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Classification, Symptoms, Treatment and Preventive Strategies of Diabetes. A guide to the basic

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ABSTRACT

Introduction

Diabetes is a chronic metabolic disorder characterized by impaired insulin secretion and action. Risk factors for diabetes include age, obesity, low physical activity, hypertension, lipid disorders, and genetic predisposition. Symptoms of diabetes typically include frequent urination, weight loss, excessive thirst, weakness, fatigue, susceptibility to fungal infections and recurrent boils. Diabetes is a prevalent and significant societal concern, often causing anxiety, uncertainty and a sense of danger upon diagnosis.

Aim of the study

The aim of the study is to provide a comprehensive analysis of diabetes, including its classification, characteristic symptoms, the most frequently occurring diabetes-related complications, and preventive strategies. Through a detailed discussion of these issues, our goal is to increase public awareness of diabetes and provide readers with comprehensive knowledge about this disease.

Material and method

This article presents the current state of knowledge about diabetes. A literature review was conducted using the PubMed, Google Scholar and Web of Science databases, utilizing keywords such as "diabetes", "diabetes mellitus", "diabetes complications".

Results

The number of people with diabetes has continued to rise. Scientists predict that in a few decades, this number could reach more than half a billion globally. Many individuals may not realize that they are at risk for this civilization disease, often due to unhealthy lifestyle choices such as smoking, obesity, and lack of physical activity. Early initiation of treatment is crucial in preventing serious complications. Despite living with diabetes for years, some

patients still report insufficient knowledge about their condition. Therefore, educating patients about the nature of the disease and its treatment is essential for improving their quality of life.

Keywords

diabetes, clinical symptoms, obesity, diabetes-related complications

Introduction

According to the World Health Organization's definition, diabetes is defined as a syndrome of metabolic diseases characterized by elevated blood glucose levels (hyperglycemia) resulting from a defect in the production or function of insulin secreted by pancreatic β cells [1,2].

Insulin is an anabolic hormone whose inactive precursor is proinsulin, composed of two chains A and B linked by a C-peptide. It is stored in the vesicles of the Golgi apparatus of the pancreatic β -cells, leading to glycogen deposition in skeletal muscle and liver [3].

Chronic hyperglycemia leads to damage and dysfunction of many organs, especially the cardiovascular system, kidneys, eyes and nervous system [4,5].

The main stimulus stimulating insulin production is the postprandial increase in blood glucose levels and the concentration of amino acids. Its target tissues are hepatocytes, myocytes, and adipocytes. In the liver, insulin stimulates glycogenesis, inhibits glycogenolysis and gluconeogenesis, leading to the production of fatty acids and stimulating VLDL synthesis. In adipose tissue, it enhances lipogenesis and inhibits lipolysis. In muscles, it facilitates glucose transport into the cell, stimulates glycogen and protein synthesis, and enhances fatty acid oxidation. Additionally, insulin exhibits mitogenic activity, activating cell proliferation and inhibiting apoptosis [6,7].

Insulin deficiency leads to metabolic disturbances of a catabolic nature, manifested by inhibition of glycolysis, increased glycogenolysis, gluconeogenesis, and disruptions in lipid and protein synthesis, resulting in increased lipolysis and ketogenesis [7].

Epidemiology

According to WHO data from 2016, the global number of people suffering from diabetes increased from 108 million (in 1980) to 422 million (in 2014) (WHO, 2016). Data from the NCD Risk Factor Collaboration show that in Poland, from 1980 to 2014, the number of people with diabetes has continuously increased. In 2014, there were 2.97 million adults diagnosed with diabetes, with approximately 90% of them having type 2 diabetes. Type 1 diabetes is most common in children. Among 44 European countries, Poland ranks 13th in terms of the percentage of adults with diabetes among men and 15th among women [8].

Projections indicate that the number of diabetes cases worldwide will continue to rise, reaching 592 million by 2035 and 700 million by 2045 [2,5].

This increase is closely linked to the growing number of obese individuals, decreasing physical activity, and demographic changes. 40-50% of people do not know about their disease [9].

Incidence is rising faster in countries with low and middle incomes per capita compared to high-income countries [10].

In Poland, diabetes complications result in the deaths of 30,000 people annually, and the disease itself leads to serious complications, often resulting in disability. Approximately 14,000 amputations due to diabetic foot complications are performed each year, with 75% of deaths associated with cardiovascular complications. The annual number of amputations in people with diabetes increased significantly from 5,049 to 7,759 between 2010 and 2019 [2,5,11].

Classification of diabetes

According to the World Health Organization and the American Diabetes Association, diabetes can be classified into four main types: type 1 diabetes, also known as juvenile diabetes or insulin-dependent diabetes; type 2 diabetes, which accounts for the majority of cases; "other specific types of diabetes," which can be triggered by various conditions and diseases; and gestational diabetes, which occurs for the first time during pregnancy and typically resolves after delivery [12,28].

Type 1 diabetes is an autoimmune disease with a multifactorial etiology. It affects less than 10% of patients and is most commonly diagnosed in children and adolescents. It is

caused by an absolute deficiency of insulin resulting from the destruction of β cells in the pancreatic islets of Langerhans, which are the only cells producing insulin [2].

The development of this disease is predisposed by HLA tissue compatibility haplotypes (HLA-DR3, -DR4, -DP, DQ2b). Many triggering factors leading to the development of the disease have been identified in genetically susceptible individuals, such as viral infections - enteroviruses, Coxsackie B6 virus, rubella virus, toxins, and nitrogen additives in food [14].

Regardless of the triggering mechanism, the autoimmune destruction of pancreatic β cells gradually leads to a loss of insulin secretion capacity. Infiltration of lymphocytes, macrophages, and the cytokines released by them lead to inflammation, causing destruction of pancreatic islets. Autoantibodies against insulin (IAA), nonspecific islet cell antibodies (ICA), autoantibodies against glutamic acid decarboxylase (GAD), and autoantibodies against tyrosine phosphatase IA-2 and IA-2 β appear in circulation. Their presence is observed in 77% of patients. Clinical symptoms appear when about 80% of β cells are destroyed [2,5].

LADA (latent autoimmune diabetes in adults) is a distinct form of autoimmune diabetes. It mainly affects individuals aged 30-50 years, usually without obesity, often with a history of autoimmune diseases. It is often misdiagnosed as type 2 diabetes, but in this type, antibodies against pancreatic islet antigens, mainly GAD, are present [2,4].

There is also a type 1 diabetes of unknown etiology, known as idiopathic diabetes. It is characterized by episodes of ketoacidosis and insulin deficiency between episodes. It occurs in individuals of African and Asian descent. There is no evidence of autoimmunity or association with tissue compatibility genes. It is typically inherited [4,5].

Type 2 diabetes, also known as non-insulin-dependent diabetes, primarily affects adults, although in recent years there has been an observed increase in incidence among adolescents. This disease is characterized by two main mechanisms: insulin resistance (meaning reduced sensitivity of peripheral tissues to insulin action) and impaired insulin secretion. Insulin resistance leads to the depletion of pancreatic islet function initially causing relative, and later absolute insulin deficiency [2,5].

It may be influenced by genetic factors (polygenic inheritance) but predominantly by environmental factors (obesity, low physical activity). It is associated with obesity in 80% of cases, especially central obesity. The risk of disease increases with higher BMI and waist circumference. Excess free fatty acids through visceral adipose tissue lead to increased lipid oxidation in the liver and muscles, slowing down glucose metabolism due to decreased hexokinase activity. This "lipotoxicity" leads to compensatory insulin secretion and may result in gradual depletion of insulin reserves and glucose metabolism breakdown [5].

MODY (Maturity Onset Diabetes of the Young), a form of type 2 diabetes occurring in young individuals, usually manifests between the ages of 15 and 35. It is characterized by impaired insulin secretion and is inherited in an autosomal dominant manner. Chromosomal mutation may localize on various chromosomes. The most common form is associated with mutations on chromosome 12 (hepatocyte nuclear factor HNF-1 α), responsible for about 70% of cases. The second most frequent mutation occurs on chromosome 7p in the glucokinase gene (GCK), which acts as a "glucose sensor" for pancreatic β cells. Patients with defects in this gene have the sensor set to a higher level, causing increased insulin production when blood glucose levels are high [4].

There is also clinically non-insulin-dependent diabetes with monogenic characteristics, but it is characterized by a different mode of inheritance, known as mitochondrial diabetes. It is associated with mutations in mitochondrial DNA and is inherited exclusively in a maternal manner. The most common cause of the disease is a point mutation at position 3243 within the gene for leucine tRNA. It typically has a mild onset, manifesting around the age of 40 [12].

In the category referred to as "other specific types of diabetes", there are forms of the disease that do not correspond to either type 1 or type 2 diabetes, accounting for less than 5% of diabetic patients. It may result from pancreatic parenchyma damage: trauma, inflammation, tumors. Genetic defects of β cells, genetic dysfunction of the insulin receptor, diseases of the exocrine part of the pancreas: cystic fibrosis, tumors, hemochromatosis, may lead to the development of diabetes. Other genetically based syndromes include Down syndrome, Klinefelter syndrome, Turner syndrome, Pader-Willi syndrome, Huntington's chorea, or porphyria. Diabetes may also be the result of endocrinological disorders resulting from excess secretion of hormones antagonistic to insulin. Such diseases include Cushing's syndrome, acromegaly, hyperthyroidism, pheochromocytoma, glucagonoma. Additionally, there are diabetes types associated with infections (congenital rubella, cytomegalovirus), rare autoimmune-based syndromes. This group also includes hyperglycemic states induced by drugs, such as glucocorticosteroids, thiazides, thyroid hormones, or poisoning [12].

Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance that occurs or is detected during pregnancy [4]. It is the most common metabolic complication of pregnancy. The increased incidence is associated with the growing prevalence of overweight or obesity, older age at pregnancy, low physical activity, and hypertension [13]. The cause of gestational diabetes is the physiological intensification of insulin resistance, induced by the increased levels of pregnancy hormones (progesterone, estrogen, placental lactogen), and impaired insulin secretion. It mainly manifests in the third trimester when these hormones act most strongly and resolves after delivery. In 70% of women with gestational diabetes, type 2 diabetes develops within 10 years after pregnancy [14, 29].

Symptoms

Diagnosing type 1 diabetes in children and adolescents is not troublesome when random blood glucose levels reach above 200 mg% and characteristic clinical symptoms are present, such as: increased thirst, excessive hunger, frequent urination, rapid weight loss, weakness, constant fatigue, lack of interest in activities, concentration problems, vision disturbances, nausea, vomiting, and ketoacidosis. In young children and infants, symptoms may escalate within a single day. Additionally, skin changes, such as dry skin, cheilitis, brittle nails, and inflammatory changes in the genital area, may also suggest suspicion of diabetes [15].

The onset of diabetic ketoacidosis poses a serious life-threatening condition and may occur in both type 1 and type 2 diabetes, although much less frequently. It is a state in which the body loses its acid-base balance and experiences disturbances in carbohydrate, fat, and protein metabolism due to a sudden deficiency of insulin.

Symptoms of diabetic ketoacidosis include excessive thirst, frequent urination, signs of dehydration (such as dry skin and mouth), nausea, vomiting, abdominal pain, changes in breathing (Kussmaul breathing), acetone odor from the mouth, altered consciousness, and coma [25].

The development of type 2 diabetes is a gradual process, and many years may pass before classic symptoms appear. These symptoms include increased thirst, frequent urination, feelings of fatigue, worsening vision, and susceptibility to skin infections. Before the onset of type 2 diabetes symptoms, a prediabetic state may occur [26].

Consequences and complications of diabetes

Acute complications of diabetes include diabetic comas: hypoglycemic, ketoacidotic, hyperosmolar, and lactic acidosis.

Hypoglycemia is characterized by blood glucose levels below <3 mmol/l (54 mg/dl) and can occur in both types of diabetes. Its occurrence may be triggered by insulin overdose,

excessive physical exertion with inadequate carbohydrate intake. Symptoms include hunger, fainting, headaches, unusual behavior, tachycardia, sweating, trembling, anxiety, and coma [2,5].

Hyperosmolar coma, on the other hand, results from high hyperglycemia, dehydration, increased serum osmolality, and usually pre-renal kidney failure. Despite very high blood glucose levels, ketoacidosis does not develop. It is most commonly diagnosed in older patients, mainly those with type 2 diabetes in cases of delayed diagnosis or inadequate treatment. Predisposing factors include infections, the use of diuretic and psychotropic drugs, worsening kidney function, excessive consumption of sweetened beverages, and alcohol intoxication [25, 27, 31].

Lactic acidosis coma occurs rarely but progresses severely. It is associated with the production of lactic acid. The most common cause is alcohol abuse by a person with diabetes treated with metformin [2,5].

Long-term complications of diabetes lead to disorders of many organs. They are associated with changes in capillaries, small arteries, and veins (microangiopathies), atherosclerotic changes in medium and large vessels (macroangiopathies), increased susceptibility to bacterial and fungal infections.

Diabetic macroangiopathy includes changes in coronary arteries responsible for heart blood supply, hence the risk of coronary heart disease (heart attack, heart failure, and angina pectoris) is twice as high, and the prognosis in a heart attack is twice worse than in the general population. Atherosclerosis of cerebral vessels manifests as neurological syndromes resulting from brain blood flow disorders. Paralysis or strokes may occur. Peripheral vascular diseases manifest as leg pain during exertion (intermittent claudication), and in cases of severe atherosclerotic changes, it can lead to infection, ulcers, and tissue destruction of the foot with neuropathy [17].

Microangiopathies in diabetes include retinopathy, nephropathy, and neuropathy. Retinopathy is one of the most severe complications of diabetes. It involves damage to the retinal microcirculation, triggering a cascade of further disturbances and changes in the eye

fundus. This leads to a gradual deterioration of vision sharpness and ultimately to vision loss.

Diabetic nephropathy progresses through several stages. The initial stage involves microalbuminuria (excretion of 30-300mg/24h of albumin in urine), followed by macroalbuminuria (>300mg/24h). Further deterioration of kidney function can lead to renal failure. Kidney changes include focal glomerular sclerosis, arterial and arteriolar sclerosis,

and necrosis of renal papillae. Genetic predispositions, hypertension, and smoking also play significant roles in kidney damage in diabetic patients [18, 30].

Diabetic neuropathy results from ischemia and metabolic changes causing nerve demyelination. It leads to severe pain that significantly affects patients' quality of life. The most common form affects the majority of nerve fibers and mainly involves peripheral parts of the limbs. Another group includes mononeuropathies, which are isolated peripheral or cranial nerve palsies [18, 30].

During gestational diabetes, glucose crosses the placental barrier via facilitated diffusion, stimulating the hypertrophy of pancreatic islets, leading to increased anabolic insulin production. This results in the overgrowth of adipose tissue, muscle (including cardiac muscle), and liver, known as fetal macrosomia. It is characterized by excessive fetal mass relative to gestational age, with a birth weight exceeding 4000-4500g (another criterion is a weight exceeding the 90th percentile for the corresponding age and sex) [13].

In infants with excessive birth weight, various metabolic disorders occur, most commonly hypoglycemia and an increased risk of developing conditions such as obesity, type 2 diabetes, and cardiovascular diseases [1].

Newborns of mothers with diabetes are more likely to have congenital defects (including neural tube defects, cardiomyopathies), perinatal injuries, respiratory disorders, hyperbilirubinemia, metabolic disorders, and intrauterine deaths. Pregnant women with diabetes are also more likely to develop pregnancy-induced hypertension, preeclampsia, or undergo cesarean section deliveries [19, 29].

Diagnostics

The fundamental test performed for diabetes diagnosis is the measurement of glucose concentration in the blood. It is also common in chronic diabetic management for continuous monitoring and evaluating the effectiveness of the initiated pharmacotherapy. Glucose concentration can be measured from venous whole blood, venous plasma, or capillary blood.

Types of tests that can be conducted include fasting glucose, random glucose, and postprandial glucose. An oral glucose tolerance test with 75g of glucose is also performed.

Diabetes can be diagnosed in 4 situations:

 random plasma glucose ≥200 mg/dl (11.1 mmol/l) with typical symptoms of hyperglycemia,

- twice fasting glycaemia ≥126 mg/dl (7.0 mmol/l) in measurements taken on different days,
- glycaemia at 120 min during an oral glucose tolerance test (OGTT) ≥200 mg/dl (11.1 mmol/l),
- HbA1c \geq 6.5% (48 mmol/mol).

For screening tests (active search for diabetes due to its often a tomatic course), we include fasting plasma glucose measurement, OGTT or HbA1c determination. Screening should be performed:

- once every 3 years for individuals aged >45 years,
- annually for individuals at risk of glucose tolerance disorders, regardless of age [19,20].

Treatment

The goal of treating individuals with diabetes is to improve their quality of life and prevent potential complications. One of the initial steps in halting the progression of the disease is to modify the existing lifestyle. This involves focusing on adopting principles of healthy eating and incorporating physical activity into daily routines. It is important to emphasize that this physical activity, to have a therapeutic effect, should be moderate but consistent. In cases where diabetes is suspected, regular medical monitoring is crucial [22].

It should be noted that the mentioned lifestyle changes may only have a therapeutic effect in the case of type 2 diabetes. Treatment of type 1 diabetes invariably requires the initiation of insulin therapy due to the complete absence of this hormone. Insulin is most commonly obtained through DNA recombination to precisely match human insulin. Analogous insulin preparations, including long-acting and short-acting analogs, are frequently used. The administration of insulin should be planned to closely mimic physiological patterns. While multiple daily injections, typically before meals and bedtime, have traditionally been utilized, insulin pump therapy is becoming increasingly common, providing a continuous insulin infusion [23].

For type 2 diabetes, the primary treatment involves oral antidiabetic medications. With the increasing incidence of the condition, there is also a growing number of drugs being utilized. These include metformin, sulfonylurea derivatives, meglitinides, thiazolidinediones, and alpha-glucosidase inhibitors. Their mechanisms of action involve limiting glucose production in the liver, increasing cell sensitivity to insulin, increasing insulin release, and inhibiting the activity of intestinal enzymes that break down polysaccharides into monosaccharides [32,33].

The additional benefits associated with the use of antidiabetic medications include weight reduction, improvement in lipid profile, decreased risk of cardiovascular complications and cardiovascular events for selected GLP-1 receptor agonists and certain SGLT2 inhibitors, reduction in the risk of progression of diabetic kidney disease, and decreased frequency of hospitalizations due to heart failure [34,35].

Prevention

The onset of Type 2 diabetes can often be delayed or even prevented through lifestyle modifications, including dietary changes and increased physical activity. The benefits of these lifestyle adjustments can be long-lasting, providing protection against diabetes for many years. However, type 1 diabetes cannot be prevented as it arises from inadequate insulin secretion by the pancreatic beta cells [36].

An important element in the prevention of obesity and type 2 diabetes is an adequate intake of macronutrients. Consuming fibre from cereal grains can reduce the risk of developing this disease. Additionally, results from the European Prospective Investigation into Cancer and Nutrition study suggest that the risk of type 2 diabetes increases with increased protein intake. In contrast, the consumption of pulses, which are a rich source of plant protein and fibre, has a beneficial effect on blood glucose and insulin levels. High intake of simple sugars is a significant risk factor for the development of type 2 diabetes. Consumption of sweetened beverages of more than 1-2 portions per day is associated with a 26% increased risk of developing the disease. Consuming alcohol in moderation can have a positive impact on health. Moderate intake of red wine is recommended due to its antioxidant properties, which may help reduce the risk of cardiovascular diseases [37].

Physical activity is a key component of a healthy lifestyle that helps reduce the risk of developing diabetes. Regular physical activity is particularly recommended for individuals with risk factors for diabetes, such as hypertension, abdominal obesity, insulin resistance, dyslipidemia, and a family history of diabetes. According to WHO recommendations, engaging in moderate physical activity for 30 minutes, five times a week, or high-intensity endurance training three times a week for 20 minutes is recommended to maintain health and prevent chronic diseases [38].

Diabetes mellitus is a diet-dependent disease, and therefore a correctly selected menu plays an important role in the treatment and prevention of late complications of this disease entity. It also seems important to increase the role of dietitians in the diagnostic process, as well as the treatment process, which in turn may reduce treatment costs by partially reducing the use of pharmacotherapy in favour of diet. Public education stands as the primary tool for prevention [39,40].

Conclusions

Diabetes is one of the most common diseases in society. It will be one of the most serious health problems in the coming years, as the number of patients continues to rise. Its chronic complications, mainly affecting the vascular system, result in a reduced quality of life and disability and therefore require specialised care. In its most severe forms or in the absence of appropriate and effective treatment, it can even lead to the death of the patient.

It is extremely important for people with diabetes to maintain good physical condition, follow a proper diet, exercise, cooperate with their doctor, visit and undergo check-ups, and prevent complications.

Author's constribution

Conceptalization, Magda Madoń and Patrycja Proszowska, methodology, Zuzanna Kotowicz, Aleksandra Pich-Czekierda and Julia Sieniawska, software, Daria Sieniawska, check Magda Madoń and Aleksandra Pich-Czekierda, formal analysis, Magda Madoń and Patrycja Proszowska, investigation Adrianna Orzeł and Daria Sieniawska, resources, Julia Sieniawska, data curation, Magda Madoń, writing-rough preparation, Magda Madoń, Aleksandra Pich-Czekierda, Zuzanna Kotowicz, visualization, Patrycja Proszowska, supervision, Julia Sieniawska, project administration, Magda Madoń, Daria Sieniawska and Adrianna Orzeł. All authors have read and agreed with the published version of the manuscript.

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