrome can result in developmental concerns and medical complications, several specialists may be involved in screening for specific conditions, making diagnoses, recommending treatments and providing care.

Teams may evolve as needs change throughout life. Care team specialists may include some or all of these professionals, and others as needed:

* Hormone disorder specialist (endocrinologist)
* Specialist in women's health (gynecologist)
* Physician who specializes in genetics (medical geneticist)
* Heart specialist (cardiologist)
* Specialist in skeletal disorders (orthopedist)
* Specialist in urinary tract disorders (urologist)
* Ear, nose and throat (ENT) specialist
* Specialist in gastrointestinal disorders (gastroenterologist)
* Specialist in vision problems and other eye disorders (ophthalmologist)
* Specialist in hearing problems (audiologist)
* Mental health professional, such as a psychologist or psychiatrist
* Developmental therapist, who specializes in therapy to help your child develop age-appropriate behaviors, social skills and interpersonal skills
* Special education instructors
* Fertility specialist (reproductive endocrinologist)

**Pregnancy and fertility treatment**

Only a small percentage of women with Turner syndrome can become pregnant without fertility treatment. Those who can are still likely to experience failure of the ovaries and subsequent infertility very early in adulthood. So it's important to discuss reproductive goals with your health care provider.

Some women with Turner syndrome can become pregnant with the donation of an egg or embryo. A reproductive endocrinologist can discuss options and help evaluate the chances of success.

In most cases, females with Turner syndrome have high-risk pregnancies. It's important to discuss those risks before pregnancy with a high-risk obstetrician — a specialist in maternal-fetal medicine who focuses on high-risk pregnancies — or a reproductive endocrinologist.

**Outlook / Prognosis**

Turner syndrome affects everyone differently. It’s impossible to predict how it’ll affect your child. The best way you can prepare is to talk to healthcare providers who specialize in Turner syndrome. They can help you navigate the lifelong treatment your child will need.

The life expectancy for people with Turner syndrome might be slightly shorter. But with close monitoring of the health issues that may come with TS, people can usually expect to live a typical lifespan.

**DIFFERENTIAL DIAGNOSIS**

Noonan syndrome is a condition that is very similar to Turner syndrome and often can be confusing to distinguish. Noonan syndrome presents with similar clinical characteristics such as a webbed neck, short stature, cardiac, and renal abnormalities. In Noonan syndrome, there is no chromosomal abnormality, unlike in Turner syndrome with the absent or non-functioning X chromosome. Therefore, Noonan syndrome can be seen in both males and females, whereas Turner syndrome is seen only in females. Genetic testing is required to differentiate between these two conditions

**EPIDEMIOLOGY**

Turner syndrome is seen in about 1 in 2000 to 1 in 2500 live female births. However, the true prevalence remains unknown as many patients with a mild phenotype may remain undiagnosed or are diagnosed late in adulthood. The occurrence of Turner syndrome is almost the same in different ethnicities and different countries. With increased awareness of prenatal ultrasound scans, the prevalence of Turner syndrome at birth is decreasing; this is because some mothers carrying fetuses with Turner syndrome choose to terminate the pregnancy.

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**Delayed Puberty**

**DEFINITION AND DESCRIPTION**

Delayed puberty is a condition where the sexual development starts later than usual, typically later than 14 years of age. Medical conditions, including diabetes, cystic fibrosis or kidney disease, can cause delayed puberty, but sometimes no cause can be identified. Disorders of the thyroid or pituitary glands may cause delayed puberty. Malnutrition can also delay puberty.

**causes delayed puberty**

Delayed puberty most often has no known cause. In some cases, it may run in families. In other cases, it may be caused by any of these:

* Chromosomal problems
* Genetic disorder
* Chronic illness
* Tumors of the pituitary gland or hypothalamus
* Underactive pituitary gland (hypopituitarism)
* Underactive thyroid (hypothyroidism)
* Abnormal development of the reproductive system
* Inability of the body to use androgen hormones (complete androgen insensitivity syndrome)
* Too much exercise
* Severe lack of eating (anorexia)

**Risk factor for delayed puberty**

A child is at risk for delayed puberty if he or she has any of these:

* Parents or siblings with delayed puberty
* Chronic medical conditions
* Congenital syndrome
* An eating disorder

Symptoms

No breast development in girls by age 13

No menstruation for five or more years after the first appearance of breast tissue

No testicles development by age 14 in boys

Incompletely developed male organs by five years after the first start to develop

Diagnosis

Complete physical exam and medical history

Blood tests to determine hormone levels

X-rays of the hand to determine bone age

In addition to a complete health history and physical exam, diagnosis of delayed puberty may include:

* **Blood tests.** These are done to check hormone levels, look for chromosomal problems, and check for chronic disorders that may delay puberty. These may include diabetes or anemia.
* **X-ray.** This test uses a small amount of radiation to make images of tissues inside the body. An X-ray may be done of the left hand and wrist. This can estimate your child's bone age. With precocious puberty, bone age is often older than calendar age. Precocious puberty means your child's body begins changing into that of an adult (puberty) too soon. This change would occur before age 8 in girls and before age 9 in boys.
* **CT scan.** This test uses a series of X-rays and a computer to make detailed images of the body. A CT scan can show bones, muscles, fat, and organs. CT scans are more detailed than regular X-rays.
* **MRI.** This test uses large magnets and a computer to make detailed images of tissues in the body.

**Treatment**

Your child's healthcare provider will consider his or her age, overall health, and other factors when advising treatment.

Treatment for delayed puberty depends on the cause of the problem. In many cases, when the cause is treated, puberty proceeds normally. If the delayed puberty is inherited, no treatment is usually needed. In some cases, treatment may be done with hormone therapy. This helps to cause secondary sexual characteristics to occur. In other cases, surgery may be done to correct a physical problem.

**possible complications of delayed puberty**

Delayed puberty can cause embarrassment and stress for adolescents.

**How can I help my child live with delayed puberty**

Most adolescents with delayed puberty will in time develop normally and not have ongoing problems. Some causes will need treatment with hormones. Emotional support can help adolescents in dealing with their delayed puberty.

**DIFFERENTIAL DIAGNOSIS**

**Delayed Puberty in Males and Females**

* Chronic illnesses: sickle cell anemia, inflammatory bowel disease, cystic fibrosis, celiac disease, etc.
* Psychological: depression, anxiety
* Social: poor environment at home

**Delayed Puberty in Males**

* Constitutional delay of puberty and growth
* Hypogonadotropic hypogonadism
* Acquired
* Chronic illness: cystic fibrosis, sickle cell anemia, celiac disease, etc.
* Psychosocial: anxiety, depression
* Genetic
* Kallman syndrome
* Brain mass or tumor
* Hypergonadotropic hypogonadism
* Acquired
* Radiation therapy
* Testicular surgery
* Genetic
* Klinefelter syndrome
* Testicular regression syndrome

**Delayed Puberty in Females**

* Constitutional delay in puberty and growth
* Hypogonadotropic hypogonadism
* Acquired
* Chronic illness: cystic fibrosis, sickle cell anemia, celiac disease, etc.
* Psychosocial: anorexia nervosa, excessive exercise, depression, anxiety
* Genetic:
* Kallman syndrome
* Brain mass or tumor
* Hypergonadotropic hypogonadism
* Acquired
* Radiation therapy
* Surgery to ovaries
* Genetic
* Autoimmune ovarian failure
* Turner syndrome

**PROGNOSIS**

The prognosis of delayed puberty depends on the underlying condition. CPDG generally has a good prognosis with either expectant therapy or treatment. The more complicated causes of pubertal delay may require additional specialists for support and care. Access to care and resources can also impact the patient's care and management if his or her diagnosis is complicated. Therefore, the prognosis is also dependent on an individual's clinical status and his or her financial and social support

**EPIDEMIOLOGY**

In a large retrospective study, with 232 subjects at an academic center in the United States, the frequency of delayed puberty was divided by its different causes.

* The most common cause of delayed puberty was CDPG, affecting 53% of adolescents 18 years or younger. CDPG was more common in males (63%) than in females (30%).
* Functional hypogonadotropic hypogonadism occurred in 19% of patients.
* Permanent hypogonadotropic hypogonadism comprised 12% of patients.
* Primary gonadal failure occurred in 13% of patients.
* Patients without a clearly classified disorder occurred in 3% of subjects.

**When to Call for Help**

If your child exhibits no signs or few signs of sexual development by age 13 for girls, or by age 14 for boys, see a doctor.

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**MENOPAUSE**

**DEFINITION AND DESCRIPTION**

For most women, menopause is marked by the end of monthly menstruation (also known as a menstrual period or ‘period’) due to loss of ovarian follicular function. This means that the ovaries stop releasing eggs for fertilization.

The regularity and length of the menstrual cycle varies across a woman’s reproductive life span, but the age at which natural menopause occurs is generally between 45 and 55 years for women worldwide.

Natural menopause is deemed to have occurred after 12 consecutive months without menstruation for which there is no other obvious physiological or pathological cause and in the absence of clinical intervention.

Some women experience menopause earlier (before 40 years of age). This premature menopause may be because of certain chromosomal abnormalities, autoimmune disorders or other unknown causes.

It is not possible to predict when an individual woman will experience menopause, although there are associations between the age at menopause and certain demographic, health and genetic factors.

Menopause can also be induced as a consequence of surgical procedures that involve removal of both ovaries or medical interventions that cause cessation of ovarian function (for example radiation therapy or chemotherapy).

Many women have already stopped menstruating before menopause, for example those who have had certain surgical procedures (hysterectomy or surgical removal of their uterine lining) as well as those using certain hormonal contraceptives and other medicines that cause infrequent or absent periods. They may still experience other changes related to the menopausal transition.

**Changes associated with menopause**

The hormonal changes associated with menopause can affect physical, emotional, mental and social well-being. The symptoms experienced during and following the menopausal transition vary substantially from person to person. Some have few if any symptoms. For others, symptoms can be severe and affect daily activities and quality of life. Some can experience symptoms for several years.

**Symptoms associated with menopause include**:

* hot flushes and night sweats. Hot flushes refer to a sudden feeling of heat in the face, neck and chest, often accompanied by flushing of the skin, perspiration (sweating), palpitations and acute feelings of physical discomfort which can last several minutes;
* changes in the regularity and flow of the menstrual cycle, culminating in cessation of menstruation;
* vaginal dryness, pain during sexual intercourse and incontinence;
* difficulty sleeping/insomnia; and
* changes in mood, depression and anxiety.

Body composition and cardiovascular risk can also be affected. Women’s advantage over men in terms of cardiovascular disease gradually disappears with the significant decline in oestrogen levels after menopause. Menopause can also result in the weakening of the pelvic support structures, increasing the risk of pelvic organ prolapse. Loss of bone density at menopause is a significant contributor to higher rates of osteoporosis and fractures.

There are a variety of non-hormonal and hormonal interventions that can help alleviate symptoms of menopause. Symptoms that impact on health and well-being should be discussed with a health-care provider to identify available management options, with consideration of medical history, values, and preferences.

Pregnancy is still possible during perimenopause. Contraception is recommended to avoid unintended pregnancy until after 12 consecutive months without menstruation. Pregnancy after menopause is unlikely without fertility treatment that involves the use of donor eggs or previously frozen embryos.

During perimenopause and following menopause, it is still possible to acquire sexually transmitted infections (STIs), including HIV, through unprotected sexual contact, including oral, anal and vaginal sex. The thinning of the vaginal wall after menopause increases the chances of lesions and tears, thereby increasing the risk of HIV transmission during vaginal sex.

**The importance of understanding menopause**

It is critical to see menopause as just one point in a continuum of life stages. A woman’s health status entering the perimenopausal period will largely be determined by prior health and reproductive history, lifestyle and environmental factors. Perimenopausal and postmenopausal symptoms can be disruptive to personal and professional lives, and changes associated with menopause will affect a woman’s health as she ages. Therefore, perimenopausal care plays an important role in the promotion of healthy ageing and quality of life.

Menopause can be an important transition from a social perspective, as well as a biological one. Socially, a women’s experience of menopause may be influenced by gender norms, familial and sociocultural factors, including how female ageing and the menopausal transition are viewed in her culture.

The global population of postmenopausal women is growing. In 2021, women aged 50 and over accounted for 26% of all women and girls globally. This was up from 22% 10 years earlier . Additionally, women are living longer. Globally, a woman aged 60 years in 2019 could expect to live on average another 21 years .

Menopause can offer an important opportunity to reassess one’s health, lifestyle, and goals.

Perimenopausal women need access to quality health services and communities and systems that can support them. Unfortunately, both awareness and access to menopause-related information and services remain a significant challenge in most countries. Menopause is often not discussed within families, communities, workplaces, or health-care settings.

Women may not know that symptoms they experience are related to menopause, or that there are counselling and treatment options that can help alleviate discomfort. Those experiencing menopausal symptoms may feel embarrassed or ashamed to draw attention to their experiences and ask for support.

Health-care providers may not be trained to recognize perimenopausal and postmenopausal symptoms and counsel patients on treatment options and staying healthy after the menopausal transition. Menopause currently receives limited attention in the training curricula for many health-care workers.

The sexual well-being of menopausal women is overlooked in many countries. This means that common gynaecological effects of menopause, including vaginal dryness and pain during intercourse, may go unaddressed. Similarly, older women may not consider themselves at risk of sexually transmitted infections, including HIV, or may not be counselled by their providers to practice safer sex or get tested.

Many governments do not have health policy and financing for the inclusion of menopause-related diagnosis, counselling, and treatment services as part of their routinely available services. Menopause-related services are a particular challenge in settings where there are often other urgent and competing priorities for health funding.

**Symptoms**

Most often, menopause happens over time. The months or years leading up to menopause are called perimenopause or the menopausal transition.

During the transition, the amount of hormones your ovaries make varies. Perimenopause can last 2 to 8 years. The average is about four years.

The hormone changes can cause symptoms such as:

* Irregular periods.
* Vaginal dryness.
* Hot flashes.
* Night sweats.
* Sleep problems.
* Mood changes.
* Trouble finding words and remembering, often called brain fog.

Different people have different menopause symptoms. Most often, periods are not regular before they end.

Skipped periods during perimenopause are common and expected. Often, menstrual periods skip a month and return. Or they skip a few months and then start monthly cycles again for a few months.

Period cycles tend to get shorter in early perimenopause, so periods are closer together. As menopause gets closer, periods get farther apart for months before they end.

You can still get pregnant during this time. If you've skipped a period but aren't sure it's due to menopause, think about taking a pregnancy test.

**When to see a doctor**

Keep seeing your healthcare professional for wellness visits and medical concerns before, during and after menopause. See your healthcare professional as soon as you can if you bleed from your vagina after menopause.

**Causes**

Menopause can result from:

* **Natural decline of hormones.** As you enter your late 30s, your ovaries start making less of the hormones that control your period. These are called estrogen and progesterone. With lower levels of them, it's harder to get pregnant.

In your 40s, your menstrual periods may get longer or shorter, heavier or lighter, and happen more often or less often. In time, your ovaries stop releasing eggs. Then you have no more periods. This happens on average around age 51.

* **Surgery that removes the ovaries, called oophorectomy.** Ovaries make hormones, including estrogen and progesterone, that control the menstrual cycle. Surgery to remove the ovaries causes instant menopause.

Your periods stop. You're likely to have hot flashes and other menopausal symptoms. Symptoms can be severe because the surgery causes hormones to drop all at once rather than slowly over several years.

Surgery that removes the uterus but not the ovaries, called hysterectomy, most often doesn't cause instant menopause. You no longer have periods. But your ovaries still release eggs and make estrogen and progesterone for a time.

* **Chemotherapy and radiation therapy.** These cancer therapies can cause menopause. They can cause symptoms such as hot flashes during or shortly after treatment. Periods sometimes return after chemotherapy. Then you can still get pregnant. So you might want to keep using birth control.

Radiation therapy aimed at the pelvis, belly and lower spine can cause menopause. Radiation to the whole body for stem cell transplant also can cause menopause. Radiation therapy to other parts of the body, such as breast tissue or the head and neck, likely won't affect menopause.

* **Primary ovarian insufficiency.** About 1% of people who have menopause get it before age 40. This is called premature menopause. Premature menopause may result from the ovaries not making the usual levels of hormones. This is called primary ovarian insufficiency. It can happen from gene changes or an autoimmune disease.

Often no cause of premature menopause can be found. Then healthcare professionals most often suggest hormone therapy. Taken at least until the typical age of menopause, hormone therapy can protect the brain, heart and bones.

**Risk factors**

People assigned female at birth go through menopause. The main risk factor is reaching the age of menopause.

Other risk factors include:

* Surgery to remove the ovaries.
* Certain cancer treatments.

**Complications**

After menopause, your risk of certain medical conditions increases. Examples include:

* **Heart and blood vessel disease.** This also is called cardiovascular disease. When your estrogen levels fall, your risk of cardiovascular disease increases. Heart disease is the leading cause of death in both women and men.
* **Weakened bones, called osteoporosis.** This condition causes bones to become brittle and weak, leading to a greater risk of breaking bones. During the first few years after menopause, you may lose bone density quickly. This ups your risk of osteoporosis. Bones often broken after menopause include the spine, hips and wrists.
* **Loss of bladder control, called urinary incontinence.** As the tissues of your vagina and urethra change, you may have sudden, strong urges to urinate often. Then you might lose urine, called urge incontinence. Or you might lose urine with coughing, laughing or lifting, called stress incontinence. You may have urinary tract infections more often.
* **Sex problems.** Menopause causes the vagina to get drier and lose its stretch. This can cause discomfort and slight bleeding during sexual intercourse. Also, less feeling in the area may lessen your desire for sex, called libido.
* **Weight gain.** Many women gain weight during and after menopause because calorie burning, called metabolism, slows.

**Diagnosis**

Most people can tell by the symptoms that they've started menopause. If you have worries about irregular periods or hot flashes, talk with your healthcare professional.

Tests most often aren't needed to diagnose menopause. But sometimes, your healthcare professional may suggest blood tests to check your levels of:

* Follicle-stimulating hormone (FSH) and estrogen (estradiol). FSH goes up and estrogen goes down during menopause. Because hormones go up and down during perimenopause, it can be hard to tell from these tests whether you're in menopause.
* Thyroid-stimulating hormone (TSH). Overactive thyroid, called hyperthyroidism, can cause symptoms like those of menopause.

You can get home tests to check FSH levels in your urine without a prescription. The tests show whether you have higher FSH levels. This might mean that you're in perimenopause or menopause.

But FSH levels rise and fall during your menstrual cycle. So home FSH tests can't really tell you whether you're in menopause.

**Treatment**

Menopause needs no treatment. Treatments aim to ease symptoms and prevent or manage ongoing conditions that may happen with aging. Treatments may include:

* **Hormone therapy.** Estrogen therapy works best for easing menopausal hot flashes. It also eases other menopause symptoms and slows bone loss.

Your healthcare professional may suggest estrogen in the lowest dose and for the time needed to relieve your symptoms. It's best used by people who are younger than 60 and within 10 years of the onset of menopause.

If you still have your uterus, you'll need progestin with estrogen. Estrogen also helps prevent bone loss.

Long-term use of hormone therapy may have some heart disease and breast cancer risks. But starting hormones around the time of menopause has shown benefits for some people. Talk with your healthcare professional about whether hormone therapy may be safe for you.

* **Vaginal estrogen.** To relieve vaginal dryness, you can apply estrogen to the vagina using a vaginal cream, tablet or ring. This treatment gives you a small amount of estrogen, which the vaginal tissues take in. It can help ease vaginal dryness, pain with intercourse and some urinary symptoms.
* **Prasterone (Intrarosa).** You put this human-made hormone dehydroepiandrosterone (DHEA) into the vagina. It helps ease vaginal dryness and pain with intercourse.
* **Low-dose medicines to treat depression, called antidepressants.** Some antidepressants may ease menopausal hot flashes. These are called selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRI). A low-dose antidepressant may help manage hot flashes in people who can't take estrogen for health reasons or for those who need an antidepressant for a mood disorder.
* **Gabapentin (Gralise, Neurontin).** Gabapentin is approved to treat seizures, but it also has been shown to help reduce hot flashes. This medicine is useful for people who can't use estrogen therapy and for those who also have nighttime hot flashes.
* **Clonidine (Catapres-TTS-1, Nexiclon XR).** This pill or patch most often treats high blood pressure. It might give some relief from hot flashes. It's not often prescribed for hot flashes because of the possible side effects, such as low blood pressure, headache, sleepiness and constipation.
* **Fezolinetant (Veozah).** This medicine is free of hormones. It treats menopause hot flashes by blocking a pathway in the brain that helps manage body temperature. It's FDA approved for managing menopause symptoms. It can cause abdominal pain, liver problems and make sleep problems worse.
* **Oxybutynin (Oxytrol).** This medicine treats overactive bladder and urinary urge incontinence. It's also been shown to relieve menopause symptoms. But in older adults, it may be linked to cognitive decline.
* **Medicines to prevent or treat the bone-thinning condition called osteoporosis.** Your healthcare professional might suggest medicine to prevent or treat osteoporosis. Several medicines can help reduce bone loss and risk of fractures. Your healthcare professional also might prescribe vitamin D supplements to help strengthen bones.
* **Ospemifene (Osphena).** Taken by mouth, this selective estrogen receptor modulator (SERM) medicine treats painful intercourse linked to the thinning of vaginal tissue. This medicine isn't for people who have had breast cancer or who are at high risk of breast cancer.

Before deciding on any form of treatment, talk with your healthcare professional about your choices and the risks and benefits of each. Review your choices yearly. Your needs and the treatment choices may change.

**Lifestyle and home remedies**

Many of the symptoms menopause causes go away on their own in time. In the meantime, the following might help:

* **Cool hot flashes.** Dress in layers, wear sleeveless tops and wear fabrics that breathe, such as cotton. Lower room temperatures and use hand or room fans. Put cold packs under your pillow and turn the pillow often so your head is on the cool side.

It might also help to avoid triggers such as caffeine, alcohol and spicy foods.

* **Ease vaginal pain.** Try a water-based vaginal lubricant (Astroglide, Sliquid, others) or a silicone-based lubricant or moisturizer (Replens, K-Y Liquibeads, others). You can get these without a prescription.

Stay sexually active by yourself or with a partner. This also can ease vaginal discomfort by increasing blood flow to the vagina.

* **Get enough sleep.** Skip caffeine and alcohol, which can make it harder to sleep. Exercise during the day, but not right before bedtime. If hot flashes disturb your sleep, find a way to help manage them so you can get better rest.
* **Find ways to relax.** There's little proof that deep breathing, guided imagery, massage and muscle relaxation can ease menopausal symptoms. But finding ways to relax is good for overall health and may help you cope with menopausal symptoms. You can learn how through books and websites.
* **Strengthen your pelvic floor.** Pelvic floor muscle exercises, called Kegel exercises, can improve some forms of urinary incontinence.
* **Eat a balanced diet.** Include a variety of fruits, vegetables and whole grains. Limit saturated fats, oils and sugars. Ask your healthcare professional if you need calcium or vitamin D supplements.
* **Manage weight.** Studies show that being obese is linked to having more and worse hot flashes. Losing weight and keeping it off may help ease them. Talk with your healthcare professional if you need help losing weight.
* **Don't smoke.** Smoking increases your risk of heart disease, stroke, osteoporosis, cancer and a range of other health problems. It also may increase hot flashes and bring on earlier menopause.
* **Exercise regularly.** Get regular physical activity or exercise on most days to help protect against heart disease, diabetes, osteoporosis and other conditions associated with aging.

**Alternative medicine**

There are many alternative medicines that claim to help ease the symptoms of menopause. But few of them have been proved in studies. Some complementary and alternative treatments that have been or are being studied include:

* **Plant estrogens, also called phytoestrogens.** There are natural estrogens in certain foods. There are two main types of phytoestrogens, called isoflavones and lignans. Soybeans, lentils, chickpeas and other legumes have isoflavones. Flaxseed, whole grains and some fruits and vegetables have lignans.

It hasn't been proved that the estrogens in these foods can ease hot flashes and other menopausal symptoms. Isoflavones have some weak estrogen-like effects. So if you've had breast cancer, talk with your healthcare provider before taking isoflavone pills.

* **Bioidentical hormones.** These hormones come from plant sources. The term "bioidentical" implies the hormones in the product are chemically the same as those the body makes.

The Food and Drug Administration (FDA) has approved some bioidentical hormones. But many are mixed in a pharmacy from a healthcare professional's prescription, called compounded. But the FDA doesn't regulate them, so quality and risks could vary.

Bioidentical hormones have not been shown to work better or be safer than other hormone therapy.

* **Cognitive behavior therapy.** This type of therapy can help you change thoughts, feelings and behaviors that aren't healthy. It's been shown to reduce how much menopause symptoms bother you.
* **Black cohosh.** Black cohosh has been popular among many people with menopause symptoms. But there's little proof that black cohosh works. And it can harm the liver and not be safe for people with a history of breast cancer.
* **Yoga.** Yoga might ease menopause symptoms at least as well as other forms of exercise. And balance exercises such as yoga or tai chi can improve strength and help you move better. That may help prevent falls that could lead to broken bones.
* **Acupuncture.** Acupuncture may help to reduce hot flashes in the short term. But research hasn't shown that it helps a lot. More research is needed.
* **Hypnosis.** This mind-body therapy involves a deeply relaxed state and mental images. Hypnotherapy may lower the number of hot flashes and how bad they are for some menopausal people.

You may have heard of or tried other dietary supplements, such as red clover, kava, dong quai, DHEA, evening primrose oil and wild yam, a natural progesterone cream. There's no scientific proof that they work. Some of these products may be harmful.

Talk with your healthcare professional before taking any herbal or dietary supplements for menopause symptoms. The FDA does not oversee herbal products. Some can be harmful or affect other medicines you take, putting your health at risk.

**EPIDEMIOLOGY**

Around 1.5 million women experience the menopause transition each year. Although 70 to 80% of women experience vasomotor symptoms, only 15 to 20% of women have significant interference with quality of life and seek help. The average duration of hot flashes is about 5.2 years, with symptom onset one year before the final menstrual period and declining thereafter. About 27 to 60% of women report vaginal dryness or dyspareunia in association with menopause. Around 50% of women report sleep disturbance. There is a reported 3-fold risk for the development of a major depressive episode during perimenopause.

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**CARCINOID SYNDROME**

Carcinoid syndrome occurs when a rare cancerous tumor called a carcinoid tumor secretes certain chemicals into your bloodstream, causing a variety of signs and symptoms. A carcinoid tumor, which is a type of neuroendocrine tumor, occurs most often in the gastrointestinal tract or the lungs.

Carcinoid syndrome typically occurs in people who have carcinoid tumors that are advanced. Treatment for carcinoid syndrome usually involves treating the cancer. However, because most carcinoid tumors don't cause carcinoid syndrome until they're advanced, a cure may not be possible. Medications may be recommended to relieve your carcinoid syndrome symptoms and make you more comfortable.

**Symptoms**

The signs and symptoms of carcinoid syndrome depend on which chemicals the carcinoid tumor secretes into your bloodstream.

The most common signs and symptoms include:

* **Skin flushing.** The skin on your face and upper chest feels hot and changes color — ranging from pink to purple. Flushing episodes may last from a few minutes to a few hours or longer.

Flushing may happen for no obvious reason, though sometimes it can be triggered by stress, exercise or drinking alcohol.

* **Facial skin lesions.** Purplish areas of spiderlike veins may appear on your nose and upper lip.
* **Diarrhea.** Frequent, watery stools sometimes accompanied by abdominal cramps may occur in people who have carcinoid syndrome.
* **Difficulty breathing.** Asthma-like signs and symptoms, such as wheezing and shortness of breath, may occur at the same time you experience skin flushing.
* **Rapid heartbeat.** Periods of a fast heart rate could be a sign of carcinoid syndrome.

**When to see a doctor**

Make an appointment with your doctor if you have signs and symptoms that concern you.

**Causes**

Carcinoid syndrome is caused by a carcinoid tumor that secretes serotonin or other chemicals into your bloodstream. Carcinoid tumors occur most often in the gastrointestinal tract, including your stomach, small intestine, appendix, colon and rectum.

Only a small percentage of carcinoid tumors secrete the chemicals that cause carcinoid syndrome. When these tumors do secrete the chemicals, the liver normally neutralizes the chemicals before they have a chance to travel through your body and cause symptoms.

However, when an advanced tumor spreads (metastasizes) to the liver itself, it may secrete chemicals that aren't neutralized before reaching the bloodstream. Most people who experience carcinoid syndrome have an advanced cancer that has spread to the liver.

Some carcinoid tumors don't have to be advanced to cause carcinoid syndrome. For instance, carcinoid lung tumors that secrete chemicals into the blood do so farther upstream from the liver, which then cannot process and eliminate the chemicals.

Carcinoid tumors in the intestine, on the other hand, secrete the chemicals into blood that must first pass through the liver before reaching the rest of the body. The liver usually neutralizes the chemicals before they can affect the rest of the body.

What causes carcinoid tumors is unclear.

**Complications**

Having carcinoid syndrome can cause the following complications:

* **Carcinoid heart disease.** Some people with carcinoid syndrome develop carcinoid heart disease. Carcinoid syndrome causes problems with the heart valves, making it difficult for them to function properly. As a result, the heart valves may leak.

Signs and symptoms of carcinoid heart disease include fatigue and shortness of breath. Carcinoid heart disease can eventually lead to heart failure. Surgical repair of damaged heart valves may be an option.

* **Carcinoid crisis.** Carcinoid crisis causes a severe episode of flushing, low blood pressure, confusion and breathing difficulty. Carcinoid crisis can occur in people with carcinoid tumors when they are exposed to certain triggers, including anesthetic used during surgery. Carcinoid crisis can be fatal. Your doctor may give you medications before surgery to reduce the risk of carcinoid crisis.

**Diagnosis**

Your doctor will assess your signs and symptoms to rule out other causes of skin flushing and diarrhea. If no other causes are found, your doctor may suspect carcinoid syndrome.

To confirm a diagnosis, your doctor may recommend further tests, including:

* **Urine test.** Your urine may contain a substance made when your body breaks down serotonin. An excess amount of this substance could indicate that your body is processing extra serotonin, the chemical most commonly secreted by carcinoid tumors.
* **Blood test.** Your blood may contain high levels of certain substances that are released by some carcinoid tumors.
* **Imaging tests.** Imaging tests may be used to locate the primary carcinoid tumor and determine whether it has spread. Your doctor may start with a CT scan of your abdomen, because most carcinoid tumors are found in the gastrointestinal tract. Other scans, such as MRI or nuclear medicine scans, may be helpful in certain situations.
* **A scope or camera to see inside your body.** Your doctor may use a long, thin tube equipped with a lens or camera to examine areas inside your body.

An endoscopy, which involves passing a scope down your throat, may help your doctor see inside your gastrointestinal tract. A bronchoscopy, which uses a scope passed down your throat and into your lungs, can help find lung carcinoid tumors. Passing a scope through your rectum (colonoscopy) can help diagnose rectal carcinoid tumors.

* **Removing tissue for laboratory testing.** A sample of tissue from the tumor (biopsy) may be collected to confirm your diagnosis. What type of biopsy you'll undergo depends on where your tumor is located.

**Treatment**

Treating carcinoid syndrome involves treating your cancer and may also involve using medications to control your specific signs and symptoms.

Treatments may include:

* **Surgery.** Surgery to remove your cancer or most of your cancer may be an option.
* **Medications to block cancer cells from secreting chemicals.** Injections of the medications octreotide (Sandostatin) and lanreotide (Somatuline Depot) may reduce the signs and symptoms of carcinoid syndrome, including skin flushing and diarrhea. A drug called telotristat (Xermelo) can be combined with these drugs to control diarrhea caused by carcinoid syndrome.
* **Drugs that deliver radiation directly to the cancer cells.** Peptide receptor radionuclide therapy (PRRT) combines a drug that seeks out cancer cells with a radioactive substance that kills them. In PRRT for carcinoid tumors, the drug is injected into your body, where it travels to the cancer cells, binds to the cells and delivers the radiation directly to them. This therapy is used in people who have advanced cancer that hasn't responded to other treatments.
* **Stopping blood supply to liver tumors.** In a procedure called hepatic artery embolization, a doctor inserts a catheter through a needle near your groin and threads it up to the main artery that carries blood to your liver (hepatic artery). The doctor injects particles designed to clog the hepatic artery, cutting off the blood supply to cancer cells that have spread to the liver. The healthy liver cells survive by relying on blood from other blood vessels.
* **Killing cancer cells in the liver with heat or cold.** Radiofrequency ablation delivers heat through a needle to the cancer cells in the liver, causing the cells to die. Cryotherapy is similar, but it works by freezing the tumor.
* **Chemotherapy.** Chemotherapy uses strong drugs to kill cancer cells. Chemotherapy drugs can be given through a vein (intravenously) or in pill form, or both methods can be used.

**Self care**

Talk to your doctor about self-care measures that may improve your signs and symptoms. Self-care measures can't replace treatment, but they may complement it. Ask your doctor if you should:

* **Avoid things that cause skin flushing.** Certain substances or situations, such as alcohol or large meals, can trigger flushing. Keep track of what causes your flushing, and try to avoid those triggers.
* **Consider taking a multivitamin.** Chronic diarrhea makes it difficult for your body to process the vitamins and nutrients in the food you eat. Ask your doctor whether taking a multivitamin may be a good idea for you.

**Prevention**

**Can carcinoid syndrome be prevented?**

No, it can’t be prevented. Carcinoid syndrome is linked to neuroendocrine tumors, and as there isn’t a known way to prevent NETs, there’s no way to prevent its symptoms.

**PROGNOSIS**

The prognosis of carcinoid syndrome is dependent on the underlying tumor characteristics, stage, and extent of metastasis, as well as the presence of associated complications, eg, carcinoid heart disease or carcinoid crisis. Well-differentiated neuroendocrine tumors typically exhibit a relatively indolent course. With advances in targeted therapies, including somatostatin analogs, PRRT, and liver-directed treatments, the prognosis for patients with metastatic disease has improved significantly. The presence of carcinoid heart disease, however, markedly worsens the prognosis due to the risk of progressive right-sided heart failure and its associated morbidity. Long-term survival in patients with carcinoid syndrome is variable and depends on the success of symptom management, control of tumor progression, and prevention or treatment of complications. While early-stage, localized tumors have a favorable prognosis with curative surgical resection, advanced or metastatic disease is often associated with a median survival ranging from 3 to 8 years, depending on the tumor burden and response to therapy. Regular follow-up and an interprofessional approach to care are critical in optimizing outcomes and maintaining the quality of life of these patients

**DIFFERENTIAL DIAGNOSIS**

Carcinoid syndrome tends to present with varying clinical features, which accounts for the wide range of its differential diagnoses. Some essential differential diagnoses that should be considered while establishing a diagnosis of carcinoid syndrome include the following:

* Irritable bowel syndrome
* Gastrointestinal motility disorders
* Celiac disease
* Anaphylaxis
* Acute urticaria
* Angioedema
* Ogilvie syndrome

**EPIDEMIOLOGY**

Neuroendocrine tumors are relatively rare, but their incidence and prevalence have increased, likely due to improved diagnostic techniques and greater clinical awareness. The annual incidence of neuroendocrine tumors is estimated to be approximately 6.98 cases per 100,000 individuals, with a prevalence of approximately 35 cases per 100,000 individuals in the United States. These tumors can affect individuals of all racial and ethnic backgrounds, although some studies suggest a slightly higher prevalence among Caucasians. Neuroendocrine tumors are generally more common in females than males, depending on the primary tumor site. For instance, a female predominance is observed in pancreatic and gastrointestinal neuroendocrine tumors. However, the gender distribution can vary across anatomical sites and tumor types. The peak age for diagnosis typically falls between the fifth and seventh decades of life.

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**OBESITY**

Obesity is a complex disease involving having too much body fat. Obesity isn't just a cosmetic concern. It's a medical problem that increases the risk of many other diseases and health problems. These can include heart disease, diabetes, high blood pressure, high cholesterol, liver disease, sleep apnea and certain cancers.

There are many reasons why some people have trouble losing weight. Often, obesity results from inherited, physiological and environmental factors, combined with diet, physical activity and exercise choices.

The good news is that even modest weight loss can improve or prevent the health problems associated with obesity. A healthier diet, increased physical activity and behavior changes can help you lose weight. Prescription medicines and weight-loss procedures are other options for treating obesity.

**Symptoms**

Body mass index, known as BMI, is often used to diagnose obesity. To calculate BMI, multiply weight in pounds by 703, divide by height in inches and then divide again by height in inches. Or divide weight in kilograms by height in meters squared. There are several online calculators available that help calculate BMI.

See BMI calculator

| **BMI** | **Weight status** |
| --- | --- |
| Below 18.5 | Underweight |
| 18.5-24.9 | Healthy |
| 25.0-29.9 | Overweight |
| 30.0 and higher | Obesity |

Asians with a BMI of 23 or higher may have an increased risk of health problems.

For most people, BMI provides a reasonable estimate of body fat. However, BMI doesn't directly measure body fat. Some people, such as muscular athletes, may have a BMI in the obesity category even though they don't have excess body fat.

Many health care professionals also measure around a person's waist to help guide treatment decisions. This measurement is called a waist circumference. Weight-related health problems are more common in men with a waist circumference over 40 inches (102 centimeters). They're more common in women with a waist measurement over 35 inches (89 centimeters). Body fat percentage is another measurement that may be used during a weight loss program to track progress.

**When to see a doctor**

If you're concerned about your weight or weight-related health problems, ask your health care professional about obesity management. You and your health care team can evaluate your health risks and discuss your weight-loss options.

**Causes**

Although there are genetic, behavioral, metabolic and hormonal influences on body weight, obesity occurs when you take in more calories than you burn through typical daily activities and exercise. Your body stores these excess calories as fat.

In the United States, most people's diets are too high in calories — often from fast food and high-calorie beverages. People with obesity might eat more calories before feeling full, feel hungry sooner, or eat more due to stress or anxiety.

Many people who live in Western countries now have jobs that are much less physically demanding, so they don't tend to burn as many calories at work. Even daily activities use fewer calories, courtesy of conveniences such as remote controls, escalators, online shopping, and drive-through restaurants and banks.

**Risk factors**

Obesity often results from a combination of causes and contributing factors:

**Family inheritance and influences**

The genes you inherit from your parents may affect the amount of body fat you store, and where that fat is distributed. Genetics also may play a role in how efficiently your body converts food into energy, how your body regulates your appetite and how your body burns calories during exercise.

Obesity tends to run in families. That's not just because of the genes they share. Family members also tend to share similar eating and activity habits.

**Lifestyle choices**

* **Unhealthy diet.** A diet that's high in calories, lacking in fruits and vegetables, full of fast food, and laden with high-calorie beverages and oversized portions contributes to weight gain.
* **Liquid calories.** People can drink many calories without feeling full, especially calories from alcohol. Other high-calorie beverages, such as sugared soft drinks, can contribute to weight gain.
* **Inactivity.** If you have an inactive lifestyle, you can easily take in more calories every day than you burn through exercise and routine daily activities. Looking at computer, tablet and phone screens is inactivity. The number of hours spent in front of a screen is highly associated with weight gain.

**Certain diseases and medications**

In some people, obesity can be traced to a medical cause, such as hypothyroidism, Cushing syndrome, Prader-Willi syndrome and other conditions. Medical problems, such as arthritis, also can lead to decreased activity, which may result in weight gain.

Some medicines can lead to weight gain if you don't compensate through diet or activity. These medicines include steroids, some antidepressants, anti-seizure medicines, diabetes medicines, antipsychotic medicines and certain beta blockers.

**Social and economic issues**

Social and economic factors are linked to obesity. It's hard to avoid obesity if you don't have safe areas to walk or exercise. You may not have learned healthy ways of cooking. Or you may not have access to healthier foods. Also, the people you spend time with may influence your weight. You're more likely to develop obesity if you have friends or relatives with obesity.

**Age**

Obesity can occur at any age, even in young children. But as you age, hormonal changes and a less active lifestyle increase your risk of obesity. The amount of muscle in your body also tends to decrease with age. Lower muscle mass often leads to a decrease in metabolism. These changes also reduce calorie needs and can make it harder to keep off excess weight. If you don't consciously control what you eat and become more physically active as you age, you'll likely gain weight.

**Other factors**

* **Pregnancy.** Weight gain is common during pregnancy. Some women find this weight difficult to lose after the baby is born. This weight gain may contribute to the development of obesity in women.
* **Quitting smoking.** Quitting smoking is often associated with weight gain. And for some, it can lead to enough weight gain to qualify as obesity. Often, this happens as people use food to cope with smoking withdrawal. But overall, quitting smoking is still a greater benefit to your health than is continuing to smoke. Your health care team can help you prevent weight gain after quitting smoking.
* **Lack of sleep.** Not getting enough sleep can cause changes in hormones that increase appetite. So can getting too much sleep. You also may crave foods high in calories and carbohydrates, which can contribute to weight gain.
* **Stress.** Many external factors that affect mood and well-being may contribute to obesity. People often seek more high-calorie food during stressful situations.
* **Microbiome.** The make-up of your gut bacteria is affected by what you eat and may contribute to weight gain or trouble losing weight.

Even if you have one or more of these risk factors, it doesn't mean that you're destined to develop obesity. You can counteract most risk factors through diet, physical activity and exercise. Behavior changes, medicines and procedures for obesity also can help.

**Complications**

People with obesity are more likely to develop a number of potentially serious health problems, including:

* **Heart disease and strokes.** Obesity makes you more likely to have high blood pressure and unhealthy cholesterol levels, which are risk factors for heart disease and strokes.
* **Type 2 diabetes.** Obesity can affect the way the body uses insulin to control blood sugar levels. This raises the risk of insulin resistance and diabetes.
* **Certain cancers.** Obesity may increase the risk of cancer of the uterus, cervix, endometrium, ovary, breast, colon, rectum, esophagus, liver, gallbladder, pancreas, kidney and prostate.
* **Digestive problems.** Obesity increases the likelihood of developing heartburn, gallbladder disease and liver problems.
* **Sleep apnea.** People with obesity are more likely to have sleep apnea, a potentially serious disorder in which breathing repeatedly stops and starts during sleep.
* **Osteoarthritis.** Obesity increases the stress placed on weight-bearing joints. It also promotes inflammation, which includes swelling, pain and a feeling of heat within the body. These factors may lead to complications such as osteoarthritis.
* **Fatty liver disease.** Obesity increases the risk of fatty liver disease, a condition that happens due to excessive fat deposit in the liver. In some cases, this can lead to serious liver damage, known as liver cirrhosis.
* **Severe COVID-19 symptoms.** Obesity increases the risk of developing severe symptoms if you become infected with the virus that causes coronavirus disease 2019, known as COVID-19. People who have severe cases of COVID-19 may need treatment in intensive care units or even mechanical assistance to breathe.

**Quality of life**

Obesity can diminish the overall quality of life. You may not be able to do physical activities that you used to enjoy. You may avoid public places. People with obesity may even encounter discrimination.

Other weight-related issues that may affect your quality of life include:

* Depression.
* Disability.
* Shame and guilt.
* Social isolation.
* Lower work achievement.

**Diagnosis**

To diagnose obesity, your health care professional may perform a physical exam and recommend some tests.

These exams and tests often include:

* **Taking your health history.** Your health care team may review your weight history, weight-loss efforts, physical activity and exercise habits. You also may talk about your eating patterns and appetite control. Your health care professional may ask about other conditions you've had, medicines you take, your stress levels and other issues about your health. They may also review your family's health history to see if you may be more likely to have certain conditions.
* **A general physical exam.** This includes measuring your height; checking vital signs, such as heart rate, blood pressure and temperature; listening to your heart and lungs; and examining your abdomen.
* **Calculating your BMI.** Your health care professional checks your body mass index, called BMI. A BMI of 30 or higher is considered obesity. Numbers higher than 30 increase health risks even more. Have your BMI checked at least once a year. This can help pinpoint your overall health risks and what treatments may be right for you.
* **Measuring your waist size.** The distance around your waist is known as the circumference. Fat stored around the waist, sometimes called visceral fat or abdominal fat, may further increase the risk of heart disease and diabetes. Women with a waist that measures more than 35 inches (89 centimeters) and men with a waist that's more than 40 inches (102 centimeters) around may have more health risks than do people with smaller waist measurements. Like the BMI measurement, waist circumference should be checked at least once a year.
* **Checking for other health problems.** If you have known health problems, your health care team will evaluate them. Your health care professional also will check for other possible health problems, such as high blood pressure, high cholesterol, underactive thyroid, liver problems and diabetes.

Gathering this information will help you and your health care team choose the type of treatment that will work best for you.

**Treatment**

The goal of obesity treatment is to reach and stay at a healthy weight. This improves overall health and lowers the risk of developing complications related to obesity.

You may need to work with a team of health professionals — including a dietitian, behavioral counselor or an obesity specialist — to help you understand and make changes in your eating and activity habits.

The first treatment goal is usually a modest weight loss — 5% to 10% of your total weight. That means that if you weigh 200 pounds (91 kilograms), you'd need to lose only about 10 to 20 pounds (4.5 to 9 kilograms) for your health to begin to improve. But the more weight you lose, the greater the benefits.

All weight-loss programs require that you change your eating habits and get more active. The treatment methods that are right for you depend on your weight, your overall health and your willingness to participate in a weight-loss plan.

**Dietary changes**

Reducing calories and practicing healthier eating habits are key to overcoming obesity. Although you may lose weight quickly at first, steady weight loss over the long term is considered the safest way to lose weight. It's also the best way to keep weight off permanently.

There is no best weight-loss diet. Choose one that includes healthy foods that you feel will work for you. Dietary changes to treat obesity include:

* **Cutting calories.** The key to weight loss is reducing how many calories you take in. The first step is to review your typical eating and drinking habits. You can see how many calories you usually consume and where you can cut back. You and your health care professional can decide how many calories you need to take in each day to lose weight. A typical amount is 1,200 to 1,500 calories for women and 1,500 to 1,800 for men.
* **Feeling full on less.** Some foods — such as desserts, candies, fats and processed foods — contain a lot of calories for a small portion. In contrast, fruits and vegetables provide a larger portion size with fewer calories. By eating larger portions of foods that have fewer calories, you can reduce hunger pangs and take in fewer calories. You also may feel better about your meal, which contributes to how satisfied you feel overall.
* **Making healthier choices.** To make your overall diet healthier, eat more plant-based foods. These include fruits, vegetables and whole grains. Also emphasize lean sources of protein — such as beans, lentils and soy — and lean meats. If you like fish, try to include fish twice a week. Limit salt and added sugar. Eat small amounts of fats, and make sure they come from heart-healthy sources, such as olive, canola and nut oils.
* **Restricting certain foods.** Certain diets limit the amount of a particular food group, such as high-carbohydrate or full-fat foods. Ask your health care professional which diet plans are effective and which might be helpful for you. Drinking sugar-sweetened beverages is a sure way to consume more calories than you intended. Limiting these drinks or eliminating them altogether is a good place to start cutting calories.
* **Meal replacements.** These plans suggest replacing one or two meals each day with their products — such as low-calorie shakes or meal bars — and eating healthy snacks. Then you have a healthy, balanced third meal that's low in fat and calories. In the short term, this type of diet can help you lose weight. But these diets likely won't teach you how to change your overall lifestyle. So you may have to stay on the diet if you want to keep your weight off.

Be wary of quick fixes. You may be tempted by fad diets that promise fast and easy weight loss. But the reality is that there are no magic foods or quick fixes. Fad diets may help in the short term, but the long-term results don't appear to be any better than other diets.

Similarly, you may lose weight on a crash diet, but you're likely to regain it when you stop the diet. To lose weight — and keep it off — you must adopt healthy-eating habits that you can maintain over time.

**Exercise and activity**

Getting more physical activity or exercise is an essential part of obesity treatment:

* **Exercise.** People with obesity need to get at least 150 minutes a week of moderate-intensity physical activity. This can help prevent further weight gain or maintain the loss of a modest amount of weight. You'll probably need to gradually increase the amount you exercise as your endurance and fitness improve.
* **Keep moving.** Even though regular aerobic exercise is the most efficient way to burn calories and shed excess weight, any extra movement helps burn calories. For example, park farther from store entrances and take the stairs instead of the elevator. A pedometer can track how many steps you take over the course of a day. Many people try to reach 10,000 steps every day. Gradually increase the number of steps you take daily to reach your goal.

**Behavior changes**

A behavior modification program can help you make lifestyle changes to lose weight and keep it off. Steps to take include looking at your current habits to find out what factors, stresses or situations may have contributed to your obesity.

* **Counseling.** Talking with a mental health professional can help address emotional and behavioral issues related to eating. Therapy can help you understand why you overeat and learn healthy ways to cope with anxiety. You also can learn how to monitor your diet and activity, understand eating triggers, and cope with food cravings. Counseling can be one-on-one or in a group.
* **Support groups.** You can find friendship and understanding in support groups where others share similar challenges with obesity. Check with your health care team, local hospitals or commercial weight-loss programs for support groups in your area.

**Weight-loss medicines**

Weight-loss medicines are meant to be used along with diet, exercise and behavior changes, not instead of them. Before selecting a medication for you, your health care professional will consider your health history, as well as possible side effects.

The most commonly used medications approved by the U.S. Food and Drug Administration (FDA) for the treatment of obesity include:

* Bupropion-naltrexone (Contrave).
* Liraglutide (Saxenda).
* Orlistat (Alli, Xenical).
* Phentermine-topiramate (Qsymia).
* Semaglutide (Ozempic, Rybelsus, Wegovy).

Weight-loss medicines may not work for everyone, and the effects may wane over time. When you stop taking weight-loss medicine, you may regain much or all of the weight you lost.

**Endoscopic procedures for weight loss**

These types of procedures don't require any cuts, also called incisions, in the skin. After you are under anesthesia, flexible tubes and tools are inserted through the mouth and down the throat into the stomach. Common procedures include:

* **Endoscopic sleeve gastroplasty.** This procedure involves placing stitches in the stomach to reduce the amount of food and liquid the stomach can hold at one time. Over time, eating and drinking less helps the average person lose weight.
* **Intragastric balloon for weight loss.** In this procedure, you have a small balloon placed into the stomach. The balloon is then filled with water to reduce the amount of space in the stomach, so you'll feel full eating less food. Intragastric balloons are left in place for up to 6 months and are then removed using an endoscope. At that time, a new balloon may be placed, or not, depending on the plan determined by you and your health care team.

**Weight-loss surgery**

Also known as bariatric surgery, weight-loss surgery limits how much food you can eat. Some procedures also limit the amount of calories and nutrients you can absorb. But this also can result in nutritional and vitamin deficiencies.

Common weight-loss surgeries include:

* **Adjustable gastric banding.** In this surgery, an inflatable band placed around the outside of the stomach divides it into two pouches. The surgeon pulls the band tight, like a belt, to create a narrow pathway between the two pouches. The band keeps the opening from getting bigger. The band often stays in place permanently.
* **Gastric bypass surgery.** In gastric bypass, also called Roux-en-Y (roo-en-wy) gastric bypass, the surgeon creates a small pouch at the top of the stomach. The small intestine is then cut a short distance below the main stomach and connected to the new pouch. Food and liquid flow directly from the pouch into this part of the intestine, bypassing most of the stomach.
* **Gastric sleeve.** In this surgery, part of the stomach is removed, creating a smaller reservoir for food. It's a less complicated surgery than gastric bypass.

Weight-loss success after surgery depends on your commitment to making lifelong changes in your eating and exercise habits.

**Other treatments**

Other treatments for obesity include:

* **Hydrogels.** Available by prescription, these edible capsules contain tiny particles that absorb water and get bigger in the stomach, to help you feel full. The capsules are taken before meals and are passed through the intestines as stool.
* **Vagal nerve blockade.** This involves implanting a device under the skin in the stomach area. The device sends electrical pulses to a nerve in that area, called the abdominal vagus nerve. This nerve tells the brain when the stomach feels empty or full.
* **Gastric aspirate.** In this procedure, a tube is placed through the abdomen into the stomach. A portion of the stomach contents are drained out after each meal.

**Lifestyle and home remedies**

Your effort to overcome obesity is more likely to be successful if you follow strategies at home along with your formal treatment plan. These can include:

* **Learning about your condition.** Education about obesity can help you learn more about why you developed obesity and what you can do about it. You may feel more empowered to take control and stick to your treatment plan. Read reputable self-help books and consider talking about them with your health care professional or therapist.
* **Setting realistic goals.** When you have to lose a lot of weight, you may set goals that are unrealistic, such as trying to lose too much too fast. Don't set yourself up for failure. Set daily or weekly goals for exercise and weight loss. Make small changes in your diet instead of attempting drastic changes that you're not likely to stick with for the long haul.
* **Sticking to your treatment plan.** Changing a lifestyle you may have lived with for many years can be hard to do. Be honest with your doctor, therapist or other health care professionals if you find your activity or eating goals slipping. You can work together to come up with new ideas or new approaches.
* **Enlisting support.** Get your family and friends on board with your weight-loss goals. Surround yourself with people who will support you and help you, not sabotage your efforts. Make sure they understand how important weight loss is to your health. You also might want to join a weight-loss support group.
* **Keeping a record.** Keep a food and activity log. This record can help you remain accountable for your eating and exercise habits. You can discover things that may be holding you back. You also might see what works well for you. You can use your log to track other important health parameters such as blood pressure, cholesterol levels and overall fitness.

**Alternative medicine**

Many dietary supplements that promise to help you shed weight quickly are available. The long-term effectiveness and safety of these products are often questionable.

**Outlook / Prognosis**

Having obesity increases your risk of some serious medical conditions. But having obesity doesn’t mean you have those conditions or there’s nothing you can do to prevent them. Remember, weight loss of just 5% to 10% can significantly improve your health risks. Sticking with a long-term treatment plan can help you maintain weight loss.

**Prevention**

Preventing obesity is easier than treating it once it’s taken hold. That’s because your body manages your body mass by shifting gears as it balances your hunger signals against the amount of energy you use from your daily activity. Once your body establishes a new high “set point," it considers that to be your new baseline weight. That new set point may put your weight higher on the scale or the BMI table. Examining your habits and making reasonable changes now can help you prevent future obesity. Here are some examples:

* **Make small changes**: Do you have a daily snack habit or “pick-me-up,” such as a sugary drink, which is high in calories? Consider replacing it. Just 150 extra calories a day can add up to 10 extra pounds in a year. That’s equal to a snack-size bag of potato chips, or just two double-stuffed sandwich cookies.
* **Add physical activity**: Alternatively, consider what you might do to spend an extra 150 calories in a day by finding an activity that’s right for you and your fitness level.
* **Shop intentionally**: Stock your home with healthy foods and save sweets and treats for special occasions when you go out.
* **Cultivate overall wellness**: Reduce your screen time, go outside and get some fresh air. Manage your stress and try to get adequate sleep to keep your hormone levels in check. Focus on positive changes and healthy activities rather than how your efforts affect your weight.

**EPIDEMIOLOGY**

**In 2024,** the NCD Risk Factor Collaboration (NCD-RisC) published findings that estimate that more than one billion people in the world are now living with obesity, nearly 880 million adults and 159 million children and adolescents aged 5-19 years. The World Obesity Federation’s analysis of this data finds that nearly 3 billion people are living with either overweight or obesity. This evidence suggests that most of the world's population lives in countries where overweight and obesity are a bigger risk to health than underweight.

**In adults,** obesity rates nearly tripled among women (6.6% to 18.5%) and quadrupled in men (3% to 14.0%) between 1975 and 2022. This is the equivalent of approximately  504 million women and 374 million men living with obesity in 2022.

Combined with the 159 million children aged 5-19 years, this is a total of over one billion people affected by obesity alone in 2022. Current projections for overweight and obesity suggest that these trends will continue unless coordinated and evidence-based action is taken – it is clear that the time for action is now.

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**GALACTORRHEA**

Galactorrhea (guh-lack-toe-REE-uh) is a milky nipple discharge not linked to the making of milk for breastfeeding. Galactorrhea isn't a disease. But it can be a sign of an underlying condition.

Galactorrhea mostly happens to people assigned female at birth. It can happen even to those who haven't had children or who have gone through menopause. But galactorrhea also can happen to people assigned male at birth and even to infants.

Too much breast handling, medicine side effects or conditions of the pituitary gland may add to galactorrhea. Often, higher levels of the hormone involved in making breast milk, called prolactin, cause galactorrhea.

Sometimes, the cause of galactorrhea can't be found. The condition may clear up on its own.

**Symptoms**

Symptoms linked to galactorrhea include:

* Milky nipple discharge that's constant or comes and goes.
* Nipple discharge from more than one milk duct.
* Nipple discharge that leaks on its own or when the breast is touched.
* Nipple discharge from one or both breasts.
* Irregular or no menstrual periods.
* Headaches or trouble with vision.

**When to see a doctor**

If one or both breasts keep leaking milky discharge, and you're not pregnant or breastfeeding, make an appointment to see your healthcare professional.

If breast stimulation, such as handling the nipple during sex, causes nipple discharge from more than one duct, there's little cause for worry. The discharge most often doesn't mean there's a problem. And the discharge often clears up on its own.

If you keep having discharges that doesn't go away, make an appointment with your healthcare professional.

Nipple discharge that isn't milky needs medical attention right away. If the discharge is bloody, or clear and comes from one duct or there's a lump you can feel, it may be a sign of breast cancer.

**CAUSES**

Galactorrhea often results from having too much of the hormone that makes milk when you have a baby. This is called prolactin. Your pituitary gland, a small bean-shaped gland at the base of your brain involved with several hormones, makes prolactin.

Possible causes of galactorrhea include:

* Medicines, such as certain sedatives, antidepressants, antipsychotics and high blood pressure medicines.
* Opioid use.
* Herbal supplements, such as fennel, anise or fenugreek seed.
* Birth control pills.
* A noncancerous pituitary tumor, called prolactinoma, or other condition of the pituitary gland.
* Underactive thyroid, also called hypothyroidism.
* Long-term kidney disease.
* Too much handling of the breast. This may be linked with sex activity, having breast self-exams with nipple handling or long-lasting rubbing from clothing.
* Nerve damage to the chest wall from chest surgery, burns or other chest injuries.
* Spinal cord surgery, injury or tumors.
* Stress.

**Idiopathic galactorrhea**

Sometimes healthcare professionals can't find a cause for galactorrhea. This is called idiopathic galactorrhea. This may mean that the breast tissue is very sensitive to the milk-making hormone prolactin. If so, even typical prolactin levels can lead to galactorrhea.

**Galactorrhea in males**

In people assigned male at birth, galactorrhea may be linked with too little of the hormone testosterone. Called male hypogonadism, this most often also causes breasts that are enlarged or tender, called gynecomastia. Not being able to get and keep an erection, called erectile dysfunction, and not wanting to have sex also are linked with too little testosterone.

**Risk factors**

Anything that triggers the release of the hormone prolactin can increase the risk of galactorrhea. Risk factors include:

* Certain medicines, illicit drugs and herbal supplements.
* Conditions that affect the pituitary gland, such as pituitary tumors that aren't cancer.
* Certain medical conditions, such as long-term kidney disease, spinal cord injury, injuries to the chest wall and underactive thyroid.
* A lot of touching and rubbing of the breasts.
* Stress.

**Diagnosis**

It can be hard to find the cause of galactorrhea because there are so many possible reasons for it.

Testing may involve:

* **A physical exam.** A healthcare professional may try to get some of the fluid from the nipple by gently squeezing the area around the nipple. This exam may include looking for breast lumps or other areas of thickened breast tissue.
* **A blood test.** This is to check the level of prolactin in your system. If your prolactin level is high, your healthcare professional may check your thyroid-stimulating hormone level, too.
* **A pregnancy test.** This is to rule out pregnancy as a cause of nipple discharge.
* **Diagnostic mammography, ultrasound or both.** You may have these imaging tests if your healthcare professional finds a breast lump or sees other breast or nipple changes during your physical exam.
* **MRI of the brain.** This is to check for a tumor or other issue of your pituitary gland if your blood test shows a high prolactin level.

**Treatment**

When needed, galactorrhea treatment aims to resolve the underlying cause.

Sometimes healthcare professionals can't find an exact cause of galactorrhea. Then you may have treatment if your nipple discharge bothers you. A medicine that blocks the effects of prolactin or lowers your body's prolactin level could help get rid of galactorrhea.

| **Underlying cause** | **Possible treatment** |
| --- | --- |
| Medicine use | Stop taking medicine, change dose or switch to another medicine. Change medicines only if your healthcare professional says it's OK to do so. |
| Underactive thyroid gland, called hypothyroidism | Take a medicine, such as levothyroxine (Levoxyl, Synthroid, others), to help your thyroid gland make enough hormones. This is called thyroid replacement therapy. |
| Pituitary tumor, called prolactinoma | Take a medicine to shrink the tumor or have surgery to remove it. |
| Unknown cause | Try a medicine, such as bromocriptine (Cycloset, Parlodel) or cabergoline, to lower your prolactin level and lessen or stop milky nipple discharge. Common side effects of these medicines include nausea, dizziness and headaches. |

**Lifestyle and home remedies**

Often, milky discharge linked with idiopathic galactorrhea goes away on its own. This is most likely if you don't handle your breasts a lot or take medicines that are known to cause nipple discharge.

To lessen breast stimulation:

* Try not to overdo touching the nipples during sexual activity.
* Avoid squeezing, pinching or otherwise handling your nipples.

**Outlook / Prognosis**

Galactorrhea often goes away without treatment. Avoiding things that cause galactorrhea is the best way to keep it from occurring. If a pituitary tumor is causing the condition, your healthcare provider may want you to have a yearly CT or MRI to look for signs of growth.

**When can I go back to my regular activities?**

Most people with galactorrhea don’t have to stop their regular activities. Some women use breast pads (absorbent liners placed in your bra) to contain milk leakage under their clothes.

**Prevention**

**Can galactorrhea be prevented?**

It’s difficult to prevent galactorrhea. The following tips could reduce your risk of developing it:

* Repeatedly stimulating your breasts and nipples.
* Conducting breast exams more often than one time per month.
* Wearing clothes that rub or scratch your breasts.

**What are the risk factors for galactorrhea?**

People at higher risk for galactorrhea include women between the ages of 20 to 35 and those who have previously given birth.

**Epidemiology**

* Prevalence Estimates:  
  Galactorrhea prevalence varies widely depending on the population studied and definitions used, ranging from about 5% to 32% of females in different reports. Some sources estimate that approximately 20% to 25% of women experience galactorrhea at some point in their lifetime.
* Population Variability:
  + Among women with polycystic ovary syndrome (PCOS), galactorrhea prevalence can be as high as 17%.
  + In unselected adult populations, the prevalence of non-pregnant hyperprolactinemia, a common cause of galactorrhea, is around 0.2%, with an incidence of about 13.8 cases per 100,000 person-years.
  + Hyperprolactinemia prevalence varies by clinical setting: approximately 0.4% in the general population, 5% in family planning clinics, 9% in women evaluated for amenorrhea, and up to 17% in women with PCOS.
* Age and Gender Distribution:
  + Galactorrhea predominantly affects women of reproductive age (15 to 50 years), most commonly between 20 and 35 years.
  + It can also occur in postmenopausal women, men, newborns (due to maternal hormone exposure), and adolescents of both sexes.
  + Prolactinomas, a frequent cause of galactorrhea, are more common in women aged 20 to 50 years, with a female-to-male ratio of about 10:1 before age 50; after 50, incidence is similar in both sexes.
* Clinical Significance:
  + Galactorrhea is the third most common breast complaint after breast masses and pain.
  + It is often associated with hyperprolactinemia, which can cause menstrual disturbances and infertility.
  + About 40% of hyperprolactinemia cases are idiopathic, while others are due to prolactin-secreting tumors (prolactinomas), medications, systemic diseases, or pituitary stalk lesions.

**DIFFERENTIAL DIAGNOSIS**

* Acromegaly
* Breast stimulation
* Bronchogenic carcinoma
* Burns
* Breast surgery
* Craniopharyngioma
* Cushing's disease
* Chest wall irritation
* Hypothyroidism
* Idiopathic
* Lymphoma
* Molar pregnancy
* Meds and herbs
* Pituitary adenomas
* Renal failure
* Sarcoid
* TB

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**Metabolic syndrome**

Metabolic syndrome is a group of conditions that together increase your risk of cardiovascular disease, Type 2 diabetes and stroke. It can lead to other health problems as well, like conditions related to plaque buildup in artery walls (atherosclerosis) and organ damage.

Other names for metabolic syndrome include:

* Syndrome X.
* Insulin resistance syndrome.
* Dysmetabolic syndrome.

**Criteria for metabolic syndrome**

A person meets the criteria for metabolic syndrome if they have at least three of the following:

* **Excess abdominal weight**: A waist circumference of more than 40 inches in males and 35 inches in females
* **Hypertriglyceridemia**: Triglyceride levels that are 150 milligrams per deciliter of blood (mg/dL) or greater.
* **Low levels of HDL cholesterol**: HDL cholesterol of less than 40 mg/dL in males or less than 50 mg/dL in females.
* **Elevated blood sugar levels**: Fasting blood sugar level of 100 mg/dL or greater. If it’s 100 to 125 mg/dL, you have prediabetes. If it’s over 125 mg/dL, you likely have Type 2 diabetes.
* **High blood pressure**: Blood pressure values of systolic 130 mmHg or higher (the top number) and/or diastolic 85 mmHg or higher (the bottom number).

All of these conditions individually increase your risk of cardiovascular disease, Type 2 diabetes and stroke. But when you have three or more, your risk increases significantly. You should see a diagnosis of metabolic syndrome as a warning sign to try to change aspects of your health to lower your risk.

Metabolic syndrome is common in the United States. About 1 out of every 3 adults have it.

**Symptoms and Causes**

**Symptoms of metabolic syndrome**

Not all aspects of metabolic syndrome cause symptoms. So, your symptoms will vary based on which of the five conditions you have. For example, high blood pressure, high triglycerides and low HDL cholesterol usually don’t cause symptoms.

High blood sugar (hyperglycemia) can cause symptoms for some people, like:

* Darkened skin in your armpits or the back and sides of your neck (acanthosis nigricans).
* Blurred vision.
* Increased thirst (polydipsia).
* Increased urination, especially at night.
* Fatigue.

See a healthcare provider if you have these symptoms.

**What causes metabolic syndrome?**

Several factors contribute to the development of metabolic syndrome — and it’s a complex web of factors. But researchers think insulin resistance is the main driver behind the syndrome.

Insulin resistance happens when cells in your muscles, fat and liver don’t respond as they should to insulin, a hormone your pancreas makes that’s essential for life and regulating blood glucose (sugar) levels.

For several reasons, your muscle, fat and liver cells can respond inappropriately to insulin. This means they can’t efficiently take up glucose from your blood or store it. This is insulin resistance. As a result, your pancreas makes more insulin to try to overcome your increasing blood glucose levels. This is called hyperinsulinemia.

If your body can’t produce enough insulin to effectively manage your blood sugar, it leads to high blood sugar (hyperglycemia) and prediabetes or Type 2 diabetes. Insulin resistance and hyperinsulinemia can also contribute to:

* Obesity.
* Cardiovascular disease.
* Fatty liver disease.
* Polycystic ovary syndrome (PCOS).

The following can all contribute to insulin resistance:

* **Excess weight around your abdomen or having obesity**: Body fat releases chemicals (called proinflammatory cytokines) that dampen the effect of insulin. The more excess body fat you have, the more it can negatively affect how insulin works. Studies show that excess body fat around your abdomen, in particular, increases your risk of insulin resistance. Excess visceral fat (fat around your organs) causes more insulin resistance than excess subcutaneous fat (fat under your skin). But they both play a role in metabolic syndrome.
* **Lack of physical activity**: Your muscles use a lot of glucose and stored glucose (glycogen) to function. Physical activity makes your body more sensitive to insulin and builds muscle that can absorb more blood glucose. A lack of physical activity can have opposite effects and cause insulin resistance.
* **Certain medications**: Certain medications can cause insulin resistance, including corticosteroids, some blood pressure medications, certain HIV treatments and some psychiatric medications.
* **Genetics**: The genes you inherited from your biological parents can contribute to insulin resistance. They can also contribute to having obesity, high blood pressure and high cholesterol.

**Diagnosis and Tests**

Metabolic syndrome increases your risk of cardiovascular disease, Type 2 diabetes and stroke. You have metabolic syndrome if you meet at least three of the criteria.

**How is metabolic syndrome diagnosed?**

A healthcare provider will do a physical exam and order blood tests if they think you might be at risk for or have metabolic syndrome. They’ll check your blood pressure and may measure the circumference around your waist.

They’ll order blood tests, like:

* **Lipid panel**: This panel includes four different cholesterol measurements and a measurement of your triglycerides.
* **Basic metabolic panel (BMP)**: This panel measures eight substances in your blood and gives an overall view of your health.
* **Fasting glucose test**: A BMP includes a blood glucose reading, but if you didn’t fast for the BMP, your provider may have you get a blood test that checks your blood sugar after fasting for eight to 12 hours.

If you have at least three of the five criteria based on the results of these tests and the exam, you’ll have metabolic syndrome.

These blood tests are typically routine tests. So, your provider may tell you that you have metabolic syndrome (or are at risk for certain health conditions) after routine tests.

**Management and Treatment**

The main goals of treating metabolic syndrome are to lower your risk of heart disease and Type 2 diabetes if you don’t already have them. Treatment can involve medications and/or lifestyle changes.

**Lifestyle changes to manage metabolic syndrome**

Lifestyle changes are key to managing the conditions that contribute to metabolic syndrome. Changes include:

* **Maintaining or working toward a weight that’s healthy for you**: Your healthcare provider may recommend trying to lose excess weight. One study revealed that losing 7% of excess weight can reduce the onset of Type 2 diabetes by 58%.
* **Getting regular exercise**: Physical activity has numerous benefits. It helps combat insulin resistance, can help keep your cardiovascular system healthy and may help you lose weight if needed. Any increase in physical activity is helpful. But before starting an exercise program, ask your provider about what level of physical activity is right for you.
* **Eating heart-healthy foods**: Your provider or nutritionist may recommend avoiding eating excessive amounts of carbohydrates (which stimulate excess insulin production) and eating less unhealthy fat, sugar, red meats and processed starches. Instead, they’ll likely recommend eating a diet of whole foods that includes more vegetables, fruits, whole grains, fish and lean poultry. The Mediterranean diet is one example of a heart-healthy diet.
* **Getting quality sleep**: Quality sleep is vital to overall health. A lack of sleep and sleeping disorders (like sleep apnea) can worsen metabolic syndrome or contribute to its development. If you’re having problems sleeping, talk to your healthcare provider. They can do tests and suggest treatments or changes to your sleeping routine.
* **Avoiding or quitting smoking**: Smoking can decrease your HDL cholesterol and increase blood pressure. It also damages your blood vessels, which can lead to coronary artery disease. If you smoke, try to quit.
* **Managing stress**: High levels of cortisol (the “stress hormone”) over long periods of time can increase triglycerides, blood sugar and blood pressure. Find strategies to manage your stress, like exercise, yoga, mindfulness or breathing exercises.

**Medications and treatments for managing metabolic syndrome**

Various medications and treatments can help manage the conditions that contribute to metabolic syndrome. They include:

* **Cholesterol medications**: Statins (HMG CoA reductase inhibitors) are prescription medicines that people take to bring their cholesterol down to healthy levels.
* **Blood pressure medications**: These medications (antihypertensives) are prescription medicines that bring your blood pressure down in various ways. Examples include thiazide, ACE inhibitors and calcium channel blockers.
* **Oral diabetes medications**: These medications work in various ways to lower your blood sugar. The most common medication is metformin, a biguanide.
* **Bariatric surgery**: Bariatric surgery (weight loss surgery) is a category of surgical operations intended to help people with obesity lose weight. Your provider may recommend bariatric surgery if other weight loss methods haven’t worked and if obesity poses a greater risk to your health than surgery.
* **Sleeping disorder treatments**: If you have a sleeping disorder, certain treatments can help, like a CPAP machine for sleep apnea or sleeping pills for insomnia.
* **Psychotherapy**: “Psychotherapy” (talk therapy) is a term for a variety of treatment techniques that aim to help a person identify and change unhealthy emotions, thoughts and behaviors. Psychotherapy may help you manage stress or understand and change unhealthy behaviors related to eating, for example.

**Can you reverse metabolic syndrome?**

Yes, it’s possible to reverse metabolic syndrome. Lifestyle changes can do a lot to improve your health. Medications can help as well. Your healthcare provider will work with you to find the best plan for you.

**Outlook / Prognosis**

Metabolic syndrome can lead to a wide range of complications, including:

* Heart disease.
* Aortic stenosis (when the aortic valve in your heart narrows and blood can’t flow normally).
* Atrial fibrillation (Afib).
* Thromboembolic disease, like venous thromboembolism.
* Stroke.
* Organ damage, especially damage to your pancreas, liver, gallbladder and kidneys.
* Certain cancers, like colon cancer, breast cancer and prostate cancer.
* Type 2 diabetes.
* Long-term inflammation and problems with your immune system.
* Erectile dysfunction.
* Pregnancy complications, such as preeclampsia, eclampsia and gestational diabetes.
* Issues with thinking and memory.

The good news is that it’s possible to reverse metabolic syndrome with lifestyle changes and medications. The sooner you can make changes to protect your health, the better.

**Prevention**

You can’t change all the factors that contribute to metabolic syndrome, like your genetics and age. But the lifestyle changes that can help treat metabolic syndrome are the same steps that can help prevent it.

If you have a family history of diabetes, high blood pressure or high cholesterol, be sure to tell your healthcare provider.

It’s also important to schedule routine provider visits. Your provider can keep track of your cholesterol, triglyceride, blood pressure and blood sugar levels. The sooner they can catch any issues, the sooner they can recommend lifestyle changes and treatments to reduce your risk.

**Living With**

**When should I see my healthcare provider?**

If you have metabolic syndrome, it’s important to get ongoing care. You should see your healthcare provider for the following:

* **To monitor the condition**: You may need to measure your blood pressure regularly or have routine blood tests to monitor your triglyceride and cholesterol levels. Be sure to keep all of your healthcare appointments.
* **For questions about your treatment plan**: Tell your provider if you have side effects from your medications or if you want to stop taking them. Also, ask any questions about lifestyle changes, like diet or exercise plans.

**DIFFERENTIAL DIAGNOSIS**

Metabolic syndrome is a combination of different atherosclerotic cardiovascular disease risk factors—the secondary causes of each are a component of the differential diagnosis. Renal parenchymal diseases, renovascular diseases, endocrine disorders, and coarctation of the aorta can be considered. Hypothyroidism is one of the causes of hypertension, dyslipidemia, and obesity, so it is regarded as a close differential of metabolic syndrome. The other differential diagnoses may include polycystic ovarian syndrome, pheochromocytoma, Cushing syndrome, and acromegaly

1. Obesity Without Metabolic Syndrome
   * Simple obesity may present with increased waist circumference but lacks the full constellation of metabolic abnormalities such as insulin resistance, dyslipidemia, or hypertension.
2. Type 2 Diabetes Mellitus (T2DM) Alone
   * T2DM may present with hyperglycemia and insulin resistance but without other components like hypertension or dyslipidemia.
3. Hypertension (Essential or Secondary)
   * Hypertension alone can occur without accompanying metabolic abnormalities.
4. Dyslipidemia Disorders
   * Familial hypertriglyceridemia or familial low HDL cholesterol can mimic parts of metabolic syndrome but may lack insulin resistance or obesity.
5. Endocrine Disorders Causing Metabolic Abnormalities
   * Cushing’s syndrome: Causes central obesity, hypertension, glucose intolerance, and dyslipidemia.
   * Hypothyroidism: Can cause weight gain, dyslipidemia, and hypertension.
   * Polycystic Ovary Syndrome (PCOS): Shares features of insulin resistance, obesity, and dyslipidemia.
   * Acromegaly: Can cause insulin resistance and hypertension.
6. Lipodystrophy Syndromes
   * Characterized by abnormal fat distribution and severe insulin resistance, sometimes mimicking metabolic syndrome.
7. Chronic Kidney Disease (CKD)
   * May present with hypertension, dyslipidemia, and insulin resistance.
8. Medications-Induced Metabolic Changes
   * Certain drugs (e.g., corticosteroids, antipsychotics, protease inhibitors) can cause weight gain, insulin resistance, and dyslipidemia.
9. Inflammatory and Autoimmune Diseases
   * Chronic inflammation can contribute to insulin resistance and metabolic abnormalities.

**EPIDEMIOLOGY**

The global incidence of metabolic syndrome rises almost parallel to the incidence of obesity. According to the National Health and Nutrition Examination Survey (NHNES), the prevalence of metabolic syndrome in adults increased from 25.3% to 34.2% in 2012. The survey further revealed that the South Asian American population had a very high incidence of metabolic syndrome, albeit a lower prevalence of obesity as compared to non-Hispanic white men and women. The prevalence of metabolic syndrome peaked at the start of the 21st century in the United States. The prevalence gradually decreased due to early diagnosis and proper treatment of dyslipidemia and hypertension (although the prevalence of obesity was increasing). In the 2009-2010 NHNES report, the prevalence of metabolic syndrome was 22% in women and 24% in men.

In Europe and Latin America, around one-fourth of the general population is reported to have metabolic syndrome. The incidence of metabolic syndrome in China has also increased over the last 3 decades. However, it is lower than in the United States and was estimated to reach 15.5% in 2017. Metabolic syndrome is no longer a disease of the adult population; this condition is also reported to involve children and adolescents. In 2020, 3% of children and 5% of adolescents were found to have metabolic syndrome globally. The incidence of metabolic syndrome is slightly higher in children of low-income countries, which suggests the high economy of the country is not a predictor of metabolic syndrome. The prevalence of metabolic syndrome increases with increasing age; almost 40% of people have metabolic syndrome in the 6th decade of their lives. Although metabolic syndrome involves both men and women equally, it is slightly more prevalent in women than men in certain ethnic groups.

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**NEUROENDOCRINE TUMOR**

Neuroendocrine tumors are cancers that begin in specialized cells called neuroendocrine cells. Neuroendocrine cells have traits similar to those of nerve cells and hormone-producing cells.

Neuroendocrine tumors are rare and can occur anywhere in the body. Most neuroendocrine tumors occur in the lungs, appendix, small intestine, rectum and pancreas.

There are many types of neuroendocrine tumors. Some grow slowly and some grow very quickly. Some neuroendocrine tumors produce excess hormones (functional neuroendocrine tumors). Others don't release hormones or don't release enough to cause symptoms (nonfunctional neuroendocrine tumors).

Diagnosis and treatment of neuroendocrine tumors depend on the type of tumor, its location, whether it produces excess hormones, how aggressive it is and whether it has spread to other parts of the body.

**Types**

Adrenal cancer

Carcinoid tumors

Merkel cell carcinoma

Pancreatic neuroendocrine tumors

Paraganglioma

Pheochromocytoma

**Symptoms**

Neuroendocrine tumors don't always cause signs and symptoms at first. The symptoms you might experience depend on the location of your tumor and whether it produces excess hormones.

In general, neuroendocrine tumor signs and symptoms might include:

* Pain from a growing tumor
* A growing lump you can feel under the skin
* Feeling unusually tired
* Losing weight without trying

Neuroendocrine tumors that produce excess hormones (functional tumors) might cause:

* Skin flushing
* Diarrhea
* Frequent urination
* Increased thirst
* Dizziness
* Shakiness
* Skin rash

**When to see a doctor**

Make an appointment with your doctor if you have any persistent signs and symptoms that worry you.

**Causes**

The exact cause of neuroendocrine tumors isn't known. These cancers begin in neuroendocrine cells that have traits similar to those of nerve cells and hormone-producing cells. Neuroendocrine cells are found throughout your body.

Neuroendocrine tumors begin when neuroendocrine cells develop changes (mutations) in their DNA. The DNA inside a cell contains the instructions that tell the cell what to do. The changes tell the neuroendocrine cells to multiply rapidly and form a tumor.

Some neuroendocrine tumors grow very slowly. Others are aggressive cancers that invade and destroy normal body tissue or spread (metastasize) to other parts of the body.

**Risk factors**

The risk of neuroendocrine tumors is higher in people who inherit genetic syndromes that increase the risk of cancer. Examples include:

* Multiple endocrine neoplasia, type 1 (MEN 1)
* Multiple endocrine neoplasia, type 2 (MEN 2)
* Von Hippel-Lindau disease
* Tuberous sclerosis
* Neurofibromatosis

**Diagnosis**

The tests and procedures you might undergo to diagnose a neuroendocrine tumor will depend on where your tumor is located in your body. In general, tests might include:

* **Physical exam.** Your doctor may examine your body to better understand your signs and symptoms. He or she may feel for swollen lymph nodes or look for signs that a tumor is producing excess hormones.
* **Tests to look for excess hormones.** Your doctor may recommend testing your blood or your urine for signs of excess hormones that are sometimes produced by neuroendocrine tumors.
* **Imaging tests.** You might undergo imaging tests, such as ultrasound, CT and MRI, to create pictures of your tumor. For neuroendocrine tumors, pictures are sometimes created using positron emission tomography (PET) with a radioactive tracer that's injected into a vein.
* **Procedures to remove a sample of cells for testing (biopsy).** To collect the cells, the doctor might insert a long, thin tube with a light and a camera on the end into your lungs (bronchoscopy), your esophagus (endoscopy) or your rectum (colonoscopy), depending on your situation. Sometimes, collecting a tissue sample requires surgery.

If there's a risk that your neuroendocrine tumor may have spread to other parts of your body, you might have additional tests to determine the extent of the cancer.

**Treatment**

The treatment options for your neuroendocrine tumor will depend on the type of tumor, its location, and whether you're experiencing signs and symptoms of excess hormones produced by the tumor.

In general, neuroendocrine tumor treatment options might include:

* **Surgery.** Surgery is used to remove the tumor. When possible, surgeons work to remove the entire tumor and some of the healthy tissue that surrounds it. If the tumor can't be removed completely, it might help to remove as much of it as possible.
* **Chemotherapy.** Chemotherapy uses strong drugs to kill tumor cells. It can be given through a vein in your arm or taken as a pill. Chemotherapy might be recommended if there's a risk that your neuroendocrine tumor might recur after surgery. It might also be used for advanced tumors that can't be removed with surgery.
* **Targeted drug therapy.** Targeted drug treatments focus on specific abnormalities present within tumor cells. By blocking these abnormalities, targeted drug treatments can cause tumor cells to die. Targeted drug therapy is usually combined with chemotherapy for advanced neuroendocrine tumors.
* **Peptide receptor radionuclide therapy (PRRT).** PRRT combines a drug that targets cancer cells with a small amount of a radioactive substance. It allows radiation to be delivered directly to the cancer cells. One PRRT drug, lutetium Lu 177 dotatate (Lutathera), is used to treat advanced neuroendocrine tumors.
* **Medications to control excess hormones.** If your neuroendocrine tumor releases excess hormones, your doctor might recommend medications to control your signs and symptoms.
* **Radiation therapy.** Radiation therapy uses powerful energy beams, such as X-rays and protons, to kill tumor cells. Some types of neuroendocrine tumors may respond to radiation therapy. It might be recommended if surgery isn't an option.

Other treatments might be available to you depending on your particular situation and your specific type of neuroendocrine tumor.

## **Outlook / Prognosis**

NETs are often mistaken for other less serious conditions, so it may take some time before you’re diagnosed. Once you learn you have a neuroendocrine tumor, your prognosis, or expected outcome, depends on several factors, including the type of NET you have and whether your tumor has spread. On average, an estimated 39% of people with NETs are alive five years after diagnosis.

But statistics on life expectancy and survival rates vary. For example, the average survival rate for people with NETs that haven’t spread is as high as 30 years. Your healthcare provider can explain what factors shape your outlook.

In the meantime, keep in mind that finishing treatment is a major milestone but not the end of your NET journey. NETs can grow very slowly and recur (return) after treatment, so your healthcare provider will want to track your well-being for several years.

### **Can a neuroendocrine tumor be cured?**

NETs are curable when your healthcare provider can remove all signs of the tumor with surgery. But one of the biggest challenges with this diagnosis is that although most NETs are slow-growing, they’ve often spread by the time they’re caught.

At this point, treatment can help slow tumor growth and provide symptom relief.

## **Prevention**

### **Can I prevent neuroendocrine tumors?**

As researchers don’t know what causes NETs, there’s nothing you can do to prevent them. Still, you can understand potential risk factors, like having an inherited condition like multiple endocrine neoplasia (MEN).

Ask your healthcare provider for help understanding whether your family health history puts you at risk of developing NETs.

## **Living With**

Neuroendocrine tumors and their treatment can take a toll on your body. You may have to manage common symptoms like fatigue — feeling extremely tired day after day — and diarrhea throughout your treatment. Try to get as much rest as you can. If diarrhea is an issue, talk to your healthcare provider about ways to reduce its frequency and severity.

Here are some other suggestions that might be helpful:

* Join support groups: Cancer can be lonely, and uncommon cancers can be lonelier still. Talk to your healthcare providers about support groups so you can connect with people who understand what you’re going through.
* Eat healthy foods and well-balanced meals: If NET symptoms and treatment side effects make eating difficult, ask a dietitian for suggestions on finding foods that will help you keep up your strength.
* Seek emotional support: If you’re having a hard time emotionally, ask your provider about mental health services that can help.
* Drink alcohol responsibly: Alcohol can trigger some NET side effects, including carcinoid syndrome. Ask your provider about drinking alcohol in moderation.

**DIFFERENTIAL DIAGNOSIS**

## 1. Well-Differentiated Neuroendocrine Tumors (WDNETs) vs Poorly Differentiated Neuroendocrine Carcinomas (PDNECs)

* WDNETs:
  + Typically low to intermediate grade (G1-G3) with organoid architecture, “salt and pepper” chromatin, and lower mitotic/Ki-67 proliferation indices.
  + Molecular markers such as loss of DAXX or ATRX expression support WDNET diagnosis (especially pancreatic NETs).
  + Retained p53 and Rb expression.
* PDNECs:
  + High-grade, poorly differentiated tumors often with small cell or large cell morphology.
  + High mitotic rate (>20/10 HPF) and Ki-67 index (>20%, often >50%).
  + Abnormal p53 expression and loss of Rb expression.
  + May be admixed with non-neuroendocrine carcinoma components (adenocarcinoma or squamous cell carcinoma).
* Importance: Differentiation is critical due to differing prognosis and treatment.

2. Neuroendocrine Neoplasms of the Larynx

* Differential diagnosis includes:
  + Carcinoid tumors (typical and atypical)
  + Small cell neuroendocrine carcinoma
  + Large cell neuroendocrine carcinoma
  + Squamous cell carcinoma with neuroendocrine differentiation
  + Paraganglioma (non-epithelial neuroendocrine tumor)
  + Medullary thyroid carcinoma (when involving the larynx region)
* Morphologic and immunohistochemical features help distinguish these entities.

3. Other Tumors to Consider in Differential Diagnosis

* Paragangliomas:
  + Arise from paraganglia, usually non-epithelial, may mimic NETs but have distinct immunoprofile (e.g., sustentacular cells positive for S100).
* Medullary Thyroid Carcinoma:
  + Neuroendocrine tumor of thyroid origin, can be confused with NET metastasis or primary laryngeal NETs.
* Non-neuroendocrine carcinomas with neuroendocrine features:
  + Squamous cell carcinoma or adenocarcinoma with focal neuroendocrine differentiation.
* Other epithelial, mesenchymal, and neuroectodermal tumors:
  + Depending on site, differential diagnosis may include melanoma, lymphoma, sarcomas, and others.

4. Diagnostic Tools to Aid Differential Diagnosis

* Histopathology: Cell morphology, growth patterns, necrosis, mitotic activity.
* Immunohistochemistry (IHC):
  + Neuroendocrine markers: Chromogranin A, synaptophysin, CD56.
  + Proliferation markers: Ki-67 index.
  + Tumor suppressors and oncogenes: p53, Rb, DAXX, ATRX.
  + Site-specific markers (e.g., calcitonin for medullary thyroid carcinoma).
* Molecular testing: May help distinguish WDNET from PDNEC.
* Imaging and clinical correlation: Functional imaging (e.g., somatostatin receptor PET/CT), biochemical markers (chromogranin A, 5-HIAA), and clinical presentation.

## **Epidemiology of Neuroendocrine Tumors (NETs)**

* Incidence and Prevalence
  + The worldwide incidence of neuroendocrine neoplasms (NENs), including NETs, is estimated at about 6 per 100,000 persons annually, with a prevalence of approximately 35 per 100,000.
  + The incidence of NETs has been steadily increasing over recent decades, with reports of a 6-fold rise over the last 40 years in many countries.
  + For gastroenteropancreatic (GEP) NETs specifically, incidence rates rose from around 2.4 -- 3.6 per 100,000 in the 1970s–2000s to 5–8 per 100,000 by 2015–2018 in North America and Europe.
  + The increase is attributed partly to improved diagnostic techniques (advanced imaging and pathology) but may also involve environmental and biological factors.
* Geographic Variation
  + Incidence varies by region:
    - North America: Incidence of GEP NETs around 3.5 to 8.3 per 100,000; most common sites are small intestine and rectum.
    - Europe: Incidence ranges from 2.5 to 8.6 per 100,000, with small intestine and pancreas as common sites.
    - Asia: Lower incidence (~1.1 to 3 per 100,000), with rectal and pancreatic NETs predominating.
    - China: Age-standardized incidence of NENs is about 1.14 per 100,000, with pancreas, stomach, and rectum as common sites.
    - Iceland: Incidence around 3.4 to 3.9 per 100,000.
* Common Primary Sites
  + The most frequent primary tumor sites differ by region but generally include:
    - Small intestine, rectum, pancreas, stomach, and lungs.
    - In North America and Europe, small intestine and pancreas predominate.
    - In Asia, rectal and pancreatic NETs are most common.
* Demographics
  + NETs can occur at any age but are more common in middle-aged and older adults, with appendiceal NETs often occurring after age 50.
  + Males tend to have higher incidence rates and more aggressive forms in some regions (e.g., pancreatic NETs).
  + Survival rates have improved over time, with females generally showing better overall survival than males.
* Trends
  + The rising incidence is seen globally, especially in North America and Europe, possibly due to better detection and awareness, but other factors are likely involved.
  + The prevalence is increasing due to improved survival and earlier diagnosis.

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**HIGH AND LOW CHOLESTEROL**

Cholesterol is a waxy substance found in the blood. The body needs cholesterol to build healthy cells. But high levels of cholesterol can raise the risk of heart disease.

With high cholesterol, fats and other substances can build up in blood vessels called arteries. This buildup is called plaque. As more plaque forms over time, the arteries can become narrowed or clogged. That makes it hard for enough blood to flow through the arteries. Sometimes a piece of plaque can break loose and form a blood clot. The clot may cause a heart attack or stroke.

High cholesterol can be inherited. That means it can pass from parents to children through genes. But high cholesterol often is the result of lifestyle choices such as not getting enough exercise, not eating a balanced diet or consuming large amounts of saturated fat. You can make changes to help prevent it. And if you have high cholesterol, you can help lower it with a healthy diet, regular exercise and sometimes medicine.

**Symptoms**

High cholesterol has no symptoms. A blood test is the only way to find out if you have it.

**When to see a doctor**

The American Heart Association recommends that children get checked, also called screened, for high cholesterol once between ages 9 and 11. Screening may start earlier if a child has a family history of high cholesterol, heart attack or stroke. Screening also may start earlier if a child has conditions such as diabetes or obesity.

The next cholesterol screening is recommended for people between ages 17 and 21. After that, many adults get their cholesterol checked every 4 to 6 years. People who have health conditions such as high blood pressure and diabetes may need to get screened more often. So might those who take cholesterol-lowering medicine. Those who have a family history of high cholesterol or heart disease also may need more-frequent screenings.

If your test results aren't within the desirable range, your healthcare professional might recommend more-frequent testing as well.

**Causes**

Lifestyle factors that may be within your control are the most common cause of high cholesterol. These factors include eating a diet high in saturated and trans fats and not getting enough exercise.

Sometimes factors that aren't within your control can lead to high cholesterol. These include gene changes that pass from parents to children, some health conditions, and some medicines.

Conditions that can cause high cholesterol include:

* Familial hypercholesterolemia.
* Chronic kidney disease.
* Chronic liver disease.
* Diabetes.
* HIV/AIDS.
* Hypothyroidism.
* Lupus.
* Overweight and obesity.
* Sleep apnea.

Some types of medicines taken for other health conditions also can make cholesterol levels worse. These include treatments for:

* Acne.
* Cancer.
* High blood pressure.
* HIV/AIDS.
* Irregular heartbeats.
* Organ transplants.

Cholesterol travels through the blood, attached to proteins. This mix of proteins and cholesterol is called lipoprotein. There are various types of cholesterol. The types are based on what the lipoprotein carries. They are:

* **Low-density lipoprotein (LDL) cholesterol.** This is known as the "bad" cholesterol. LDL carries cholesterol particles throughout the body. "Bad" cholesterol builds up in the walls of arteries. This makes the arteries hard and narrow.

When a gene change causes high cholesterol, the body has trouble removing LDL cholesterol from the blood. Or the body has trouble breaking down LDL cholesterol in the liver.

* **High-density lipoprotein (HDL) cholesterol.** This is known as the "good" cholesterol. HDL picks up extra cholesterol and takes it back to the liver.

Most often, a blood test to check cholesterol levels also measures a type of fat in the blood that is not a type of cholesterol, called triglycerides. Having a high triglyceride level also can raise the risk of heart disease. Lifestyle factors that you may be able to control play a role in triglyceride levels.

**Risk factors**

Risk factors for high cholesterol levels include:

* **Eating habits.** Eating too much saturated fat or trans fats can lead to high cholesterol. Saturated fats are found in fatty cuts of meat and full-fat dairy products. Sometimes trans fats are found in packaged snacks or desserts.
* **Obesity.** This complex disease involves having too much body fat.
* **Lack of exercise.** Exercise helps boost the body's "good" HDL cholesterol.
* **Smoking.** Cigarette smoking may lower the level of HDL.
* **Alcohol.** Drinking lots of alcohol can raise total cholesterol. Try to limit alcohol to up to one drink a day for women and up to two drinks a day for men.
* **Age.** Even young children can have high cholesterol. But it's much more common in people over 40. As you age, your liver becomes less able to remove "bad" LDL cholesterol.

**COMPLICATIONS**

High cholesterol can lead to other health conditions called complications. With high cholesterol, a dangerous amount of plaque can build up on the walls of arteries. This is called atherosclerosis. Over time, the plaque buildup can cause arteries to narrow and block blood flow. Less blood flow through the arteries can cause complications such as:

* **Chest pain, also called angina.** If the arteries that supply the heart with blood are affected, that may cause chest pain. It also may cause other symptoms of a common type of heart disease called coronary artery disease.
* **Heart attack.** If plaques tear or break, a blood clot can form. The clot may block the flow of blood at the site where it broke. Or it may completely break free and block an artery farther away. If blood flow to part of the heart stops, a heart attack happens. A heart attack is an emergency that needs treatment right away.
* **Stroke.** A stroke happens when a blood clot blocks blood flow to part of the brain. It's also an emergency that needs treatment right away.

**Prevention**

The same heart-healthy lifestyle changes that can lower cholesterol also can help prevent high cholesterol. You can practice the following habits:

* Eat a diet that focuses on lean protein, fruits, vegetables and whole grains. Limit sodium and added sugar.
* Also limit the amount of saturated and trans fats you eat. Instead, eat foods with healthy fats such as fatty or oily fish, nuts, and olive or canola oil.
* Lose extra weight and keep it off.
* If you smoke, ask your care team to help you quit.
* Exercise on most days of the week for at least 30 minutes.
* Drink less alcohol, if at all. Limit alcohol to no more than up to one drink a day for women and up to two drinks a day for men.

**Diagnosis**

Diagnosis involves the steps that your healthcare professional takes to find out if you have high cholesterol. You receive a blood test to check cholesterol levels. You might hear the blood test called a lipid panel or a lipid profile. The results of the test usually show your:

* Total cholesterol.
* Low-density lipoprotein (LDL) cholesterol.
* High-density lipoprotein (HDL) cholesterol.
* Triglycerides.

In general, you can't have food or liquids other than water for around 9 to 12 hours before the test. This is called fasting. Some cholesterol tests don't require fasting, so follow your healthcare professional's instructions.

**Interpreting the numbers**

In the United States, cholesterol levels are measured in milligrams (mg) of cholesterol per deciliter (dL) of blood. In Canada and many European countries, cholesterol levels are measured in millimoles per liter (mmol/L). To interpret your test results, use these general guidelines.

| **Total cholesterol (U.S. and some other countries)** | **Total cholesterol\* (Canada and most of Europe)** | **Results** |
| --- | --- | --- |
| \*Canadian and European guidelines differ slightly from U.S. guidelines. These conversions are based on U.S. guidelines. | | |
| Below 200 mg/dL | Below 5.2 mmol/L | Desirable |
| 200-239 mg/dL | 5.2-6.2 mmol/L | Borderline high |
| 240 mg/dL and above | Above 6.2 mmol/L | High |
| **LDL cholesterol (U.S. and some other countries)** | **LDL cholesterol\* (Canada and most of Europe)** | **Results** |
| \*Canadian and European guidelines differ slightly from U.S. guidelines. These conversions are based on U.S. guidelines. | | |
| Below 70 mg/dL | Below 1.8 mmol/L | Desirable for people who have coronary artery disease or other forms of atherosclerosis. Optimal for people at high risk or very high risk of coronary artery disease or other forms of atherosclerosis. In some people the desired value could be below 55 mg/dL. |
| Below 100 mg/dL | Below 2.6 mmol/L | Optimal for healthy people without coronary artery disease or other forms of atherosclerosis. |
| 100-129 mg/dL | 2.6-3.3 mmol/L | Near optimal for people who do not have coronary artery disease or other forms of atherosclerosis. High if there is coronary artery disease or other forms of atherosclerosis. |
| 130-159 mg/dL | 3.4-4.1 mmol/L | Borderline high for people who do not have coronary artery disease or other forms of atherosclerosis. High if there is coronary artery disease or other forms of atherosclerosis. |
| 160-189 mg/dL | 4.1-4.9 mmol/L | High for people who do not have coronary artery disease. Very high if there is coronary artery disease or other forms of atherosclerosis. |
| 190 mg/dL and above | Above 4.9 mmol/L | Very high. |
| **HDL cholesterol (U.S. and some other countries)** | **HDL cholesterol\* (Canada and most of Europe)** | **Results** |
| \*Canadian and European guidelines differ slightly from U.S. guidelines. These conversions are based on U.S. guidelines. | | |
| Below 40 mg/dL, men | Below 1.0 mmol/L, men | Low |
| Below 50 mg/dL, women | Below 1.3 mmol/L, women |
| 40-59 mg/dL, men | 1-1.5 mmol/L, men | Better |
| 50-59 mg/dL, women | 1.3-1.5 mmol/L, women |
| 60 mg/dL and above | Above 1.5 mmol/L | Best |
| **Triglycerides (U.S. and some other countries)** | **Triglycerides\* (Canada and most of Europe)** | **Results** |
| \*Canadian and European guidelines differ slightly from U.S. guidelines. These conversions are based on U.S. guidelines. | | |
| Below 150 mg/dL | Below 1.7 mmol/L | Desirable |
| 150-199 mg/dL | 1.7-2.2 mmol/L | Borderline high |
| 200-499 mg/dL | 2.3-5.6 mmol/L | High |
| 500 mg/dL and above | Above 5.6 mmol/L | Very high |

**Children and cholesterol testing**

The American Heart Association recommends that children get checked, also called screened, for high cholesterol once between ages 9 and 11. Screening may start earlier if a child has a family history of high cholesterol, heart attack or stroke. Screening also may start earlier if a child has conditions such as diabetes or obesity. The next cholesterol screening is recommended between ages 17 and 21.

**Treatment**

Treatment choices to reach ideal cholesterol and triglyceride levels should be tailored to meet your needs. Talk with your healthcare professional about what levels are best for you.

Treatment for high cholesterol can include medicine. Together with healthy lifestyle changes, medicine can lower the risk of heart attacks and strokes.

You may benefit from one or more medicines. It depends on things such as your risk factors, age, health and possible medicine side effects. Your healthcare professional helps choose the right treatments for you.

Common cholesterol medicines include:

**Statins**

Statins block a substance that the liver needs to make cholesterol. This causes the liver to make less cholesterol and to remove cholesterol from the blood.

Statin choices include:

* Atorvastatin (Lipitor).
* Fluvastatin (Lescol XL).
* Lovastatin (Altoprev).
* Pitavastatin (Livalo, Zypitamag).
* Pravastatin.
* Rosuvastatin (Crestor).
* Simvastatin (Zocor).

**Cholesterol absorption inhibitors**

The small intestine absorbs the cholesterol from food and releases it into the bloodstream. The medicine ezetimibe (Zetia) helps lower the amount of cholesterol absorbed from food. Your healthcare professional may prescribe ezetimibe with a statin.

**Bempedoic acid**

Bempedoic acid (Nexletol) works in much the same way as statins. Your healthcare professional may prescribe it if statins cause serious side effects for you. Adding bempedoic acid to a statin can help lower LDL. A pill that contains both bempedoic acid and ezetimibe, called Nexlizet, also is available.

**Bile acid sequestrants**

The liver uses cholesterol to make bile acids. The body needs these substances for digestion. Bile acid sequestrants bind to bile acids. This prompts the liver to use extra cholesterol to make more bile acids. In turn, that lowers the level of cholesterol in the blood.

Bile acid sequestrants include cholestyramine (Prevalite), colesevelam (Welchol) and colestipol (Colestid).

**PCSK9 inhibitors**

These medicines can help the liver absorb more LDL cholesterol. This lowers the amount of cholesterol in the blood. Alirocumab (Praluent), evolocumab (Repatha) or inclisiran (Leqvio) might be used for people who have a genetic condition that causes very high levels of LDL. These medicines also may be used in people with a history of heart disease when statins or other cholesterol medicines don’t do enough to lower cholesterol levels. PCSK9 inhibitors are given as a shot under the skin.

**Medicines for high triglycerides**

If you also have high triglycerides, your healthcare professional may prescribe:

* **Fibrates.** The medicines fenofibrate (Lipofen) and gemfibrozil (Lopid) speed the removal of triglycerides from the blood. They also help lower LDL cholesterol. Using a fibrate with a statin can raise the risk of statin side effects.
* **Niacin.** Niacin limits the liver's ability to make LDL cholesterol. But niacin doesn't provide more benefits than a statin. Niacin also has been linked with liver damage and strokes. Most healthcare professionals now recommend it only for people who can't take statins.
* **Omega-3 fatty acids.** Omega-3 fatty acids can help lower triglycerides. They are available with or without a prescription. If you choose to take supplements without a prescription, talk with your healthcare professional first. Omega-3 fatty acids may affect other medicines that you take. The effectiveness and cost of omega-3 fatty acids varies.

**Medicine side effects**

Let your healthcare professional know if your cholesterol medicine causes side effects. For instance, side effects of statins can include:

* Muscle pains.
* Muscle damage (very rare).
* Increased blood sugar.

If you decide to take cholesterol medicine, your healthcare professional may recommend liver function tests. These tests help check the medicine's effect on your liver.

**Children and cholesterol treatment**

Most often, making changes to diet and exercise is the first treatment for children age 2 and older who have high cholesterol. Children age 10 and older who have very high cholesterol levels might be prescribed cholesterol-lowering drugs such as statins.

**Lifestyle and home remedies**

Lifestyle changes are important if you have high cholesterol. Try to make the following healthy changes:

* **Lose extra weight.** Losing weight can help lower cholesterol.
* **Eat a heart-healthy diet.** Focus on plant-based foods. These include fruits, vegetables and whole grains. Limit added sugar and sodium. Also limit saturated fats and trans fats. Healthy fat, found in olive and canola oils, is a better option. Avocados, nuts and oily fish are other sources of healthy fat.
* **Be active in your daily life and exercise regularly.** Talk with your healthcare professional if you're not active already. Work up to at least 30 minutes of exercise five times a week.
* **Don't smoke.** If you smoke, you can ask your healthcare professional to help you quit.
* **Limit alcohol or don't drink it.** Limit alcohol to no more than up to one drink a day for women and up to two for men.
* **Manage stress.** Activities such as exercise and meditation can help.
* **Get enough sleep.** It's ideal for adults to get about 7 to 9 hours of sleep each night.

**Epidemiology of High and Low Cholesterol**

High Cholesterol (Raised Total Cholesterol)

* Global Prevalence:  
  Approximately 39% of adults worldwide had raised total cholesterol in 2008, with similar rates in males (37%) and females (40%).
* Mortality and Disease Burden:  
  High cholesterol is a major risk factor for cardiovascular diseases (CVD), including heart disease and stroke, causing an estimated 4.4 million deaths annually worldwide and contributing to nearly 98.6 million disability-adjusted life years (DALYs) in 2019.
* Regional Trends:
  + Deaths attributable to high non-HDL cholesterol have decreased in high-income Western countries due to better management.
  + Conversely, deaths have more than doubled in Southeast Asia and tripled in East Asia since 1990, shifting the global burden toward middle-income countries in Asia, Oceania, and parts of Latin America.
  + Eastern Europe, Central Asia, and North Africa/Middle East regions have some of the highest age-standardized mortality rates related to high LDL cholesterol.
* Future Projections:
  + Cardiovascular disease prevalence is projected to increase by 90% between 2025 and 2050, driven largely by aging populations and risk factors including high cholesterol.
  + Despite this, age-standardized cardiovascular mortality is expected to decline due to improved treatment and prevention.
* Public Health Goals:  
  The World Heart Federation’s Roadmap aims to reduce atherosclerotic cardiovascular disease by targeting cholesterol management, aligning with Sustainable Development Goals to reduce non-communicable diseases by 30% by 2030.

Low Cholesterol

* Epidemiology:  
  Low cholesterol is less commonly reported as a public health issue but may be associated with malnutrition, chronic illness, or genetic disorders. It is not a primary driver of global disease burden like high cholesterol.
* Clinical Context:  
  Low cholesterol can be seen in severe chronic diseases, hyperthyroidism, liver disease, or malabsorption states but lacks large-scale epidemiological data comparable to high cholesterol.

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**Autoimmune Polyendocrine Syndrome**

Autoimmune Polyendocrine Syndrome is a rare disorder where the immune system mistakenly attacks healthy tissues in different organs of the body. This results in dysfunction of various endocrine glands, leading to abnormal hormone levels and affecting the body's ability to regulate essential functions. The primary impact of this syndrome on health is the disruption of hormone production and balance, which can cause a range of symptoms and complications that impact overall well-being and quality of life.

**Symptoms of Autoimmune Polyendocrine Syndrome**

Autoimmune Polyendocrine Syndrome typically presents with a variety of symptoms affecting multiple organs and systems in the body.

Fatigue

Weight loss

Low blood pressure

Dizziness

Nausea and vomiting

Diarrhea

Joint and muscle pain

Skin discoloration

Shakiness or tremors

Loss of appetite

**Causes of Autoimmune Polyendocrine Syndrome**

Autoimmune Polyendocrine Syndrome is primarily caused by the immune system mistakenly attacking the body's own tissues and organs, leading to dysfunction in multiple endocrine glands. Causes of Autoimmune Polyendocrine Syndrome:

Genetic predisposition

Environmental triggers

Autoimmune dysfunction in the body

**Types of Autoimmune Polyendocrine Syndrome**

Autoimmune Polyendocrine Syndrome encompasses a variety of conditions that involve the immune system mistakenly attacking multiple organs in the body.

Autoimmune Polyendocrine Syndrome Type 1 (APS1): A rare genetic disorder characterized by the presence of multiple autoimmune conditions affecting various endocrine glands.

Autoimmune Polyendocrine Syndrome Type 2 (APS2): Involves autoimmune destruction of multiple endocrine glands, commonly affecting the adrenal glands and thyroid.

Autoimmune Polyendocrine Syndrome Type 3 (APS3): Features a combination of autoimmune thyroid disease with other autoimmune conditions such as type 1 diabetes and autoimmune gastritis.

Autoimmune Polyendocrine Syndrome Type 4 (APS4): Involves autoimmune thyroid disease along with other autoimmune conditions like type 1 diabetes and various skin disorders.

Autoimmune Polyendocrine Syndrome Type 5 (APS5): A less common form characterized by autoimmune thyroid disease in combination with other autoimmune disorders affecting the endocrine system.

**Risk Factors**

Autoimmune Polyendocrine Syndrome risk factors are primarily linked to genetic predisposition, family history of autoimmune diseases, and environmental triggers.

Genetic predisposition

Family history of autoimmune diseases

Certain infections

Exposure to environmental factors

Gender (more common in females)

**Diagnosis of Autoimmune Polyendocrine Syndrome**

Autoimmune Polyendocrine Syndrome is typically diagnosed through a combination of medical history, physical examination, and specific laboratory tests.

Blood tests

Imaging studies

Hormone level testing

Genetic testing

**Treatment for Autoimmune Polyendocrine Syndrome**

The treatment for Autoimmune Polyendocrine Syndrome focuses on managing symptoms and addressing any hormone deficiencies.

Hormone Replacement Therapy: Essential for managing hormone deficiencies in Autoimmune Polyendocrine Syndrome, involves taking synthetic hormones to replace the ones the body is not producing adequately.

Immunomodulatory Therapy: Helps regulate the immune system's abnormal response, often using medications like corticosteroids or immunosuppressants to reduce inflammation and slow down autoimmune activity.

Regular Monitoring and Blood Tests: Crucial for adjusting treatment regimens and ensuring hormone levels are within the target range to prevent complications and maintain overall health.

Symptom Management: Addressing specific symptoms such as diabetes, thyroid dysfunction, or adrenal insufficiency through medications or lifestyle modifications.

Patient Education and Lifestyle Modifications: Educating patients on the importance of adherence to treatment, healthy eating, stress management, and regular exercise to support overall wellbeing and symptom control.

**EPIDEMIOLOGY**

AP is a rare syndrome with an approximate prevalence of 1:100,000 for type I and 1:20,000 for types II to IV in the United States Type I has been studied far more thoroughly than the adult types II to IV, and still little is known about the precise prevalence and incidence of AP in different countries and ethnic groups around the world. The highest prevalence of AP1 has been found in populations with a high degree of kindredship or descendants of small founder populations such as Iranian Jews (1:600 to 1:9000) and Finns (1:25,000) ). Compared with the AP–candidiasis–ectodermal dystrophy syndrome, type II is the more common syndrome, with a prevalence of 1.4 to 2 per 100,000, without any apparent preference of ethnic groups . The incidence of types II to IV varies between 1.4 and 4.5 per 100,000 depending on the published source. However, owing to the heterogeneous expression pattern, it is assumed that there are higher numbers of unreported cases. The actual incidence is therefore estimated at 1:20,000 . What particularly makes AP a rare syndrome is the combination of AITD with a prevalence of 27 to 448 per 100,000 subjects per year for AT and 21 to 120 per 100,000 subjects per year for GD , together with other infrequent autoimmune-mediated diseases, with prevalence between 0.0002% and 8.5%.

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**INFERTILITY**

**DEFINITION AND DESCRIPTION**

Infertility is a condition of your reproductive system that causes women to be unable to get pregnant (conceive). Infertility can affect anyone and has many causes. Getting pregnant involves several steps:

1. Your brain must produce reproductive hormones that control ovarian function.
2. An egg must mature in your ovary.
3. Your ovary must release an egg (ovulation).
4. Your fallopian tube must pick up the egg.
5. Sperm must travel up your vagina and through the uterus to your fallopian tube.
6. The sperm fertilizes the egg to create an embryo.
7. The embryo travels through your fallopian tube to the uterus where it implants.

A pregnancy can’t occur if anything in this process doesn’t happen.

If you’re younger than 35, your healthcare provider may diagnose infertility after one year (12 months) of trying to conceive. Trying to conceive is defined as having regular, unprotected sex. If you’re 35 or older, your provider may diagnose infertility after six months of regular, unprotected sex.

Infertility is more common than you might think. Fortunately, there are many treatment options available for women who wish to begin or expand their family.

**Types of infertility**

Types of infertility include:

* **Primary infertility:** You’ve never been pregnant and can’t conceive after one year (or six months if you’re 35 or older) of regular, unprotected sexual intercourse.
* **Secondary infertility:** You can’t get pregnant again after having at least one successful pregnancy.
* **Unexplained infertility:** Fertility testing hasn’t found a reason that a woman or couple is unable to get pregnant.

**How common is infertility?**

Infertility affects both men and women. Infertility is very common. In the United States, 1 in 5 women between 15 and 49 years old struggle with primary infertility and about 1 in 20 women struggle with secondary infertility. Approximately 48 million couples live with infertility around the world.

**Symptoms and Causes**

The main sign of infertility is being unable to get pregnant after six months or one year of regular, unprotected sex. You may not have any other symptoms. But some women or men may show physical symptoms such as:

* Pelvic or abdominal pain.
* Irregular vaginal bleeding, irregular periods or no periods.
* Penile disorders or issues with ejaculation.

**What causes infertility?**

There are many causes of infertility, and sometimes, there isn’t a simple answer as to why you’re not getting pregnant. Only a healthcare provider can determine the cause and find the best treatment for you.

While causes of infertility vary, studies show that:

* 33% of infertility involves women.
* 33% of infertility involves men.
* 33% of infertility involves both partners or is unexplained.

Twenty-five percent of infertile couples have more than one factor that contributes to their infertility.

**Infertility causes**

Some causes of infertility affect just one partner, while others affect both partners. Risk factors for infertility include:

* Age, particularly being in your late 30s or 40s. For men, age begins affecting fertility closer to 50.
* Eating disorders, including anorexia nervosa and bulimia.
* Excessive alcohol consumption.
* Exposure to environmental toxins, such as chemicals, lead and pesticides.
* Over-exercising.
* Radiation therapy or chemotherapy.
* Sexually transmitted infections (STIs).
* Smoking and using tobacco products. (This behavior plays a role in about 13% to 15% of infertility cases.)
* Substance abuse.
* Having obesity or being underweight.
* Abnormalities of the hormone-producing centers of your brain (hypothalamus or pituitary).
* Chronic conditions and diseases.

**Infertility causes for women**

Ovulation disorders are the most common cause of infertility in women. Ovulation is the process in which your ovary releases an egg to meet sperm for fertilization.

These factors can contribute to female infertility:

* Endometriosis.
* Structural abnormalities of your vagina, uterus or fallopian tubes.
* Autoimmune conditions like celiac disease or lupus.
* Kidney disease.
* Pelvic inflammatory disease (PID).
* Hypothalamic and pituitary gland disorders.
* Polycystic ovary syndrome (PCOS).
* Primary ovarian insufficiency or poor egg quality.
* Sickle cell anemia.
* Uterine fibroids or uterine polyps.
* Thyroid disease.
* Prior surgical sterilization (tubal ligation or salpingectomy).
* Genetic or chromosomal disorders.
* Sexual dysfunction.
* Surgical or congenital absence of your ovaries.
* Infrequent or absent menstrual periods.

**Infertility causes for men**

The most common cause of male infertility involves problems with the shape, movement (motility) or amount (low sperm count) of sperm.

Other causes of male infertility include:

* Enlarged veins (varicocele) in your scrotum, the sac that holds your testicles.
* Genetic disorders, such as cystic fibrosis.
* Chromosomal disorders, such as Klinefelter syndrome.
* High heat exposure to your testicles from tight clothing, frequent use of hot tubs and saunas, and holding laptops or heating pads on or near your testes.
* Injury to your scrotum or testicles.
* Low testosterone (hypogonadism).
* Misuse of anabolic steroids.
* Sexual dysfunction, such as erectile dysfunction, anejaculation, premature ejaculation or retrograde ejaculation.
* Undescended testicles.
* Previous chemotherapy or radiation therapy.
* Surgical or congenital absence of testes.
* Prior surgical sterilization (vasectomy).

**Diagnosis and Tests**

**How is female infertility diagnosed?**

First, your healthcare provider will get your full medical and sexual history.

Fertility for females involves ovulating healthy eggs. This means your brain has to send hormonal signals to your ovary to release an egg to travel from your ovary, through your fallopian tube and to your uterine lining. Fertility testing involves detecting an issue with any of these processes.

These tests can also help diagnose or rule out problems:

* **Pelvic exam:** Your provider will perform a pelvic exam to check for structural problems or signs of disease.
* **Blood test:** A blood test can check hormone levels to see if hormonal imbalance is a factor or if you’re ovulating.
* **Transvaginal ultrasound:** Your provider inserts an ultrasound wand into your vagina to look for issues with your reproductive system.
* **Hysteroscopy:** Your provider inserts a thin, lighted tube (hysteroscope) into your vagina to examine your uterus.
* **Saline sonohysterogram (SIS):** Your provider fills your uterus with saline (sterilized salt water) and conducts a transvaginal ultrasound.
* **Sono hysterosalpingogram (HSG):** Your provider fills your fallopian tubes with saline and air bubbles during an SIS procedure to check for tubal blockages.
* **X-ray hysterosalpingogram (HSG):** X-rays capture an injectable dye as it travels through your fallopian tubes. This test looks for blockages.
* **Laparoscopy:** Your provider inserts a laparoscope (thin tube with a camera) into a small abdominal incision. It helps identify problems like endometriosis, uterine fibroids and scar tissue.

**How is male infertility diagnosed?**

Diagnosing infertility in men typically involves making sure they ejaculate healthy sperm. Most fertility tests look for problems with sperm.

These tests can help diagnose or rule out problems:

* **Semen analysis:** This test checks for low sperm count and poor sperm mobility. Some people need a needle biopsy to remove sperm from their testicles for testing.
* **Blood test:** A blood test can check thyroid and other hormone levels. Genetic blood tests look for chromosomal abnormalities.
* **Scrotal ultrasound:** An ultrasound of your scrotum identifies varicoceles or other testicular problems.

**Management and Treatment**

Treatment for infertility depends mostly on the cause and your goals. Your age, how long you’ve been trying to conceive and your personal preferences are factors in deciding on a treatment. Sometimes, one person needs treatment, but other times, treatment involves both partners.

In most cases, women and couples with infertility have a high chance of pregnancy. Things like medication, surgery or assisted reproductive technology (ART) can help. Often, lifestyle changes or improving the frequency and timing of intercourse can improve your chances of pregnancy. Treatment can also include a combination of methods.

**Infertility treatment for women**

Treatments for infertility in women include:

* **Lifestyle modification:** Gaining or losing weight, stopping smoking or using drugs, and improving other health conditions can improve your chance of pregnancy.
* **Medications:** Fertility drugs stimulate your ovaries to ovulate more eggs, which increases your chance of getting pregnant.
* **Surgery:** Surgery can open blocked fallopian tubes and remove polyps, fibroids or scar tissue.

Providers may make suggestions on how you can improve your odds of conceiving. These may include things like:

* Tracking ovulation through basal body temperature, using a fertility tracking app and noting the texture of your cervical mucus.
* Using a home ovulation kit, a kit you can purchase at the drugstore or online to help predict ovulation.

**Infertility treatment for men**

Treatments for infertility in men include:

* **Medications:** Medications can raise testosterone or other hormone levels. There are also drugs for erectile dysfunction to help you maintain an erection during sex.
* **Surgery:** Some men need surgery to open blockages in the tubes that carry sperm or to repair structural problems. Varicocele surgery can make sperm healthier and improve the odds of conception.

**Common fertility treatments**

Some couples need more help conceiving using assisted reproductive technology (ART). ART is any fertility treatment that involves a healthcare provider handling the sperm or egg. To increase pregnancy odds, you can take medications to stimulate ovulation before trying one of these options:

* **In vitro fertilization (IVF):** IVF involves retrieving eggs from your ovary, then placing them with sperm in a lab dish. The sperm fertilizes the eggs. A provider transfers one to three of the fertilized eggs (embryos) into your uterus.
* **Intracytoplasmic sperm injection (ICSI):** This procedure may be performed during the IVF process. An embryologist injects a single sperm directly into each egg. Then, a provider transfers one to three of the embryos into your uterus.
* **Intrauterine insemination (IUI):** A healthcare provider uses a long, thin tube to place sperm directly into your uterus. IUI is sometimes called artificial insemination.
* **Assisted hatching:** A process that involves opening the outer layer of an embryo to make it easier for it to implant in your uterine lining.
* **Third-party ART:** Couples may use donor eggs, donor sperm or donor embryos. Some couples need a gestational carrier or surrogate.

**What are complications of treatment?**

Complications of infertility treatment include:

* **Higher chance of multiples (twins, triplets or more):** Producing multiple eggs and transferring more than one embryo increases your risk of becoming pregnant with more than one fetus. Complications such as miscarriage, premature birth, low birth weight, neonatal death, and long-term health complications are more common in women pregnant with multiple fetuses.
* **Ovarian hyperstimulation syndrome (OHSS):** A condition that causes painful and swollen ovaries as a result of fertility medications. It can become serious and require immediate medical attention.
* **Ectopic pregnancy:** IVF has an increased risk of ectopic pregnancy.
* **Failed cycles:** A failed cycle is when you go through infertility treatment and it doesn’t end in pregnancy.

**Can infertility be cured?**

Yes, but it depends on the cause. In 85% to 90% of cases, lifestyle modification, medication, ART or surgery can treat infertility and allow a woman to conceive.

**Outlook / Prognosis**

Approximately 9 out of 10 couples get pregnant after undergoing fertility treatments. Success rates vary depending on the cause of infertility, the couple’s ages and other factors.

Infertility has emotional, physical, financial and psychological side effects. Don’t forget to practice self-care and be patient with yourself and your partner throughout the process. Infertility isn’t easy, so surround yourself with supportive people or consider joining an online support group. Sometimes, sharing your feelings with people who understand what you’re going through can be helpful.

**Prevention**

**How can I prevent infertility?**

You can take these steps to protect your fertility, especially while trying to conceive:

* Eat a well-balanced diet and maintain a weight that’s healthy for you.
* Don’t smoke, misuse drugs or drink alcohol.
* Get treated for STIs.
* Limit exposure to environmental toxins.
* Stay physically active, but don’t overdo exercise.
* Don’t delay conception until an advanced age.
* Undergo fertility preservation procedures (freezing eggs or sperm).

**Living With**

**Does insurance cover infertility treatment?**

Health insurance policies vary, so you should always check with your insurance provider. Most insurers cover medically necessary procedures, such as surgeries to treat endometriosis and uterine fibroids. Some policies cover fertility procedures like IUI, but may not cover ovulation-stimulating medications or IVF.

Certain states have laws that require employers to provide infertility coverage as part of their health insurance policy for employees. As of June 2022, The National Infertility Association (Resolve) states:

* Twenty states have passed fertility insurance coverage laws; 14 of those laws include IVF coverage; and 12 states have fertility preservation laws for iatrogenic (medically induced) infertility.

If you live or work in a state that has an infertility coverage law in place and want to know your coverage details, you should contact your employer.

## **Epidemiology of Infertility**

* Global Prevalence:  
  Approximately 1 in 6 individuals worldwide experience infertility, corresponding to about 17.5% of the adult population.
  + About 13.4% of women report difficulties becoming pregnant or carrying a pregnancy to term.
  + Around 19% of couples are unable to conceive after one year of unprotected intercourse, increasing to 10% after two years.
* Number of Affected Individuals:  
  In 2021, an estimated 110 million women and 55 million men worldwide were living with infertility.  
  Female infertility prevalence was approximately 3.7% (3,713 cases per 100,000), and male infertility about 1.8% (1,820 cases per 100,000).
* Trends Over Time:  
  Infertility prevalence has been increasing globally since 1990 and is projected to continue rising through 2040.
  + The annual percentage increase in infertility prevalence was about 0.5% for men and 0.7% for women between 1990 and 2021.
  + Population growth accounts for nearly 65% of the overall increase in infertility burden.
* Age and Regional Distribution:
  + Infertility primarily affects individuals aged 35-39 years, especially females.
  + Highest prevalence is observed in middle socio-demographic index (SDI) regions, including East and South Asia and Eastern Europe.
  + Asia, particularly China, India, and Indonesia, has the largest absolute number of infertility cases.
  + The Central African Republic and some African countries have the highest age-standardized prevalence rates of female infertility.
* Socioeconomic Variation:
  + Infertility rates show limited variation between high-, middle-, and low-income countries, indicating it is a global health challenge.
  + Slight negative correlation exists between infertility rates and SDI, with some low-middle SDI regions experiencing faster increases in male infertility.
* Gender Differences:  
  Female infertility prevalence is consistently higher than male infertility globally, but the fastest rise in male infertility is projected in low-middle SDI areas.
* Impact:  
  Infertility causes significant psychological, social, and economic burdens worldwide, emphasizing the need for increased access to affordable and high-quality fertility care

## **DIFFERENTIAL DIAGNOSIS**

## Female Infertility Causes

1. Ovulatory Disorders
   * Polycystic Ovary Syndrome (PCOS): Most common cause of anovulation.
   * Thyroid dysfunction: Both hypothyroidism and hyperthyroidism can disrupt ovulation.
   * Hyperprolactinemia: Elevated prolactin levels impair ovulation.
   * Premature Ovarian Failure (Primary Ovarian Insufficiency): Loss of ovarian function before age 40.
   * Hypothalamic or pituitary disorders: Tumors, hypopituitarism affecting hormonal regulation.
   * Excessive exercise, eating disorders, stress.
2. Tubal and Pelvic Factors
   * Blocked or damaged fallopian tubes due to:
     + Pelvic inflammatory disease (often from untreated STIs).
     + Endometriosis causing adhesions and scarring.
     + Previous pelvic or abdominal surgery causing scarring.
     + Ectopic pregnancy or tubal ligation.
   * Hydrosalpinx (fluid-filled, blocked tubes).
3. Uterine and Cervical Causes
   * Uterine fibroids (leiomyomas) interfering with implantation or causing distortion.
   * Uterine polyps or congenital anomalies (e.g., septate uterus).
   * Endometrial disorders such as chronic endometritis.
   * Cervical factors:
     + Abnormal cervical mucus impairing sperm passage.
     + Cervical stenosis or scarring from surgery (e.g., cone biopsy).
     + Immunological factors affecting sperm survival.
4. Endometriosis
   * Ectopic growth of endometrial tissue causing inflammation, adhesions, and impaired fertility.
5. Other Female Factors
   * Age-related decline in egg quality and quantity.
   * Poor egg quality due to genetic abnormalities.
   * Chronic systemic diseases (e.g., diabetes, autoimmune diseases).

Male Infertility Causes

1. Sperm Production Disorders
   * Varicocele causing impaired spermatogenesis.
   * Genetic abnormalities (e.g., Klinefelter syndrome).
   * Testicular failure from infections, trauma, chemotherapy, radiation.
   * Hormonal imbalances affecting testosterone and gonadotropin levels.
2. Sperm Transport and Ejaculation Disorders
   * Obstruction of reproductive tract (e.g., vas deferens, ejaculatory ducts).
   * Ejaculatory dysfunctions such as premature ejaculation or retrograde ejaculation.
   * Congenital absence of vas deferens (e.g., in cystic fibrosis).
3. Sperm Function Abnormalities
   * Poor sperm motility (asthenozoospermia).
   * Abnormal sperm morphology (teratozoospermia).
   * Low sperm count (oligospermia) or absence (azoospermia).
4. Environmental and Lifestyle Factors
   * Exposure to toxins, pesticides, radiation.
   * Smoking, excessive alcohol, drug use (e.g., cannabis, cocaine).
   * Heat exposure (e.g., saunas, hot tubs).
   * Nutritional deficiencies and obesity.

Combined and Unexplained Infertility

* In some couples, both partners have contributing factors.
* Approximately 10-20% of infertility cases remain unexplained after thorough evaluation.

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