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DIABETES MELLITUS: FROM MOLECULAR MECHANISMS TO PATHOPHYSIOLOGY AND PHARMACOLOGY

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Abstract

Diabetes mellitus is a metabolic disorder characterized by a persistent elevation of blood glucose levels, often accompanied by various long-term clinical manifestations. The disease is spreading rapidly across the globe, and its prevalence is expected to rise significantly in the coming years. This review aims to explore the mechanisms underlying the development of diabetes, its pathophysiological characteristics, and pharmacological aspects. According to the analyzed literature, diabetes mellitus is a chronic condition influenced by multiple risk factors and associated with severe complications that greatly affect patients' quality of life. Nevertheless, advances in modern science are leading to improved methods for predicting, diagnosing, treating, and managing the different forms of this disease.

Keywords

Mechanism, Pathophysiology, Pharmacology, Diabetes Mellitus.

Introduction

Diabetes is a chronic disease that develops as a result of the body's impaired ability to process and regulate blood glucose levels. This condition may arise either from excessive insulin secretion by the pancreas or from a disruption in the hormone's action at the cellular level.[1].

Insulin is a polypeptide hormone produced by the β-cells of the pancreatic islets of Langerhans. Its main roles include maintaining normal blood sugar levels and facilitating the uptake and utilization of glucose by the body's cells.[2].

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In diabetic patients, a condition known as insulin resistance is often observed, where cells lose sensitivity to the effect of insulin, resulting in the body's weakened reaction to this hormone. In other words, tissue sensitivity to the metabolic effects of insulin decreases and glucose utilization decreases, which contributes to the accumulation of sugar in the blood and, consequently, the development of type 2 diabetes mellitus. [3].

The causes of diabetes are diverse, and approaches to its treatment are determined by the specific type of disease. Although there are several types of diabetes, the main ones include three forms: type 1 diabetes, type 2 diabetes, and gestational diabetes (occurs during pregnancy) (see Fig.. 1).

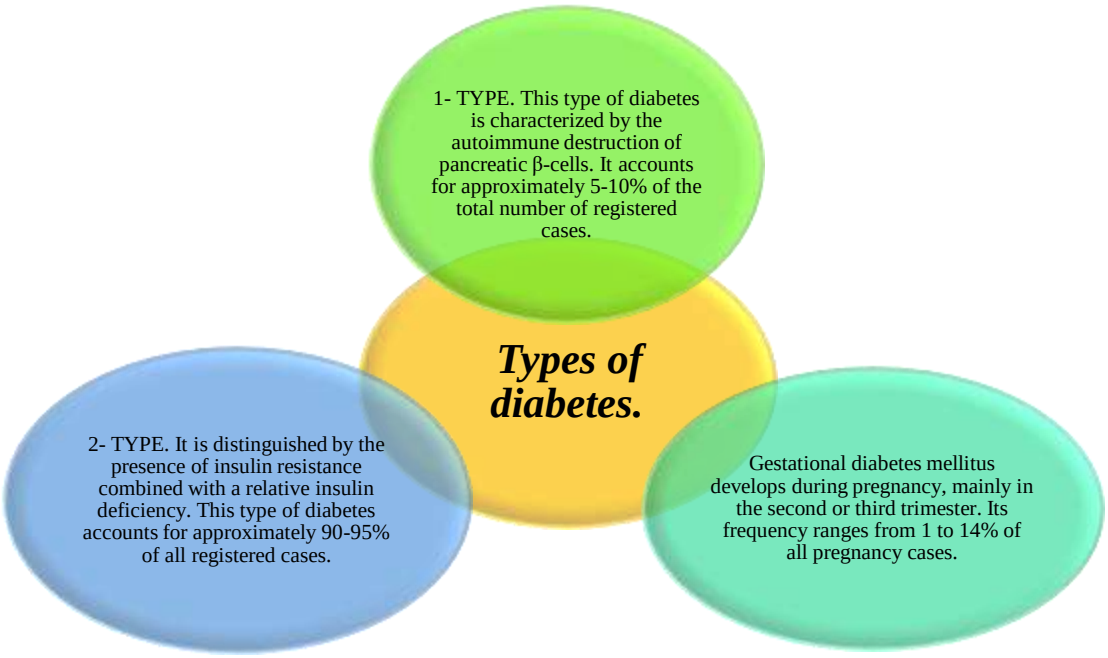

Fig. 1. Types of diabetes mellitus.

1.1. Type 1 diabetes

Type 1 diabetes mellitus is a chronic autoimmune disease characterized by insufficient insulin production and, consequently, increased blood glucose levels (hyperglycemia) [4]. The main cause of its development is the autoimmune destruction of pancreatic β-cells, which leads to complete absence of insulin secretion [5]. This disease is widespread worldwide and requires constant medical supervision, as without proper treatment, it can lead to severe complications such as cardiovascular and renal pathologies, vision impairment, and stroke. The main method of therapy for type 1 diabetes is insulin therapy, which refers to "exogenous insulin replacement therapy." However, despite the effectiveness of this approach, a significant portion of patients cannot achieve ideal control of blood glucose levels. [6].

1.2. Type 2 diabetes

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Type 2 diabetes mellitus is one of the most common metabolic disorders, the development of which is associated with two key mechanisms: reduced insulin production by pancreatic β-cells and impaired tissue response to its effects [8].

The main risk factors for this disease include elevated blood sugar levels, excess body weight, high triglyceride levels, improper nutrition, low physical activity, age-related changes, hereditary predisposition, and psycho-emotional states such as stress, anxiety, and depression [9]. For effective control and treatment of type 2 diabetes, insulin therapy is used in combination with metformin and other hypoglycemic agents [10].

1.3. Gestational diabetes (diabetes associated with pregnancy)

Gestational diabetes is a condition in which a woman's blood glucose levels are elevated during pregnancy. It develops only during pregnancy in a certain group of women and can negatively affect both mother's health and fetal development. The main factors contributing to this disorder include excess body weight, hereditary predisposition to diabetes, and the mother's age. The disease has a connection with the development of type 2 diabetes and coronary heart disease [11].

Generally, gestational diabetes is diagnosed in the second or third trimester in women who previously had no signs of diabetes. It is considered the most common pregnancy complication [12]. Control of this condition is carried out using two main approaches: insulin therapy and lifestyle changes, including a rational diet and nutritional support [13].

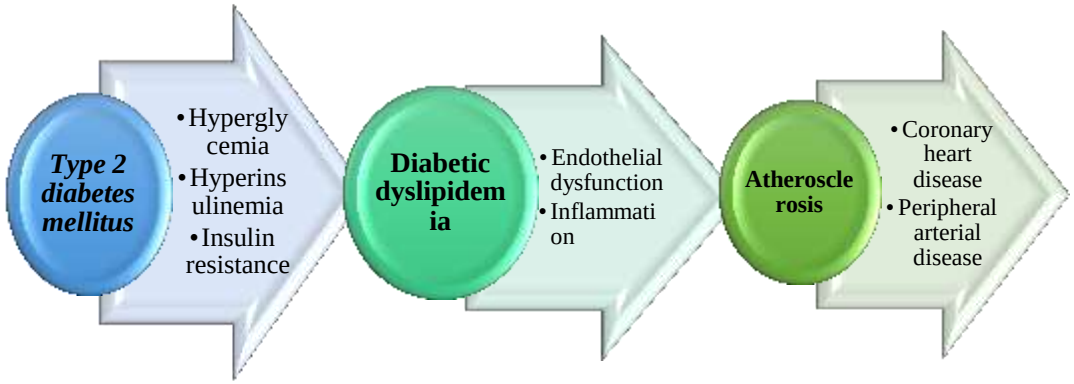

Fig. 2. Complications of type 2 diabetes mellitus.

According to global epidemiological estimates, today more than half a billion people suffer from diabetes, which is more than 10.5% of the adult population of the planet [14] (see Fig. 2 and Fig. 3).

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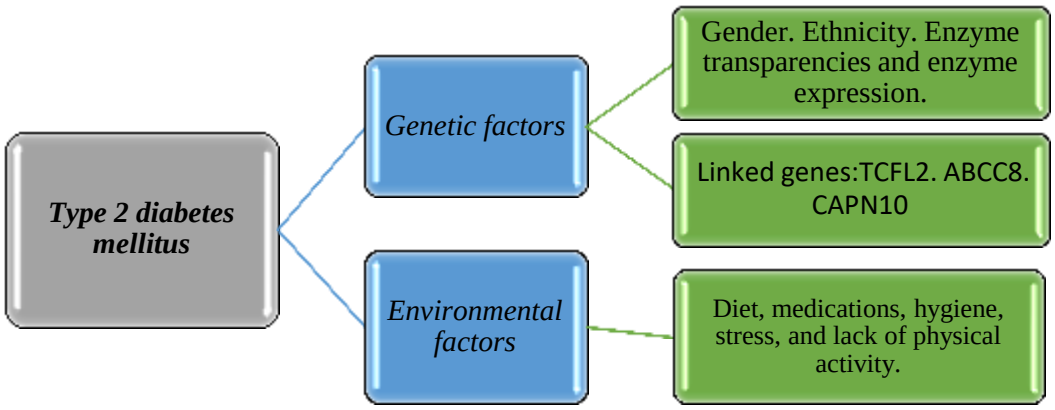

Fig. 3. Factors affecting type 2 diabetes mellitus.

Glucose metabolism

Glucose is the main source of energy and nutrient substrate for human body cells. It enters with food, undergoes processing in the body, and is transported from the blood to target cells. The movement of glucose through the plasma membrane plays an important role in metabolic processes [15]. Lipids, proteins, and carbohydrates are eventually metabolized to form glucose, which provides the body's energy needs.

Glucose metabolism involves several key biochemical pathways, such as glycogenesis, glycolysis, gluconeogenesis, and glycogenolysis. Glycolysis is an enzymatically catalyzed catabolic process in which glucose is broken down in cells into pyruvate [16].

To maintain a stable blood glucose level, especially during fasting, several metabolic reactions occur in the cytosol and mitochondria of liver cells, ensuring the synthesis of glucose from non-carbohydrate compounds. This process is regulated by the main hormones - insulin, glucagon, and cortisol [17].

In addition, during fasting, the pancreas secretes glucagon, which activates the process of glycogenolysis - the biochemical mechanism of glycogen breakdown into glucose and glucose-1-phosphate. The reverse process - glycogenesis - ensures the synthesis of glycogen, in which glucose molecules combine to store it in the body.

Circadian cycle and blood glucose regulation

Circadian rhythms play a key role in maintaining the balance of glucose levels in the body. In humans, maximum tolerance to glucose is observed in the morning hours, which is associated with increased activity of pancreatic β-cells during this period. By evening, on the contrary, glycogen reserves increase, and after noon, fat tissue shows increased sensitivity to the effect of insulin. Thus, daily fluctuations in metabolic activity form a continuous chain of glucose metabolism processes.

Normally, the blood glucose level on an empty stomach (three to four hours after the last meal) is approximately 80-90 mg/dL. After eating (post-prandial period), the glucose concentration can temporarily increase to 120-140 mg/dl,

however, due to feedback mechanisms, the body returns it to normal values within two hours.

During fasting, the body receives glucose through gluconeogenesis - the process of glucose synthesis from non-carbohydrate sources. When blood sugar levels rise, insulin production is stimulated, which promotes the transfer of glucose from the extracellular environment into the cells, thereby reducing its concentration in the blood. Conversely, when the sugar level decreases, the secretion of glucagon is activated, which increases the glucose level due to the activation of glycogen breakdown.

Consequently, the clinical significance of this mechanism lies in the fact that the disruption or insufficient production of insulin leads to the development of diabetes mellitus.

Glucose transport and its disorders

Glucose transport is a regulated biological process that occurs through facilitated diffusion involving special carrier proteins that ensure glucose molecules pass through cell membranes. There are several types of such carriers, but GLUT1-GLUT5 glucose transporters play a key role. Their activity is sensitive to various types of metabolic stress, including growth factor effects, hypoglycemia, stress hormones, and hypoxia. The regulating mechanisms of these conveyors are controlled by a multitude of signaling paths.

The glucose transfer process is crucial for providing cells with the energy necessary for metabolic reactions. Under certain conditions, glucose carrier proteins can change under stress factors such as hormonal fluctuations, exposure to toxins, inflammatory processes, or activation of kinase signaling pathways. These changes can relate to the structure, level of expression, localization, synthesis, or functional activity of carriers. Such impaired glucose transport can contribute to the development and progression of diabetes mellitus.

One of the main pathological processes underlying type 2 diabetes and impaired glucose tolerance is reduced glucose transport and utilization. Studies of these mechanisms in type 2 diabetes are focused on studying the function of the insulin-dependent GLUT4 transporter. In patients with this disease, there is a decrease in glucose absorption by brain cells, visceral adipose tissue, and skeletal muscles, which serves as the most accurate indicator of insulin resistance.

Pathophysiology of type 2 diabetes mellitus

The pathophysiology of diabetes is largely based on insulin resistance, and many studies have studied environmental factors and genetic factors contributing to the development of type 2 diabetes mellitus. Type 2 diabetes mellitus (T2DM) is multifactorial in nature, based on the combination of the organism's genetic

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characteristics and environmental factors. The main pathophysiological mechanisms for its development are considered to be the decrease in insulin secretion and insulin resistance (IR) that occurs in peripheral tissues.

Disruption of pancreatic β-cell function leads to a decrease in insulin production, making it impossible to maintain normal blood glucose levels. At the same time, insulin resistance contributes to increased glucose synthesis in the liver and a decrease in its utilization in skeletal muscles, liver, and adipose tissue. This combination of factors disrupts the normal feedback mechanism between insulin action and secretion, ultimately leading to chronic hyperglycemia.

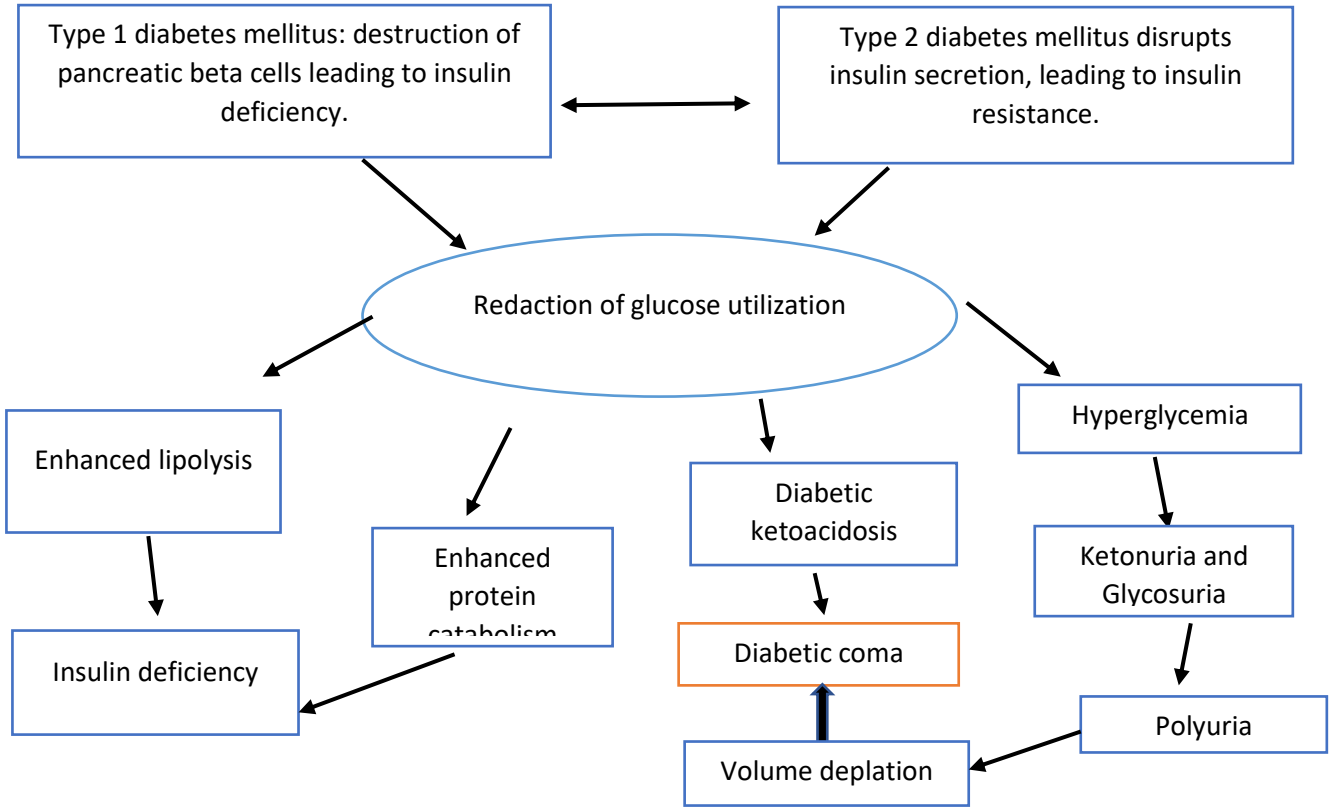

Fig. 4. Pathophysiology of Diabetes

The underlying pathophysiological mechanism of diabetes primarily involves insulin resistance. Numerous studies have explored the various contributors—both genetic predispositions and environmental influences—that play a significant role in the onset and progression of type 2 diabetes mellitus (see Fig. 4).

The maintenance of normal blood glucose levels relies on both the body's production of insulin and how efficiently this hormone is utilized. In type 1 diabetes mellitus, insulin synthesis is completely absent, while in type 2 diabetes mellitus, peripheral cells exhibit resistance to its action. The brain, which depends

almost entirely on glucose as its primary energy source, benefits from the secretion of insulin by pancreatic β-cells in response to elevated glucose levels.

To counteract high blood sugar, insulin therapy and oral hypoglycemic agents are the main pharmacological options. Moreover, variations in blood glucose concentration send regulatory signals to the central nervous system, helping to control energy release and utilization. When glucose levels fall below normal, the autonomic nervous system becomes more active. Hypoglycemia—an abnormally low blood glucose level—serves as an important diagnostic marker of disordered glucose metabolism.

During hypoglycemia, a series of compensatory mechanisms are activated: insulin secretion decreases, while the release of glucagon and epinephrine—the key hormones opposing insulin's action—increases. These hormonal adjustments trigger sympathetic nervous system responses and, in severe cases, may result in cognitive dysfunction, seizures, fainting, stroke, or even coma. The most effective and rapid way to restore normal glucose levels is through glucose administration, either orally or intravenously.

In type 1 diabetes mellitus, the development and severity of the disease largely depend on how rapidly the autoimmune system destroys the pancreatic β-cells. One of the serious complications associated with this condition is diabetic ketoacidosis (DKA). In this state, the body accelerates the breakdown of fats, leading the liver to convert these fats into ketone bodies, which then acidify the blood. DKA most frequently occurs in children and young adults, typically serving as the initial clinical indication of β-cell destruction. The progression of type 1 diabetes is usually gradual, marked by a slow rise in fasting plasma glucose levels. As insulin production continues to decline, patients become entirely insulin-dependent, often presenting with pronounced hyperglycemia and ketoacidosis. Because of the disease's progressive nature and the total loss of endogenous insulin secretion, lifelong insulin therapy becomes essential for survival.

In contrast, the pathophysiology of type 2 diabetes mellitus is characterized by both insufficient insulin secretion and a diminished cellular response to insulin. These abnormalities are closely associated with elevated inflammatory cytokines and increased plasma free fatty acids, resulting in impaired glucose uptake by target tissues, excessive lipid breakdown, and enhanced hepatic glucose synthesis. Chronic hyperglycemia arises from an imbalance between excessive glucagon release by α-cells and insufficient insulin secretion by β-cells. Type 2 diabetes is diagnosed when the pancreas can no longer compensate for insulin resistance by producing adequate amounts of insulin, leading to persistent hyperglycemia .

Early stages of type 2 diabetes often go unnoticed because the disease advances slowly and may not initially cause noticeable symptoms, aside from mild elevations in blood glucose. Overt signs such as excessive thirst (polydipsia), unintended weight loss, blurred vision, and stunted growth tend to appear only in later stages. The origins of this form of diabetes involve a complex interplay between genetic predisposition and environmental influences. Contributing risk factors include poor dietary habits, advancing age, physical inactivity, obesity, family history of diabetes, prior gestational diabetes in women, and accompanying metabolic disorders such as atherosclerosis, dyslipidemia, and hypertension.

Conclusion and future perspective

Diabetes mellitus is a chronic disorder influenced by multiple risk factors and accompanied by severe complications that significantly impair quality of life. Nevertheless, scientific research has contributed greatly to improving methods of prognosis, diagnosis, therapy, and long-term management of the disease. The treatment strategy is guided by the understanding of the disease's pathophysiology and diagnostic findings. While available pharmacological agents have proven effective, they also present various side effects. Ongoing studies continue to refine how these medications are used, particularly regarding optimal combinations and individualized treatment approaches. Maintaining a balanced diet, engaging in regular physical exercise, and keeping blood glucose levels within a healthy range remain key preventive measures.

It is also important to note that diabetes and its associated metabolic disorders remain areas of active scientific debate and exploration. While this overview focuses on central aspects of the condition, several additional factors merit attention — such as the role of nitric oxide synthase and endothelial function in insulin signaling, the influence of regulatory hormones like amylin and glucagon, the mechanisms of gestational and steroid-induced diabetes, as well as processes involved in insulin gene transcription and degradation. Moreover, topics such as gene therapy, emerging therapeutic targets, and experimental animal models that have deepened our understanding of metabolism and genetic regulation were not covered here.

In recent years, major advancements in deciphering the metabolic processes underlying diabetes have led to significant progress in treatment approaches. Modern therapies now address both insulin resistance and impaired insulin secretion. However, it remains uncertain whether these interventions fully correct the fundamental metabolic disturbances at the root of the disease. Future improvements in prevention and therapy will depend on a more detailed understanding of the molecular mechanisms involved. Advances in genetics, cell

signaling, and the neural regulation of energy metabolism are paving the way for more targeted, precise, and potentially personalized therapeutic strategies—offering hope for more effective management and a deeper understanding of diabetes itself.

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