Diabetes

Diabetes mellitus (**DM**), commonly known as **diabetes**, is a group of metabolic disorders characterized by a high blood sugar level over a prolonged period of time.[10] Symptoms of high blood sugar include frequent urination, increased thirst, and increased hunger.[2] If left untreated, diabetes can cause many complications.[2] Acute complications can include diabetic ketoacidosis, hyperosmolar hyperglycemic state, or death.[3] Serious long-term complications include cardiovascular disease, stroke, chronic kidney disease, foot ulcers, damage to the nerves, and damage to the eyes.[2]

Diabetes is due to either the pancreas not producing enough insulin, or the cells of the body not responding properly to the insulin produced.[11] There are three main types of diabetes mellitus:[2]

- Type 1 diabetes results from the pancreas's failure to produce enough insulin due to loss of beta cells.[2] This form was previously referred to as "insulin-dependent diabetes mellitus" (IDDM) or "juvenile diabetes".[2] The loss of beta cells is caused by an autoimmune response.[12] The cause of this autoimmune response is unknown.[2]
- Type 2 diabetes begins with insulin resistance, a condition in which cells fail to respond to insulin properly.[2] As the disease progresses, a lack of insulin may also develop.[13] This form was previously referred to as "non insulin-dependent diabetes mellitus" (NIDDM) or "adult-onset diabetes".[2] The most common cause is a combination of excessive body weight and insufficient exercise.[2]
- Gestational diabetes is the third main form, and occurs when pregnant women without a previous history of diabetes develop high blood sugar levels.[2]

Prevention and treatment involve maintaining a healthy diet, regular physical exercise, a normal body weight, and avoiding use of tobacco.[2] Control of blood pressure, maintaining proper foot care, and eye care are important for people with the disease.[2] Type 1 diabetes must be managed with insulin injections.[2] Type 2 diabetes may be treated with medications with or without insulin.[14] Insulin and some oral medications can cause low blood sugar.[15] Weight loss surgery in those with

Diabetes mellitus

Universal blue circle symbol for diabetes.[1]

Pronunciation	/daɪə'biːtiːz, -təs/
Specialty	Endocrinology
Symptoms	Frequent urination, increased thirst, increased hunger[2]
Complications	Diabetic ketoacidosis, hyperosmolar hyperglycemic state, heart disease, stroke, chronic kidney failure, foot ulcers, gastroparesis[2][3][4]
Risk factors	**Type 1**: Family history[5] **Type 2**: Obesity, lack of exercise, genetics[2][6]
Diagnostic method	High blood sugar[2]
Treatment	Healthy diet, physical exercise[2]
Medication	Insulin, anti-diabetic medication like metformin[2][7][8]

obesity is sometimes an effective measure in those with type 2 diabetes.[16] Gestational diabetes usually resolves after the birth of the baby.[17]

Frequency	425 million (8.8%)[9]
Deaths	3.2–5.0 million per year[9]

As of 2017, an estimated 425 million people had diabetes worldwide,[9] with type 2 diabetes making up about 90% of the cases.[18][19] This represents 8.8% of the adult population,[9] with equal rates in both women and men.[20] Trends suggest that rates will continue to rise.[9] Diabetes at least doubles a person's risk of early death.[2] In 2017, diabetes resulted in approximately 3.2 to 5.0 million deaths.[9] The global economic cost of diabetes related health expenditure in 2017 was estimated at US$727 billion.[9] In the United States, diabetes cost nearly US$245 billion in 2012.[21] Average medical expenditures among people with diabetes are about 2.3 times higher.[22]

Contents

Signs and symptoms

The classic symptoms of untreated diabetes are unintended weight loss, polyuria (increased urination), polydipsia (increased thirst), and polyphagia (increased hunger).[23] Symptoms may develop rapidly (weeks or months) in type 1 diabetes, while they usually develop much more slowly and may be subtle or absent in type 2 diabetes. Other symptoms of diabetes include weight loss and tiredness.[24]

Overview of the most significant symptoms of diabetes

Several other signs and symptoms can mark the onset of diabetes although they are not specific to the disease. In addition to the known ones above, they include blurred vision, headache, fatigue, slow healing of cuts, and itchy skin. Prolonged high blood glucose can cause glucose absorption in the lens of the eye, which leads to changes in its shape, resulting in vision changes. Long-term vision loss can also be caused by diabetic retinopathy. A number of skin rashes that can occur in diabetes are collectively known as diabetic dermadromes.[25]

Diabetic emergencies

People (usually with type 1 diabetes) may also experience episodes of diabetic ketoacidosis (DKA), a metabolic disturbance characterized by nausea, vomiting and abdominal pain, the smell of acetone on the breath, deep breathing known as Kussmaul breathing, and in severe cases a decreased level of consciousness.[26]

A rare but equally severe possibility is hyperosmolar hyperglycemic state (HHS), which is more common in type 2 diabetes and is mainly the result of dehydration.[26]

Treatment-related low blood sugar (hypoglycemia) is common in people with type 1 and also type 2 diabetes depending on the medication being used. Most cases are mild and are not considered medical emergencies. Effects can range from feelings of unease, sweating, trembling, and increased appetite in mild cases to more serious effects such as confusion, changes in behavior such as aggressiveness, seizures, unconsciousness, and (rarely) permanent brain damage or death in severe cases.[27][28] Rapid breathing, sweating, and cold, pale skin are characteristic of low blood sugar but not definitive.[29] Mild to moderate cases are self-treated by eating or drinking something high in sugar. Severe cases can lead to unconsciousness and must be treated with intravenous glucose or injections with glucagon.[30]

Complications

All forms of diabetes increase the risk of long-term complications. These typically develop after many years (10–20) but may be the first symptom in those who have otherwise not received a diagnosis before that time.

The major long-term complications relate to damage to blood vessels. Diabetes doubles the risk of cardiovascular disease[31] and about 75% of deaths in people with diabetes are due to coronary artery disease.[32] Other macrovascular diseases include stroke, and peripheral artery disease.

Retinopathy, nephropathy, and neuropathy are potential complications of diabetes

The primary complications of diabetes due to damage in small blood vessels include damage to the eyes, kidneys, and nerves.[33] Damage to the eyes, known as diabetic retinopathy, is caused by damage to the blood vessels in the retina of the eye, and can result in gradual vision loss and eventual blindness.[33] Diabetes also increases the risk of having glaucoma, cataracts, and other eye problems. It is recommended that people with diabetes visit an eye doctor once a year.[34] Damage to the kidneys, known as diabetic nephropathy, can lead to tissue scarring, urine protein loss, and eventually chronic kidney disease, sometimes requiring dialysis or kidney transplantation.[33] Damage to the nerves of the body, known as diabetic neuropathy, is the most common complication of diabetes.[33] The symptoms can include numbness, tingling, pain, and altered pain sensation, which can lead to damage to the skin. Diabetes-related foot problems (such as diabetic foot ulcers) may occur, and can be difficult to treat, occasionally requiring amputation. Additionally, proximal diabetic neuropathy causes painful muscle atrophy and weakness.

There is a link between cognitive deficit and diabetes. Compared to those without diabetes, those with the disease have a 1.2 to 1.5-fold greater rate of decline in cognitive function.[35] Having diabetes, especially when on insulin, increases the risk of falls in older people.[36]

Causes

Diabetes mellitus is classified into four broad categories: type 1, type 2, gestational diabetes, and "other specific types".[11] The "other specific types" are a collection of a few dozen individual causes.[11] Diabetes is a more variable disease than once thought and people may have combinations of forms.[38] The term "diabetes", without qualification, refers to diabetes mellitus.[39]

Comparison of type 1 and 2 diabetes[18]

Feature	Type 1 diabetes	Type 2 diabetes
Onset	Sudden	Gradual
Age at onset	Mostly in children	Mostly in adults
Body size	Thin or normal[37]	Often obese
Ketoacidosis	Common	Rare
Autoantibodies	Usually present	Absent
Endogenous insulin	Low or absent	Normal, decreased or increased
Concordance in identical twins	50%	90%
Prevalence	~10%	~90%

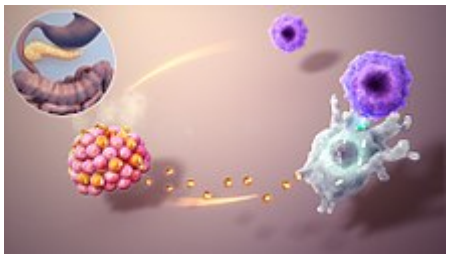
Type 1

Type 1 diabetes is characterized by loss of the insulin-producing beta cells of the pancreatic islets, leading to insulin deficiency. This type can be further classified as immune-mediated or idiopathic. The majority of type 1 diabetes is of the immune-mediated nature, in which a T cell-mediated autoimmune attack leads to the loss of beta cells and thus insulin.[40] It causes approximately 10% of diabetes mellitus cases in North America and Europe. Most affected people are otherwise healthy and of a healthy weight when onset

occurs. Sensitivity and responsiveness to insulin are usually normal, especially in the early stages. Although it has been called "juvenile diabetes" due to the frequent onset in children, the majority of individuals living with type 1 diabetes are now adults.[5]

"Brittle" diabetes, also known as unstable diabetes or labile diabetes, is a term that was traditionally used to describe the dramatic and recurrent swings in glucose levels, often occurring for no apparent reason in insulin-dependent diabetes. This term, however, has no biologic basis and should not be used.[41] Still, type 1 diabetes can be accompanied by irregular and unpredictable high blood sugar levels, and the potential for diabetic ketoacidosis or serious low blood sugar levels. Other complications include an impaired counterregulatory response to low blood sugar, infection, gastroparesis (which leads to erratic absorption of dietary carbohydrates), and endocrinopathies (e.g., Addison's disease).[41] These phenomena are believed to occur no more frequently than in 1% to 2% of persons with type 1 diabetes.[42]

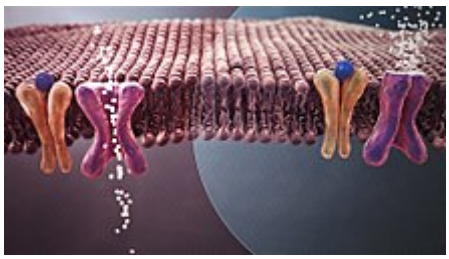
Type 1 diabetes is partly inherited, with multiple genes, including certain HLA genotypes, known to influence the risk of diabetes. In genetically susceptible people, the onset of diabetes can be triggered by one or more environmental factors,[43] such as a viral infection or diet. Several viruses have been implicated, but to date there is no stringent evidence to support this hypothesis in humans.[43][44] Among dietary factors, data suggest that gliadin (a protein present in gluten) may play a role in the development of type 1 diabetes, but the mechanism is not fully understood.[45][46]


Autoimmune attack in type 1 diabetes.

Type 1 diabetes can occur at any age, and a significant proportion is diagnosed during adulthood. Latent autoimmune diabetes of adults (LADA) is the diagnostic term applied when type 1 diabetes develops in adults; it has a slower onset than the same condition in children. Given this difference, some use the unofficial term "type 1.5 diabetes" for this condition. Adults with LADA are frequently initially misdiagnosed as having type 2 diabetes, based on age rather than cause[47]

Type 2

Type 2 diabetes is characterized by insulin resistance, which may be combined with relatively reduced insulin secretion.[11] The defective responsiveness of body tissues to insulin is believed to involve the insulin receptor. However, the specific defects are not known. Diabetes mellitus cases due to a known defect are classified separately. Type 2 diabetes is the most common type of diabetes mellitus.[2] Many people with type 2 diabetes have evidence of prediabetes (impaired fasting glucose and/or impaired glucose tolerance) before meeting the criteria for type 2 diabetes.[48] The progression of prediabetes to overt type 2 diabetes can be slowed or reversed by lifestyle changes or medications that improve insulin sensitivity or reduce the liver's glucose production.[49]


Reduced insulin secretion and absorption leads to high glucose content in the blood.

Type 2 diabetes is primarily due to lifestyle factors and genetics.[50] A number of lifestyle factors are known to be important to the development of type 2 diabetes, including obesity (defined by a body mass index of greater than 30), lack of physical activity, poor diet, stress, and urbanization.[18] Excess body fat is associated with 30% of cases in those of Chinese and Japanese descent, 60–80% of cases in those of European and African descent, and 100% of Pima Indians and Pacific Islanders.[11] Even those who are not obese often have a high waist–hip ratio.[11]

Dietary factors also influence the risk of developing type 2 diabetes. Consumption of sugar-sweetened drinks in excess is associated with an increased risk.[51][52] The type of fats in the diet is also important, with saturated fat and trans fats increasing the risk and polyunsaturated and monounsaturated fat decreasing the risk.[50] Eating lots of white rice also may increase the risk of diabetes, whereas substitution of brown rice or other whole grains for white rice may lower the risk of diabetes.[53] A lack of physical activity is believed to cause 7% of cases.[54]

Gestational diabetes

Gestational diabetes mellitus (GDM) resembles type 2 diabetes in several respects, involving a combination of relatively inadequate insulin secretion and responsiveness. It occurs in about 2–10% of all pregnancies and may improve or disappear after delivery.[55] However, after pregnancy approximately 5–10% of women with GDM are found to have DM, most commonly type 2.[55] GDM is fully treatable, but requires careful medical supervision throughout the pregnancy. Management may include dietary changes, blood glucose monitoring, and in some cases, insulin may be required[56]

Though it may be transient, untreated GDM can damage the health of the fetus or mother. Risks to the baby include macrosomia (high birth weight), congenital heart and central nervous system abnormalities, and skeletal muscle malformations. Increased levels of insulin in a fetus's blood may inhibit fetal surfactant production and cause infant respiratory distress syndrome. A high blood bilirubin level may result from red blood cell destruction. In severe cases, perinatal death may occur, most commonly as a result of poor placental perfusion due to vascular impairment. Labor induction may be indicated with decreased placental function. A caesarean section may be performed if there is marked fetal distress or an increased risk of injury associated with macrosomia, such as shoulder dystocia.[57]

Other types

Maturity onset diabetes of the young (MODY) is a rare autosomal dominant inherited form of diabetes, due to one of several single-gene mutations causing defects in insulin production.[58] It is significantly less common than the three main types, constituting 1-2% of all cases. The name of this disease refers to early hypotheses as to its nature. Being due to a defective gene, this disease varies in age at presentation and in severity according to the specific gene defect; thus there are at least 13 subtypes of MODY. People with MODY often can control it without using insulin.[59]

Some cases of diabetes are caused by the body's tissue receptors not responding to insulin (even when insulin levels are normal, which is what separates it from type 2 diabetes); this form is very uncommon. Genetic mutations (autosomal or mitochondrial) can lead to defects in beta cell function. Abnormal insulin action may also have been genetically determined in some cases. Any disease that causes extensive damage to the pancreas may lead to diabetes (for example, chronic pancreatitis and cystic fibrosis). Diseases associated with excessive secretion of insulin-antagonistic hormones can cause diabetes (which is typically resolved once the hormone excess is removed). Many drugs impair insulin

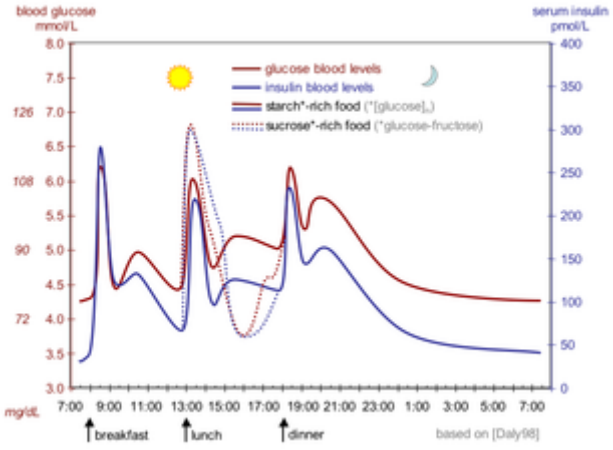
secretion and some toxins damage pancreatic beta cells, whereas others increase insulin resistance (especially glucocorticoids which can provoke "steroid diabetes"). The ICD-10 (1992) diagnostic entity, *malnutrition-related diabetes mellitus* (MRDM or MMDM, ICD-10 code E12), was deprecated by the World Health Organization (WHO) when the current taxonomy was introduced in 1999.[60]

The following is a list of disorders that may increase the risk of diabetes:[61]

- Genetic defects of β-cell function
  - Maturity onset diabetes of the young
  - Mitochondrial DNA mutations
- Genetic defects in insulin processing or insulin action
  - Defects in proinsulin conversion
  - Insulin gene mutations
  - Insulin receptor mutations
- Exocrine pancreatic defects
  - Chronic pancreatitis
  - Pancreatectomy
  - Pancreatic neoplasia
  - Cystic fibrosis
  - Hemochromatosis
  - Fibrocalculous pancreatopathy
- Endocrinopathies
  - Growth hormone excess (acromegaly)
  - Cushing syndrome
  - Hyperthyroidism
  - Hypothyroidism
  - Pheochromocytoma
  - Glucagonoma
- Infections
  - Cytomegalovirus infection
  - Coxsackievirus B
- Drugs
  - Glucocorticoids
  - Thyroid hormone
  - β-adrenergic agonists
  - Statins[62]

Pathophysiology

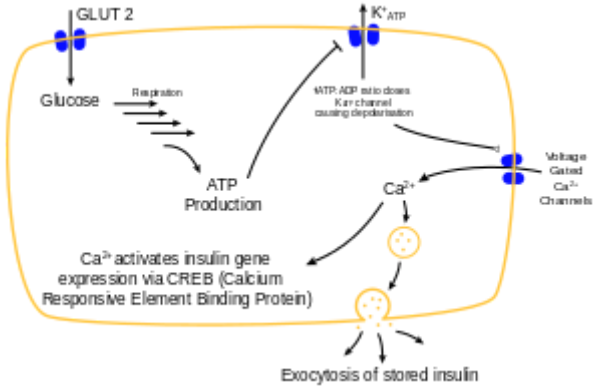
Insulin is the principal hormone that regulates the uptake of glucose from the blood into most cells of the body, especially liver, adipose tissue and muscle, except smooth muscle, in which insulin acts via the IGF-1. Therefore, deficiency of insulin or the insensitivity of its receptors play a central role in all forms of diabetes mellitus.[63]



The fluctuation of blood sugar (red) and the sugar-lowering hormone insulin (blue) in humans during the course of a day with three meals. One of the effects of a sugar-rich vs a starch-rich meal is highlighted.

The body obtains glucose from three main sources: the intestinal absorption of food; the breakdown of glycogen (glycogenolysis), the storage form of glucose found in the liver; and gluconeogenesis, the generation of glucose from non-carbohydrate substrates in the body.[64] Insulin plays a critical role in regulating glucose levels in the body. Insulin can inhibit the breakdown of glycogen or the process of gluconeogenesis, it can stimulate the transport of glucose into fat and muscle cells, and it can stimulate the storage of glucose in the form of glycogen.[64]

Insulin is released into the blood by beta cells (β-cells), found in the islets of Langerhans in the pancreas, in response to rising levels of blood glucose, typically after eating. Insulin is used by about two-thirds of the body's cells to absorb glucose from the blood for use as fuel, for conversion to other needed molecules, or for storage. Lower glucose levels result in decreased insulin release from the beta cells and in the breakdown of glycogen to glucose. This process is mainly controlled by the hormone glucagon, which acts in the opposite manner to insulin.[65]



Mechanism of insulin release in normal pancreatic beta cells. Insulin production is more or less constant within the beta cells. Its release is triggered by food, chiefly food containing absorbable glucose.

If the amount of insulin available is insufficient, or if cells respond poorly to the effects of insulin (insulin resistance), or if the insulin itself is defective, then glucose is not absorbed properly by the body cells that require it, and is not stored appropriately in the liver and muscles. The net effect is persistently high levels of blood glucose, poor protein synthesis, and other metabolic derangements, such as metabolic acidosis in cases of complete insulin deficiency.[64]

When glucose concentration in the blood remains high over time, the kidneys reach a threshold of reabsorption, and the body excretes glucose in the urine (glycosuria).[66] This increases the osmotic pressure of the urine and inhibits reabsorption of water by the kidney, resulting in increased urine production (polyuria) and increased fluid loss. Lost blood volume is replaced osmotically from water in body cells and other body compartments, causing dehydration and increased thirst (polydipsia).[64] In addition, intracellular glucose deficiency stimulates appetite leading to excessive food intake (polyphagia).[67]

Diagnosis

WHO diabetes diagnostic criteria[68][69]

Condition	2-hour glucose	Fasting glucose	HbA_{1c}	
Unit	*mmol/L(mg/dL)*	*mmol/L(mg/dL)*	*mmol/mol*	*DCCT %*
Normal	<7.8 (<140)	<6.1 (<110)	<42	<6.0
Impaired fasting glycaemia	<7.8 (<140)	≥6.1(≥110) & <7.0(<126)	42-46	6.0–6.4
Impaired glucose tolerance	≥7.8 (≥140)	<7.0 (<126)	42-46	6.0–6.4
Diabetes mellitus	≥11.1 (≥200)	≥7.0 (≥126)	≥48	≥6.5

Diabetes mellitus is characterized by recurrent or persistent high blood sugar, and is diagnosed by demonstrating any one of the following:[60]

- Fasting plasma glucose level ≥ 7.0 mmol/L (126 mg/dL)
- Plasma glucose ≥ 11.1 mmol/L (200 mg/dL) two hours after a 75 gram oral glucose load as in a glucose tolerance test (OGTT)
- Symptoms of high blood sugar and casual plasma glucose ≥ 11.1 mmol/L (200 mg/dL)

- Glycated hemoglobin (HbA_{1C}) ≥ 48 mmol/mol (≥ 6.5 DCCT %).[70]

A positive result, in the absence of unequivocal high blood sugar, should be confirmed by a repeat of any of the above methods on a different day. It is preferable to measure a fasting glucose level because of the ease of measurement and the considerable time commitment of formal glucose tolerance testing, which takes two hours to complete and offers no prognostic advantage over the fasting test.[71] According to the current definition, two fasting glucose measurements above 7.0 mmol/L (126 mg/dL) is considered diagnostic for diabetes mellitus.

Per the WHO, people with fasting glucose levels from 6.1 to 6.9 mmol/L (110 to 125 mg/dL) are considered to have impaired fasting glucose.[72] People with plasma glucose at or above 7.8 mmol/L (140 mg/dL), but not over 11.1 mmol/L (200 mg/dL), two hours after a 75 gram oral glucose load are considered to have impaired glucose tolerance. Of these two prediabetic states, the latter in particular is a major risk factor for progression to full-blown diabetes mellitus, as well as cardiovascular disease.[73] The American Diabetes Association (ADA) since 2003 uses a slightly different range for impaired fasting glucose of 5.6 to 6.9 mmol/L (100 to 125 mg/dL).[74]

Glycated hemoglobin is better than fasting glucose for determining risks of cardiovascular disease and death from any cause.[75]

Prevention

There is no known preventive measure for type 1 diabetes.[2] Type 2 diabetes—which accounts for 85–90% of all cases worldwide—can often be prevented or delayed by maintaining a normal body weight, engaging in physical activity, and eating a healthy diet.[2] Higher levels of physical activity (more than 90 minutes per day) reduce the risk of diabetes by 28%.[76] Dietary changes known to be effective in helping to prevent diabetes include maintaining a diet rich in whole grains and fiber, and choosing good fats, such as the polyunsaturated fats found in nuts, vegetable oils, and fish.[77] Limiting sugary beverages and eating less red meat and other sources of saturated fat can also help prevent diabetes.[77] Tobacco smoking is also associated with an increased risk of diabetes and its complications, so smoking cessation can be an important preventive measure as well.[78]

The relationship between type 2 diabetes and the main modifiable risk factors (excess weight, unhealthy diet, physical inactivity and tobacco use) is similar in all regions of the world. There is growing evidence that the underlying determinants of diabetes are a reflection of the major forces driving social, economic and cultural change: globalization, urbanization, population aging, and the general health policy environment.[79]

Management

Diabetes management concentrates on keeping blood sugar levels as close to normal, without causing low blood sugar. This can usually be accomplished with dietary changes, exercise, weight loss, and use of appropriate medications (insulin, oral medications).

Learning about the disease and actively participating in the treatment is important, since complications are far less common and less severe in people who have well-managed blood sugar levels.[80][81] Per the American College of Physicians, the goal of treatment is an HbA_{1C} level of 7-8%.[82] Attention is also paid to other health problems that may accelerate the negative effects of diabetes. These include smoking, high blood pressure, metabolic syndrome obesity, and lack of regular exercise.[83] Specialized

footwear is widely used to reduce the risk of ulcers in at-risk diabetic feet although evidence for the efficacy of this remains equivocal.[84]

Play media

Overview of the management of diabetes

Lifestyle

People with diabetes can benefit from education about the disease and treatment, dietary changes, and exercise, with the goal of keeping both short-term and long-term blood glucose levels within acceptable bounds. In addition, given the associated higher risks of cardiovascular disease, lifestyle modifications are recommended to control blood pressure.[85][86]

Weight loss can prevent progression from prediabetes to diabetes type 2, decrease the risk of cardiovascular disease, or result in a partial remission in people with diabetes.[87][88] No single dietary pattern is best for all people with diabetes.[89] Healthy dietary patterns, such as the Mediterranean diet, low-carbohydrate diet, or DASH diet are often recommended, although evidence does not support one over the others.[87][88] According to the ADA, "reducing overall carbohydrate intake for individuals with diabetes has demonstrated the most evidence for improving glycemia", and for individuals with type 2 diabetes who can not meet the glycemic targets or where reducing anti-glycemic medications is a priority, low or very-low carbohydrate diets are a viable approach.[88] For overweight people with type 2 diabetes, any diet that achieves weight loss is effective.[89][90]

Medications

Glucose control

Most medications used to treat diabetes act by lowering blood sugar levels through different mechanisms. There is broad consensus that when people with diabetes maintain tight glucose control – keeping the glucose levels in their blood within normal ranges – that they experience fewer complications like kidney problems and eye problems.[91][92] There is however debate as to whether this is appropriate and cost effective for people later in life where the risk of hypoglycemia may be more significant.[93]

There are a number of different classes of anti-diabetic medications. Type 1 diabetes can only be treated with insulin, typically with a combination of regular and NPH insulin, or synthetic insulin analogs. Type 2 diabetes may also be treated with insulin at later stages. Some medications for type 2 diabetes are available by mouth, such as metformin, while others are only available by injection such as GLP-1 agonists.

Metformin is generally recommended as a first line treatment for type 2 diabetes, as there is good evidence that it decreases mortality.[7] It works by decreasing the liver's production of glucose.[94] Several other groups of drugs, mostly given by mouth, may also decrease blood sugar in type 2 diabetes. These include agents that increase insulin release (sulfonylureas), agents that decrease absorption of sugar from the intestines (acarbose), agents that make the body more sensitive to insulin (Thiazolidinedione) and agents that increase the excretion of glucose in the urine (SGLT2 inhibitors).[94] When insulin is used in type 2 diabetes, a long-acting formulation is usually added initially, while continuing oral medications.[7] Doses of insulin are then increased to glucose targets.[7][95]

Blood pressure

Since cardiovascular disease is a serious complication associated with diabetes, some have recommended blood pressure levels below 130/80 mmHg.[96] However, evidence supports less than or equal to somewhere between 140/90 mmHg to 160/100 mmHg. The only additional benefit found for blood pressure targets beneath this range was an isolated decrease in stroke risk, and this was accompanied by an increased risk of other serious adverse events.[97][98] A 2016 review found potential harm to treating lower than 140 mmHg.[99] Among medications that lower blood pressure, angiotensin converting enzyme inhibitors (ACEIs) improve outcomes in those with diabetes while the similar medications angiotensin receptor blockers (ARBs) do not.[100] Aspirin is also recommended for people with cardiovascular problems, however routine use of aspirin has not been found to improve outcomes in uncomplicated diabetes.[101]

Surgery

Weight loss surgery in those with obesity and type 2 diabetes is often an effective measure.[16] Many are able to maintain normal blood sugar levels with little or no medications following surgery[102] and long-term mortality is decreased.[103] There is, however, a short-term mortality risk of less than 1% from the surgery.[104] The body mass index cutoffs for when surgery is appropriate are not yet clear.[103] It is recommended that this option be considered in those who are unable to get both their weight and blood sugar under control.[105]

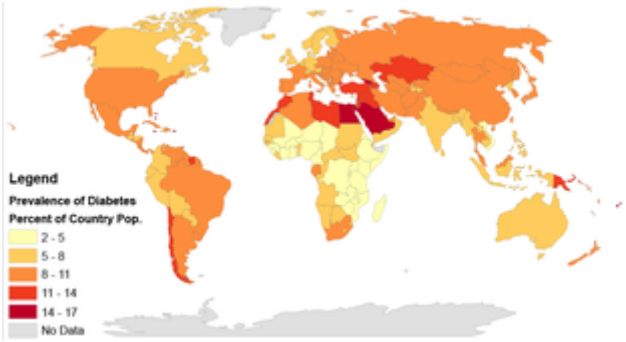
A pancreas transplant is occasionally considered for people with type 1 diabetes who have severe complications of their disease, including end stage kidney disease requiring kidney transplantation.[106]

Support

In countries using a general practitioner system, such as the United Kingdom, care may take place mainly outside hospitals, with hospital-based specialist care used only in case of complications, difficult blood sugar control, or research projects. In other circumstances, general practitioners and specialists share care in a team approach. Home telehealth support can be an effective management technique.[107]

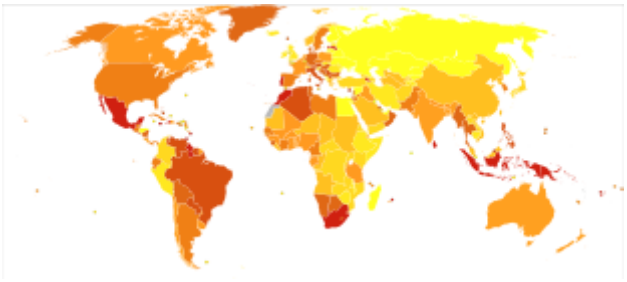
Epidemiology

In 2017, 425 million people had diabetes worldwide,[9] up from an estimated 382 million people in 2013[19] and from 108 million in 1980.[108] Accounting for the shifting age structure of the global population, the prevalence of diabetes is 8.8% among adults, nearly double the rate of 4.7% in 1980.[9][108] Type 2 makes up about 90% of the cases.[18][20] Some data indicate rates are roughly equal in women and men,[20] but male excess in diabetes has been found in many populations with higher type 2 incidence, possibly due to sex-related differences in insulin sensitivity, consequences of obesity and regional body fat deposition, and other contributing factors such as high blood pressure, tobacco smoking, and alcohol intake.[109][110]



Rates of diabetes worldwide in 2014. The worldwide prevalence was 9.2%.

The WHO estimates that diabetes resulted in 1.5 million deaths in 2012, making it the 8th leading cause of death.[14][108] However another 2.2 million deaths worldwide were attributable to high blood glucose and the increased risks of cardiovascular disease and other associated complications (e.g. kidney failure), which often lead to premature death and are often listed as the underlying cause on death certificates rather than diabetes.[108][111] For example, in 2017, the International Diabetes Federation (IDF) estimated that diabetes resulted in 4.0 million deaths worldwide,[9] using modeling to estimate the total number of deaths that could be directly or indirectly attributed to diabetes.[9]



Mortality rate of diabetes worldwide in 2012 per million inhabitants

28–91	164–184	310–404
92–114	185–209	405–1879
115–141	210–247	
142–163	248–309	

Diabetes occurs throughout the world but is more common (especially type 2) in more developed countries. The greatest increase in rates has however been seen in low- and middle-income countries,[108] where more than 80% of diabetic deaths occur.[112] The fastest prevalence increase is expected to occur in Asia and Africa, where most people with diabetes will probably live in 2030.[113] The increase in rates in developing countries follows the trend of urbanization and lifestyle changes, including increasingly sedentary lifestyles, less physically demanding work and the global nutrition transition, marked by increased intake of foods that are high energy-dense but nutrient-poor (often high in sugar and saturated fats, sometimes referred to as the "Western-style" diet).[108][113] The global number of diabetes cases might increase by 48% between 2017 and 2045.[9]

History

Diabetes was one of the first diseases described,[114] with an Egyptian manuscript from c. 1500 BCE mentioning "too great emptying of the urine."[115] The Ebers papyrus includes a recommendation for a drink to take in such cases.[116] The first described cases are believed to have been type 1 diabetes.[115] Indian physicians around the same time identified the disease and classified it as *madhumeha* or "honey urine", noting the urine would attract ants.[115][116]

The term "diabetes" or "to pass through" was first used in 230 BCE by the Greek Apollonius of Memphis.[115] The disease was considered rare during the time of the Roman empire, with Galen commenting he had only seen two cases during his career.[115] This is possibly due to the diet and lifestyle of the ancients, or because the clinical symptoms were observed during the advanced stage of the disease. Galen named the disease "diarrhea of the urine" (diarrhea urinosa).[117]

The earliest surviving work with a detailed reference to diabetes is that of Aretaeus of Cappadocia (2nd or early 3rd century CE). He described the symptoms and the course of the disease, which he attributed to the moisture and coldness, reflecting the beliefs of the "Pneumatic School". He hypothesized a correlation between diabetes and other diseases, and he discussed differential diagnosis from the snakebite, which also provokes excessive thirst. His work remained unknown in the West until 1552, when the first Latin edition was published in Venice.[117]

Two types of diabetes were identified as separate conditions for the first time by the Indian physicians Sushruta and Charaka in 400–500 CE with one type being associated with youth and another type with being overweight.[115] The term "mellitus" or "from honey" was added by the Briton John Rolle in the late 1700s to separate the condition from diabetes insipidus, which is also associated with frequent urination.[115] Effective treatment was not developed until the early part of the 20th century, when Canadians Frederick Banting and Charles Herbert Best isolated and purified insulin in 1921 and 1922.[115] This was followed by the development of the long-acting insulin NPH in the 1940s.[115]

Etymology

The word *diabetes* (/ˌdaɪ.əˈbiːtiːz/ or /ˌdaɪ.əˈbiːtɪs/) comes from Latin *diabētēs*, which in turn comes from Ancient Greek διαβήτης (*diabētēs*), which literally means "a passer through; a siphon".[118] Ancient Greek physician Aretaeus of Cappadocia (fl. 1st century CE) used that word, with the intended meaning "excessive discharge of urine", as the name for the disease.[119][120] Ultimately, the word comes from Greek διαβαίνειν (*diabainein*), meaning "to pass through,"[118] which is composed of δια- (*dia-*), meaning "through" and βαίνειν (*bainein*), meaning "to go".[119] The word "diabetes" is first recorded in English, in the form *diabete*, in a medical text written around 1425.

The word *mellitus* (/məˈlaɪtəs/ or /ˈmɛlɪtəs/) comes from the classical Latin word *mellītus*, meaning "mellite"[121] (i.e. sweetened with honey;[121] honey-sweet[122]). The Latin word comes from *mell-*, which comes from *mel*, meaning "honey";[121][122] sweetness;[122] pleasant thing,[122] and the suffix *-ītus*,[121] whose meaning is the same as that of the English suffix "-ite".[123] It was Thomas Willis who in 1675 added "mellitus" to the word "diabetes" as a designation for the disease, when he noticed the urine of a person with diabetes had a sweet taste (glycosuria). This sweet taste had been noticed in urine by the ancient Greeks, Chinese, Egyptians, Indians, and Persians.

Society and culture

The 1989 "St. Vincent Declaration"[124][125] was the result of international efforts to improve the care accorded to those with diabetes. Doing so is important not only in terms of quality of life and life expectancy but also economically – expenses due to diabetes have been shown to be a major drain on health – and productivity-related resources for healthcare systems and governments.

Several countries established more and less successful national diabetes programmes to improve treatment of the disease.[126]

People with diabetes who have neuropathic symptoms such as numbness or tingling in feet or hands are twice as likely to be unemployed as those without the symptoms.[127]

In 2010, diabetes-related emergency room (ER) visit rates in the United States were higher among people from the lowest income communities (526 per 10,000 population) than from the highest income communities (236 per 10,000 population). Approximately 9.4% of diabetes-related ER visits were for the uninsured.[128]

Naming

The term "type 1 diabetes" has replaced several former terms, including childhood-onset diabetes, juvenile diabetes, and insulin-dependent diabetes mellitus (IDDM). Likewise, the term "type 2 diabetes" has replaced several former terms, including adult-onset diabetes, obesity-related diabetes, and

noninsulin-dependent diabetes mellitus (NIDDM). Beyond these two types, there is no agreed-upon standard nomenclature.

Diabetes mellitus is also occasionally known as "sugar diabetes" to differentiate it from diabetes insipidus.[129]

Other animals

In animals, diabetes is most commonly encountered in dogs and cats. Middle-aged animals are most commonly affected. Female dogs are twice as likely to be affected as males, while according to some sources, male cats are also more prone than females. In both species, all breeds may be affected, but some small dog breeds are particularly likely to develop diabetes, such as Miniature Poodles.[130]

Feline diabetes is strikingly similar to human type 2 diabetes. The Burmese breed, along with the Russian Blue, Abyssinian, and Norwegian Forest cat breeds, showed an increased risk of DM, while several breeds showed a lower risk. There is an association between overweight and an increased risk of feline diabetes.[131]

The symptoms may relate to fluid loss and polyuria, but the course may also be insidious. Diabetic animals are more prone to infections. The long-term complications recognized in humans are much rarer in animals. The principles of treatment (weight loss, oral antidiabetics, subcutaneous insulin) and management of emergencies (e.g. ketoacidosis) are similar to those in humans.[130]

Research

Inhalable insulin has been developed. The original products were withdrawn due to side effects. Afrezza, under development by the pharmaceuticals company MannKind Corporation, was approved by the United States Food and Drug Administration (FDA) for general sale in June 2014.[132] An advantage to inhaled insulin is that it may be more convenient and easy to use.[133]

Transdermal insulin in the form of a cream has been developed and trials are being conducted on people with type 2 diabetes.[134][135]

Major clinical trials

The Diabetes Control and Complications Trial (DCCT) was a clinical study conducted by the United States National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) that was published in the *New England Journal of Medicine* in 1993. Test subjects all had type 1 diabetes and were randomized to a tight glycemic arm and a control arm with the standard of care at the time; people were followed for an average of seven years, and people in the treatment had dramatically lower rates of diabetic complications. It was as a landmark study at the time, and significantly changed the management of all forms of diabetes.[93][136][137]

The United Kingdom Prospective Diabetes Study (UKPDS) was a clinical study conducted by Z that was published in *The Lancet* in 1998. Around 3,800 people with type 2 diabetes were followed for an average of ten years, and were treated with tight glucose control or the standard of care, and again the treatment arm had far better outcomes. This confirmed the importance of tight glucose control, as well as blood pressure control, for people with this condition.[93][138][139]

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External links

- Diabetes (https://curlie.org/Health/Conditions_and_Diseases/Endocrine_Disorders/Pancreas/Diabetes/) at Curlie
- American Diabetes Association (http://www.diabetes.org)
- IDF Diabetes Atlas (http://www.diabetesatlas.org/)
- National Diabetes Education Program (http://ndep.nih.gov/)
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Classification	**ICD-10**: E10 (http://apps.who.int/classifications/icd10/browse/2016/en#/E10)–E14 (http://apps.who.int/classifications/icd10/browse/2016/en#/E14) · **ICD-9-CM**: 250 (http://www.icd9data.com/getICD9Code.ashx?icd9=250) · **MeSH**: D003920 (https://www.nlm.nih.gov/cgi/mesh/2015/MB_cgi?field=uid&term=D003920)
External resources	**MedlinePlus**: 001214 (https://www.nlm.nih.gov/medlineplus/ency/article/001214.htm) · **eMedicine**: med/546 (https://emedicine.medscape.com/med/546-overview) emerg/134 (http://www.emedicine.com/emerg/topic134.htm#) · **Patient UK**: Diabetes (https://patient.info/doctor/management-of-type-1-diabetes)