DIABETES

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Annotation: The current relevance of diabetes.

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Diabetes mellitus (**DM**), commonly known as just **diabetes**, is a group of metabolic disorders characterized by a high blood sugar level over a prolonged period of time. Symptoms often include frequent urination, increased thirst and increased appetite, If left untreated, diabetes can cause many health complications. Acute complications can include diabetic ketoacidosis, hyperosmolar hyperglycemic state, or death. Serious long-term complications include cardiovascular disease, stroke, chronic kidney disease, foot ulcers, damage to the nerves, damage to the eyes and cognitive impairment. Diabetes is due to either the pancreas not producing enough insulin, or the cells of the body not responding properly to the insulin produced. There are three main types of diabetes mellitus: Type 1 diabetes results from failure of the pancreas to produce enough insulin due to loss of beta cells. This form was previously referred to as "insulin-dependent diabetes mellitus" (IDDM) or "juvenile diabetes". The loss of beta cells is caused by an autoimmune response. The cause of this autoimmune response is unknown. Type 2 diabetes begins with insulin resistance, a condition in which cells fail to respond to insulin properly. As the disease progresses, a lack of insulin may also develop This form was previously referred to as "non insulin-dependent diabetes mellitus" (NIDDM) or "adult-onset diabetes The most common cause is a combination of excessive body weight and insufficient exercise Gestational diabetes is the third main form, and occurs when pregnant women without a previous history of diabetes develop high blood sugar levels. Type 1 diabetes must be managed with insulin injections Prevention and treatment of type 2 diabetes involves maintaining a healthy diet, regular physical exercise, a normal body weight, and avoiding use of tobacco. Type 2 diabetes may be treated with medications such as insulin sensitizers with or without insulin Control of blood pressure and maintaining proper foot and eye care are important for people with the disease. Insulin and some oral medications can cause low blood sugar. Weight loss surgery in those with obesity is sometimes an effective measure in those with type 2 diabetes. Gestational diabetes usually resolves after the birth of the babyAs of 2019, an estimated 463 million people had diabetes worldwide (8.8% of the adult population), with type 2 diabetes making up about 90% of the cases.[10] Rates are similar in women and men. Trends suggest that rates will continue to rise. Diabetes at least doubles a person's risk of early death. In 2019, diabetes resulted in approximately 4.2 million deaths. It is the 7th leading cause of death globally. The global economic cost of diabetes related health expenditure in 2017 was

estimated at US\$727 billion. In the United States, diabetes cost nearly US\$327 billion in 2017. Average medical expenditures among people with diabetes are about 2.3 times higher

Signs and Symptoms

The classic symptoms of untreated diabetes are unintended weight loss, polyuria (increased urination), polydipsia (increased thirst), and polyphagia (increased hunger). 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. 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.

Causes

Diabetes mellitus is classified into six categories: type 1 diabetes, type 2 diabetes, hybrid forms of diabetes, hyperglycemia first detected during pregnancy, "unclassified diabetes", and "other specific types". The "hybrid forms of diabetes" contains slowly evolving, immune-mediated diabetes of adults and ketosis-prone type 2 diabetes. The "hyperglycemia first detected during pregnancy" contains gestational diabetes mellitus and diabetes mellitus in pregnancy (type 1 or type 2 diabetes first diagnosed during pregnancy). The "other specific types" are a collection of a few dozen individual causes. Diabetes is a more variable disease than once thought and people may have combinations of forms. The term "diabetes", without qualification, refers to diabetes mellitus.

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 an immune-mediated nature, in which a T cell-mediated autoimmune attack leads to the loss of beta cells and thus insulin. 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. "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. 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). These phenomena are believed to occur no more frequently than in 1% to 2% of persons with type 1 diabetes.

Type 1 diabetes is partly <u>inherited</u>, with multiple genes, including certain <u>HLA genotypes</u>, known to influence the risk of diabetes. In genetically susceptible people, the onset of diabetes can be triggered by one or more <u>environmental factors</u>, such as a <u>viral infection</u> or diet. Several viruses have been implicated, but to date there is no stringent evidence to support this hypothesis in humans. Among dietary factors, data suggest that <u>gliadin</u> (a protein present in <u>gluten</u>) may play a role in the development of type 1 diabetes, but the mechanism is not fully understood. Type 1 diabetes can occur at any age, and a significant proportion is diagnosed during adulthood. <u>Latent autoimmune diabetes of adults</u> (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 a cause.

Type 2

Reduced insulin secretion and absorption leads to high glucose content in the blood.Type 2 diabetes is characterized by <u>insulin resistance</u>, which may be combined with relatively reduced insulin secretion. The defective responsiveness of body tissues to insulin is believed to involve the <u>insulin receptor</u>. 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. Many people with type 2 diabetes have evidence of <u>prediabetes</u> (impaired fasting glucose and/or impaired glucose tolerance) before meeting the criteria for type 2 diabetes. The progression of prediabetes to overt type 2 diabetes can be slowed or reversed by lifestyle changes or <u>medications</u> that improve insulin sensitivity or reduce the <u>liver's glucose production</u>.

Type 2 diabetes is primarily due to lifestyle factors and genetics. A number of lifestyle factors are known to be important to the development of type 2 diabetes, including <u>obesity</u> (defined by a <u>body mass index</u> of greater than 30), lack of <u>physical activity</u>, poor <u>diet</u>, <u>stress</u>, and <u>urbanization</u>. Excess body fat is associated with 30% of cases in people of Chinese and Japanese descent, 60–80% of cases in those of European and African descent, and 100% of Pima Indians and Pacific Islanders. Even those who are not obese may have a high <u>waist–hip ratio</u>.Dietary factors such as <u>sugar</u>-sweetened drinks are associated with an increased risk. The type of <u>fats</u> in the diet is also important, with <u>saturated fat</u> and <u>trans fats</u> increasing the risk and <u>polyunsaturated</u> and <u>monounsaturated fat</u> decreasing the risk. Eating <u>white rice</u> excessively may increase the risk of diabetes, especially in Chinese and Japanese people. Lack of physical activity may increase the risk of diabetes in some people. <u>Adverse childhood experiences</u> (ACEs), including abuse, neglect, and household difficulties, increase the likelihood of type 2 diabetes later in life by 32%, with <u>neglect</u> having the strongest effect.

Pathophysiology

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.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.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. 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. 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. Insulin is released into the blood by beta cells (ß-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. 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. 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). 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). In addition, intracellular glucose deficiency stimulates appetite leading to excessive food intake (polyphagia).

Diagnosis

See also: Glycated hemoglobin and Glucose tolerance test Diabetes mellitus is diagnosed with a test for the glucose content in the blood, and is diagnosed by demonstrating any one of the following:

- Fasting plasma glucose level ≥ 7.0 mmol/L (126 mg/dL). For this test, blood is taken after a period of fasting, i.e. in the morning before breakfast, after the patient had sufficient time to fast overnight.
- 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 plasma glucose ≥ 11.1 mmol/L (200 mg/dL) either while fasting or not fasting
- Glycated hemoglobin (HbA$_{1C}$) ≥ 48 mmol/mol (≥ 6.5 DCCT %).

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

Prevention

There is no known preventive measure for type 1 diabetes. 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. Higher levels of physical activity (more than 90 minutes per day) reduce the risk of diabetes by 28%. 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. Limiting sugary beverages and eating less red meat and other sources of saturated fat can also help prevent diabetes. 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. 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 .

Epidemiology

In 2017, 425 million people had diabetes worldwide, up from an estimated 382 million people in 2013 and from 108 million in 1980. 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. Type 2 makes up about 90% of the cases. Some data indicate rates are roughly equal in women and men, 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. The WHO estimates that diabetes resulted in 1.5 million deaths in 2012, making it the 8th leading cause of death. 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. For example, in 2017, the International Diabetes Federation (IDF) estimated that diabetes resulted in 4.0 million deaths worldwide using modeling to estimate the total number of deaths that could be directly or indirectly attributed to diabetes. 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, where more than 80% of

diabetic deaths occur. The fastest prevalence increase is expected to occur in Asia and Africa, where most people with diabetes will probably live in 2030. 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). The global number of diabetes cases might increase by 48% between 2017 and 2045.

Resources used

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