



DIABETES MELLITUS IN ITS VARIOUS FORMS: A PERSPECTIVE ON ITS TYPOLOGIES

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Diabetes mellitus represents one of the major public health challenges of the 21st century, due to both its steadily rising prevalence and its significant impact on population morbidity and mortality. Over time, the classification of diabetes mellitus has evolved significantly, reflecting advances in the understanding of the disease's etiopathogenesis, molecular mechanisms, and clinical heterogeneity. While early classification systems relied primarily on clinical criteria and insulin requirements, contemporary approaches integrate genetic, immunological, and metabolic data, fostering the development of personalized medicine. This paper aims to analyze the evolution of diabetes mellitus classification – from traditional typologies to new paradigms based on distinct biological subgroups – while highlighting the clinical and therapeutic implications of these shifts.

Keywords: diabetes mellitus, etiopathogenesis, classification evolution, traditional typologies, contemporary approaches

INTRODUCTION

Diabetes mellitus – one of the most widespread chronic diseases of the 21st century, with a significant impact on healthcare systems and patients' quality of life – is a complex metabolic disorder characterized by chronic hyperglycemia caused by defects in insulin secretion (the pancreas can no longer produce enough insulin or produces none at all) and/or insulin sensitivity (when the body can no longer use insulin properly) [1].

Current estimates (2024) indicate a global total of approximately 589 million adults with diabetes, corresponding to a prevalence of 11.1%. Approximately 43% of this total – about 252 million people – remain undiagnosed*. The total number of people living with diabetes is projected

to rise to 643 million by 2030 and 783 million by 2045; by 2050, there will be approximately 853 million adults with diabetes, with prevalence reaching about 13% of the adult population (approximately 1 in 8 adults) – an increase of around 46% compared to current levels [2].

Type 2 diabetes (formerly known as adult-onset or non-insulin-dependent diabetes) accounts for approximately 91–92% of all cases (530–540 million), while type 1 diabetes (insulin-dependent) represents approximately 5–6% of diagnosed cases based on clinical classification [9–11].

Globally, approximately 9.2–9.5 million people live with type 1 diabetes. Of these, approximately 1.8–1.9 million are children and adolescents (under 20 years of age). The global prevalence is approximately 110–120 cases per 100,000 inhabitants. The number of cases is rising, with IDF/T1D Index models projecting approximately 14.7 million people with type 1 diabetes by 2040 and 15–18 million by 2050. Regarding type 2 diabetes, the International Diabetes Federation (IDF) estimates a significant increase, projecting a figure of 780–800 million by 2050 [2].

* Undiagnosed individuals are not individually known to have diabetes; their numbers are statistically estimated through population-based studies. For example, in a study of 10,000 adults, 1,000 were found to have diabetes based on test results: 570 were already aware of their condition, while 430 were unaware, even though their results met the criteria for diabetes. This indicates that 43% of the people with diabetes in that sample were undiagnosed. This percentage is then extrapolated to the global population.

For Europe, the data differ significantly from the global average because the population is older and has the highest concentration of people with type 1 diabetes.

According to the latest IDF estimates [3], there are approximately 65.6 million adults (aged 20–79) with diabetes in Europe – roughly one in ten adults. The total (regional) prevalence of diabetes among people aged 20–79 is 9.8%. The number of undiagnosed cases is estimated at 22 million (33.6–34%). The IDF projects that the number of people with diabetes in Europe will rise to approximately 72.4 million by 2050, an increase of about 10% compared to 2024. This rate of growth is much slower than the global figure (+46%), as Europe has a relatively stable population and more developed healthcare systems.

Europe is the region with the highest number of people with type 1 diabetes in the world – approximately 2.7 million, of whom about 419,000 are children and adolescents under the age of 20 and also has the highest annual incidence, with 31,000 new cases per year [3].

In Romania, over 1.48 million people are registered as having been diagnosed with diabetes (11.6% of the adult population suffers from diabetes mellitus), with approximately 115,000–120,000 of these individuals being insulin-dependent. Although the majority of cases are type 2, type 1 diabetes accounts for a significant share – approximately 10% of all individuals requiring insulin treatment, representing about 11,000–12,000 people. An additional 3 million people are in the pre-diabetic stage (16.5%), with over 110,000 new cases recorded annually [4,5]. It is estimated that approximately 21.4% of the population suffers from undiagnosed diabetes, amounting to around 282,000 people.

The PREDATORR study highlighted significant regional variations in the prevalence of this condition in Romania, with values ranging from 8.2% in the West region to 13.39% in the South region, compared to a national prevalence of 11.6% [4,5].

Region	Diabetes prevalence
South	13,39%
Bucharest-Ilfov	12,79%
North-East	12,38%
South-West	12,10%
North-West	11,69%
South-East	10,44%
Center	9,99%

West	8,20%
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The South-Muntenia region is in the top of the list of regions with the highest number of people with diabetes, recording a prevalence of 13.39%, followed by the Bucharest-Ilfov region with a prevalence of 12.79%.

CONTENTS

The first descriptions of diabetes appear in ancient Egyptian and Indian medical documents, yet the understanding of the disease's mechanisms remained limited for centuries.

In the 19th century, diabetes was considered a single clinical entity, defined by the presence of glycosuria (glucose in the urine) and classic symptoms: polyuria, polydipsia, and polyphagia accompanied by weight loss.

In the early 20th century, clinical observations highlighted the existence of distinct forms of the disease. Some patients exhibited early onset, rapid progression, and absolute insulin dependence, whereas others developed the disease in adulthood and could be managed through dietary measures. The discovery of insulin in 1921 marked a pivotal moment, enabling a clearer differentiation between the clinical forms of diabetes.

Between the 1950s and 1970s, the classification of diabetes was based primarily on the therapeutic need for insulin, distinguishing between insulin-dependent diabetes (type 1) and non-insulin-dependent diabetes (type 2). Although practically useful, this approach did not always reflect the biological mechanisms of the disease and frequently led to diagnostic confusion.

The understanding of diabetes mellitus has undergone profound changes in recent decades. Once considered a relatively homogeneous condition, diabetes is now viewed as a heterogeneous group of metabolic diseases that share the common feature of hyperglycemia but differ in their pathogenic mechanisms, clinical manifestations, and therapeutic responses.

Advances in endocrinology, genetics, and immunology have led to major transformations in the classification of diabetes, reflecting the growing understanding of the disease's pathogenic mechanisms. This paradigm shift has necessitated the continuous revision of classification and diagnostic systems.

Diabetes mellitus is currently viewed as a complex and heterogeneous condition situated at

the intersection of genetic, metabolic, behavioral, and sociocultural factors. Advances in genetics, immunology, and personalized medicine have led to the development of new classification and treatment paradigms focused on the individual characteristics of the patient.

In 1997, the American Diabetes Association (ADA) introduced the modern etiological classification, marking the point at which the older terms used to classify diabetes – IDDM (Insulin-Dependent Diabetes Mellitus, Type 1) and NIDDM (Non-Insulin-Dependent Diabetes Mellitus, Type 2) – were abandoned [7].

The current medical classification, recommended by the American Diabetes Association (ADA) [8] and the WHO [9], comprises four major categories; however, it emphasizes that these are imperfect and that the future lies in a classification based on genetic, immunological, and metabolic mechanisms.

1) Type 1 diabetes mellitus

Formerly known as juvenile diabetes or insulin-dependent diabetes mellitus (IDDM), this type is characterized by the autoimmune destruction of pancreatic β -cells, leading to an absolute insulin deficiency. The process is influenced by genetic predisposition and environmental factors that trigger the pathological immune response. Although it frequently manifests during childhood and adolescence, onset can occur at any age.

The identification of specific auto-antibodies and genetic predisposition associated with the major histocompatibility complex has significantly contributed to understanding the underlying pathogenic mechanisms [8].

Patients with type 1 diabetes require lifelong insulin therapy and constant blood glucose monitoring; a lack of treatment can rapidly lead to diabetic ketoacidosis and death. While it accounts for approximately 5–10% of all diabetes cases, its clinical impact is substantial.

2) Type 2 diabetes mellitus

Type 2 diabetes mellitus, formerly known as non-insulin-dependent diabetes mellitus (NIDDM) or adult-onset diabetes, is the predominant form of the disease, accounting for over 90% of diagnosed cases worldwide. It is characterized by insulin resistance in peripheral tissues (muscle, liver, and adipose tissue) associated with a progressive decline in β -cell function and a progressive deficit in insulin secretion [10]. The balance between

insulin resistance and beta-cell dysfunction varies among individuals; some exhibit primarily insulin resistance with only a minor defect in insulin secretion, while others show minor insulin resistance and primarily a lack of insulin secretion [11]. Other potentially important mechanisms associated with type 2 diabetes and insulin resistance include: accelerated lipid breakdown within adipocytes, incretin resistance and deficiency, elevated blood glucagon levels, increased renal salt and water retention, and dysregulation of metabolism by the central nervous system [12]. However, not everyone with insulin resistance develops diabetes, as a decline in pancreatic beta-cell insulin secretion is also required [11].

Genetic factors, obesity, a sedentary lifestyle, and an unbalanced diet play significant roles in the onset of the condition [13]. Visceral obesity plays a central role through the secretion of pro-inflammatory cytokines and the disruption of metabolic homeostasis. While some factors – such as diet and obesity – can be controlled, others, such as advancing age, female sex, and genetics – cannot. Lack of sleep has also been linked to the development of type 2 diabetes; this is believed to occur through its impact on metabolism [14]. Furthermore, the nutritional status of the pregnant woman during fetal development may play a role, with altered DNA methylation processes considered to be one of the underlying mechanisms [15].

In type 2 diabetes, the pancreas produces sufficient insulin, but the body does not use it efficiently. It frequently occurs in adults, but modern lifestyles have led to an increase in its incidence among children, alongside rising obesity rates in this age group [12]. Currently, American adolescents are diagnosed with type 2 diabetes just as often as with type 1.

The disease can remain undiagnosed for many years; diagnosis often occurs only when a complication arises or as a result of routine blood or urine glucose testing. It is frequently – though not always – associated with being overweight or obese, conditions that can themselves lead to insulin resistance and elevated blood glucose levels.

In the early stages, blood sugar levels can be managed through a balanced lifestyle. Over time, however, oral medications or insulin injections may be required to keep them under control.

Type 2 diabetes was long accepted as a single, uniform condition; however, modern research has demonstrated considerable heterogeneity among patients, raising questions about the suitability of this broad classification.

3) Specific types of diabetes caused by other factors (e.g., monogenic syndromes [MODY, neonatal diabetes]; diseases of the exocrine pancreas [type 3c diabetes]; endocrinopathies; drug- or chemical-induced diabetes; genetic syndromes; post-transplant diabetes), which collectively affect approximately 2% of the population. Many of these forms of the disease are misdiagnosed, leading to delays in prescribing the correct treatment.

- **Maturity-onset diabetes of the young (MODY)** is a rare form of diabetes – distinct from types 1 and 2 – that manifests before the age of 25. It is genetically determined; lifestyle and weight do not influence the risk of developing this form of the disease;

- **Neonatal diabetes** is diabetes diagnosed before the age of 6 months. It is caused by a genetic alteration that affects insulin production and leads to a significant rise in blood glucose levels. Neonatal diabetes can be permanent or transient – resolving on its own by the age of 12 months;

- **Type 3c diabetes** arises from pancreatic damage due to various causes: pancreatitis, pancreatic cancer, cystic fibrosis, pancreatectomy, or hemochromatosis. In type 3c diabetes, the pancreas ceases to produce both insulin and the enzymes required for digestion;

- **Drug-induced diabetes** occurs as a side effect of certain treatments. It is most commonly induced by steroids (corticosteroids). Other medications that can trigger diabetes include thiazide diuretics, beta-blockers, certain antipsychotics [16], or statins [17];

- **Diabetes associated with genetic syndromes** is triggered by conditions such as Wolfram, Alström, Klinefelter, Turner, and Cushing syndromes, among others.

- **Latent autoimmune diabetes in adults (LADA)** is also known as type 1.5 diabetes because it shares characteristics of both type 1 and type 2 diabetes. Its symptoms resemble those of both types, but they develop more slowly than in type 1 diabetes and more rapidly than in type 2. Currently, it is not classified as a distinct form of diabetes; studies are underway to identify its specific characteristics.

4) Gestational diabetes

Gestational diabetes is defined as hyperglycemia diagnosed for the first time during pregnancy. This form of diabetes is associated with maternal and fetal complications and represents a significant risk factor for the future development of type 2 diabetes in both the mother and the child. Women who have had gestational diabetes are at risk of developing type 2 diabetes within 3 to 6 years after delivery. Their children, having been exposed to hyperglycemia in utero, may experience hypoglycemia at birth, as well as low calcium and magnesium levels. Furthermore, there is a risk of them becoming overweight or obese. Gestational diabetes usually resolves after delivery; however, diagnosis and treatment are important to prevent future complications.

This classification emphasizes the disease's etiology and the underlying pathogenic mechanisms, moving beyond older criteria based solely on treatment or age. Furthermore, current guidelines highlight that the boundaries between categories are not always rigid, as intermediate forms and phenotypic overlaps exist [8].

Impaired glucose tolerance* and **impaired fasting glucose†** represent intermediate states between normal glucose regulation and diabetes, collectively known as *prediabetes*. These conditions carry a risk of progression to type 2 diabetes, though this progression is not inevitable [18,19].

In 2025, the International Diabetes Federation officially recognized **type 5 diabetes** – **Malnutrition-Related Diabetes Mellitus (MRDM)** as a distinct entity from types 1 and 2, primarily affecting severely undernourished individuals in resource-limited settings [20]. It is considered a separate nosological entity that is still being characterized.

The concept of type 5 diabetes refers to a severe form of diabetes characterized by significant insulin deficiency and poor metabolic control. It is believed to stem from impaired pancreatic development caused by long-term nutritional deficiencies.

* Impaired glucose tolerance: Non-diabetic fasting blood glucose levels (ranging from normal to elevated, but <126 mg/dL in venous plasma) and blood glucose levels above normal 2 hours after the oral administration of 75g of glucose (between 140 and 199 mg/dL), without, however, reaching the levels characteristic of diabetes mellitus.

† Impaired fasting glucose (110–125 mg/dL): Fasting blood glucose levels elevated above the normal range but not reaching diagnostic levels for diabetes mellitus; blood glucose level is normal 2 hours after the oral administration of 75g of glucose.

The condition was first observed in the mid-20th century (in Jamaica in 1955) and was often misclassified as type 1 or type 2 diabetes. It typically affects thin, undernourished adolescents and young adults in low- and middle-income countries who have a body mass index (BMI) of less than 19. Although often misdiagnosed with type 1 diabetes, these individuals do not develop ketonuria or ketosis despite having high blood glucose and low insulin levels; they are insulin-deficient but do not exhibit insulin resistance. Many can manage their diabetes with oral medication rather than insulin injections. Although type 5 diabetes has been recognized for over 70 years, it has largely been overlooked in global health discussions. Subsequent studies revealed a high prevalence of the disease in impoverished nations. In response to these reports, the World Health Organization (WHO) recognized diet-related diabetes as a distinct form of the disease in 1985. However, in 1999, the WHO withdrew this recognition due to a lack of further studies and supporting evidence.

It is estimated that between 20 and 25 million people worldwide, particularly in Asia and Africa, have type 5 diabetes.

A recent study published in *The Lancet: Diabetes & Endocrinology* (2018) [21] highlights the need for an updated diabetes classification system. The current system "has not been significantly updated in the last 20 years, and very few attempts have been made to explore the heterogeneity of type 2 diabetes" – despite calls from expert groups over the years.

The new paradigm for classifying diabetes mellitus represents a shift from the rigid binary model (Type 1 and Type 2) to a classification based on pathophysiological mechanisms and precision medicine. It involves phenotypic stratification into five distinct subgroups (clusters), based on the analysis of clinical and metabolic data. This innovative classification, originally proposed in a landmark study by Emma Ahlqvist and her colleagues, paves the way for precision medicine and personalized treatment.

Research into anti-glutamate decarboxylase antibodies (GADA) and genomic sequencing has demonstrated that type 2 diabetes is highly heterogeneous. Based on these new data, specialists have sought to establish a clearer, more refined classification of diabetes – moving beyond broad categorizations – to enable personalized treatment and identify patients at high risk of developing complications. This classification relies

on the presence or absence of auto-antibodies against pancreatic β -cell antigens at the time of diagnosis.

According to a study conducted by specialists in Sweden and Finland, there are five distinct types of diabetes – differing in physiological effects and genetic profiles – that an adult can develop. The study is considered a significant breakthrough for the future of personalized medicine in diabetes. The data leading to this conclusion were derived from nearly 15,000 patients enrolled in five cohorts across Sweden and Finland. The research utilized six variables: the presence of GADA (anti-glutamate decarboxylase antibodies), age at diagnosis, body mass index (BMI), HbA1c levels, and two variables calculated using the HOMA (Homeostatic Model Assessment) calculator [21].

New findings indicate the existence of three severe forms of diabetes and two mild forms. One corresponds to type 1 diabetes, while the other four can be considered subtypes of type 2 diabetes under the current classification.

In terms of patient numbers, the results highlighted three categories:

- Individuals with insulin resistance and a high risk of diabetic nephropathy;
- Individuals with a relatively mild insulin deficiency and poor metabolic control (high glycated hemoglobin HbA1c levels);
- A large group consisting of older individuals with a mild form of the disease.

The conclusions categorized patients into five groups: the first corresponds to type 1 diabetes, groups 4 and 5 correspond to type 2 diabetes, and groups 2 and 3 fall between these two extremes, exhibiting the following characteristics:

- Group 1: **Severe Autoimmune Diabetes (SAID)**

Early-onset (corresponding to Type 1 and LADA), relatively low BMI, poor metabolic control, deficient insulin production, GADA-positive. This type corresponds to what is currently classified as type 1 diabetes. In individuals with this type of diabetes, the immune system produces antibodies that destroy pancreatic beta cells (the cells that produce insulin). The disease management plan for individuals with type 1 diabetes includes close monitoring of blood glucose levels and daily insulin injections or the use of an insulin pump.

- Group 2: **Severe Insulin-Deficient Diabetes (SIDD)**

Similar to SAID, but without GADA; characterized by high HbA1c levels and the highest incidence of retinopathy.

Individuals with this type of diabetes closely resembled those with type 1 diabetes: they were young, not overweight, and had insufficient insulin production. The difference was the absence of antibodies that destroy pancreatic beta cells, meaning their immune system was not the underlying cause of their condition.

In people with SIDD, damage to insulin-producing cells caused the body to produce too little insulin. This group faced the highest risk of vision loss.

The diabetes management plan for individuals with this type of diabetes is similar to that for patients with type 1 diabetes, though they may also take oral medications.

- **Group 3: Severe Insulin-Resistant Diabetes (SIRD)**

This type of diabetes is characterized by insulin resistance, meaning the patients' bodies do not respond properly to their own insulin. Individuals with SIRD are generally overweight, a factor that further contributes to insulin resistance. The study found that patients falling into this diabetes subgroup are at higher risk of developing kidney disease.

Researchers also discovered that, among the five subgroups, diabetes management plans for individuals with SIRD were the least effective.

- **Group 4: Mild Obesity-related Diabetes (MOD)**

Individuals with this milder form of diabetes are obese and exhibit some degree of insulin resistance. Since the insulin resistance is not as severe as in SIRD, this milder form of diabetes is believed to be caused by obesity.

- **Group 5: Mild Age-related Diabetes (MARD)**

Individuals with MARD were older and had a milder form of diabetes than those who developed the condition in middle age. The study found this to be the most common form of diabetes.

According to experts, there was no genetic profile common to all five new types of diabetes. Moreover, each new type exhibited a genetic profile distinct from that of type 2 diabetes (based on the classification currently used in clinical practice).

However, this classification has not yet been officially adopted by all guidelines. Further research is needed to determine whether these five

new categories are also applicable to populations outside Scandinavia.

Risk factors for type 1 diabetes are still being investigated. Unlike type 2 diabetes, it is not caused by lifestyle or excess weight. However, having a family member (parent, sibling) with type 1 diabetes slightly increases the risk of developing the disease. Nevertheless, the majority of people with type 1 diabetes do not have affected relatives. Geographic and ethnic origins may also play a role in the onset of this type of diabetes, with higher incidence rates observed in certain populations, particularly in Northern European countries. Environmental factors and exposure to certain viral infections (*e.g.*, enteroviruses) are also linked to the risk of developing type 1 diabetes; it is an autoimmune condition with a multifactorial etiology, resulting from a complex interaction between various genetic and environmental factors.

Risk factors associated with type 2 diabetes include: family history of diabetes (the risk is higher if one or both parents or siblings have type 2 diabetes); high BMI, particularly abdominal fat accumulation, which is one of the most significant modifiable risk factors; unhealthy diet; sedentary lifestyle; advancing age; hypertension; dyslipidemia (elevated triglyceride levels and/or low levels of HDL cholesterol – “good cholesterol”); impaired glucose tolerance; history of gestational diabetes; poor nutrition during pregnancy; polycystic ovary syndrome (associated with insulin resistance and an increased risk of type 2 diabetes); genetic predisposition (numerous genes influence susceptibility to the disease); and ethnicity.

The classic symptoms of diabetes are polyuria (frequent urination), polydipsia (excessive thirst), polyphagia (increased hunger), and weight loss. Other symptoms present at diagnosis include: recurrent blurred vision, pruritus, peripheral neuropathy, recurrent fungal skin infections, slow wound healing, lack of energy, and extreme fatigue.

In the case of type 2 diabetes, many people show no symptoms during the initial years and are diagnosed during routine tests. Rarely, they may experience hyperosmolar hyperglycemic state (without ketoacidosis) – a condition caused by very high blood glucose levels, associated with impaired consciousness and low blood pressure.

Persistent hyperglycemia in diabetes causes oxidative stress, chronic inflammation, and endothelial dysfunction – mechanisms implicated in the development of microvascular and macrovascular complications. Over time, the

disease can affect blood vessels, the heart, the eyes, the kidneys, and the (peripheral) nerves. Diabetes mellitus is a leading cause of cardiovascular disease, blindness, kidney failure, and lower-limb amputation. Furthermore, individuals with diabetes exhibit increased susceptibility to infections. The life expectancy of patients with diabetes is 10–15 years shorter than that of the general population [12].

Diabetes affects the *heart and blood vessels* and can lead to fatal complications such as coronary artery disease (which can result in acute myocardial infarction) and stroke. Adults with diabetes face a 2 to 4-fold higher risk of acute myocardial infarction and stroke. Cardiovascular disease is the leading cause of mortality and morbidity among people with diabetes [22,23].

Kidney disease (diabetic nephropathy), caused by damage to the small blood vessels in the kidneys, leads to reduced renal function and kidney failure. Diabetes is the primary cause of end-stage kidney disease (ESKD) in many countries.

Eye disease (diabetic retinopathy): as a result of long-term damage to the small blood vessels in the retina, the majority of people with diabetes will develop some form of eye disease (retinopathy) that causes vision loss or blindness. In developed countries, and increasingly in the rest of the world, diabetes is the most common cause of non-traumatic blindness [24].

Peripheral nerve disease (diabetic neuropathy): Combined with reduced blood flow, diabetes can cause damage to the body's nerves [25]. The extremities – particularly the lower limbs – are among the most frequently affected areas. Nerve damage in these regions can lead to pain, tingling sensations, and a loss of sensation. This loss of sensation allows injuries to go unnoticed, leading to serious infections and potential amputations. People with diabetes face a risk of amputation at least 25 times higher than those without the condition [12].

Autonomic diabetic neuropathy is a specific form of diabetic neuropathy characterized by damage to the autonomic nerve fibers that control the body's involuntary functions. This complication can affect the cardiovascular, digestive, genitourinary, sudomotor, and metabolic systems, with significant consequences for the morbidity and mortality of diabetic patients [26,27]. Epidemiological studies have shown that the prevalence of autonomic neuropathy increases with the duration of diabetes and the degree of metabolic imbalance.

The pathogenic mechanisms involved in the development of autonomic diabetic neuropathy are complex and multifactorial [28]. Chronic hyperglycemia is the primary factor responsible for the progressive deterioration of autonomic nerve fibers. Prolonged exposure to elevated blood glucose levels triggers the activation of abnormal metabolic pathways that impair neuronal structure and function.

Oxidative stress plays a crucial role in the pathogenesis of diabetic neuropathy. Hyperglycemia stimulates the excessive production of free radicals and impairs antioxidant defense systems. An excess of reactive oxygen species leads to cellular DNA damage, protein modification, and the destruction of neuronal membranes.

Another important mechanism involves damage to the nerve vasculature. Diabetes-associated microvascular changes reduce endoneurial blood flow and promote chronic ischemia of autonomic nerve fibers. The resulting hypoxia contributes to axonal degeneration and demyelination. Numerous studies have demonstrated the involvement of inflammatory processes in the development of diabetic neuropathy. Pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF- α) and interleukin-6 (IL-6), contribute to the progressive deterioration of nerve structures.

The clinical presentation is highly varied and depends on the affected system.

Cardiovascular autonomic neuropathy is one of the most severe forms of the disease and serves as an independent predictor of mortality. Manifestations include resting tachycardia, exercise intolerance, reduced heart rate variability, orthostatic hypotension, silent myocardial ischemia, and an increased risk of sudden cardiac death [29].

Diabetic gastroparesis is one of the most well-known manifestations and is characterized by delayed gastric emptying in the absence of mechanical obstruction. Symptoms include nausea, vomiting, bloating, early satiety, and abdominal pain. Dysphagia, chronic constipation, or recurrent episodes of diarrhea may also occur.

Autonomic involvement of the urinary tract can lead to urinary retention, reduced bladder sensation, urinary incontinence, and recurrent urinary tract infections.

Sweat gland dysfunction can cause anhidrosis, hypohidrosis, or compensatory hyperhidrosis. These changes contribute to skin dryness and the development of skin lesions.

Diabetes has also been associated with an increased risk of cognitive dysfunction and

dementia, involving pathological processes such as Alzheimer's disease and vascular dementia [30]. Other complications include acanthosis nigricans, sexual dysfunction, and frequent infections.

Diabetes mellitus treatment must be individualized based on the type of disease, patient characteristics, and the presence of complications or other medical conditions. Insulin is essential for type 1 diabetes, whereas type 2 diabetes benefits from a multifaceted approach combining lifestyle modifications with modern pharmacological therapies. Gestational, monogenic, and secondary forms of diabetes require specific therapeutic strategies.

Treatment for *type 1 diabetes* includes: mandatory lifelong insulin therapy; frequent blood glucose monitoring via self-testing with a glucometer or continuous glucose monitoring (CGM) systems; a balanced diet and carbohydrate counting; regular physical activity (which increases insulin sensitivity, reduces cardiovascular risk, and helps maintain body weight); and therapeutic education, which is essential for recognizing hypoglycemia and hyperglycemia, adjusting insulin doses, and managing special situations (such as infections, travel, or sports activities).

The treatment of *type 2 diabetes* is multifaceted and includes lifestyle modifications [31,32] and pharmacological therapy. Lifestyle modification encompasses dietary management, physical activity, and weight loss. Dietary management aims to reduce caloric intake in overweight individuals; it involves increased consumption of vegetables, fruits, and whole grains, limiting saturated fats and refined sugar, and controlling portion sizes. Regarding physical activity, the recommendations are: a minimum of 150 minutes of moderate aerobic exercise per week and resistance exercises 2–3 times a week. A 5–10% reduction in body weight can significantly improve glycemic control and the cardiovascular profile [33–35].

Pharmacological treatment includes:

- Metformin – the first-line medication because it reduces hepatic glucose production, improves insulin sensitivity, typically does not cause hypoglycemia, and can promote weight loss.

- GLP-1 receptor agonists* (*e.g.*, semaglutide (Ozempic, Wegovy), liraglutide (Victoza), dulaglutide (Trulicity)) – reduce blood glucose levels, promote weight loss, and lower cardiovascular risk in certain patient groups.

- SGLT2 inhibitors† (*e.g.*, empagliflozin (Jardiance), dapagliflozin (Forxiga), canagliflozin (Invokana), ertugliflozin (Steglatro)) – increase urinary glucose excretion, provide cardiovascular protection, and slow the progression of diabetic kidney disease. Currently, SGLT2 inhibitors are considered among the most valuable medications for type 2 diabetes because they offer benefits beyond simple blood glucose lowering, protecting the heart and kidneys and reducing the risk of major complications.

- DPP-4 inhibitors‡ (*e.g.*, sitagliptin (Januvia), vildagliptin (Galvus), linagliptin (Trajenta), saxagliptin (Onglyza), alogliptin (Nesina)) – have a moderate effect on blood glucose and a low risk of hypoglycemia. By inhibiting DPP-4, they increase concentrations of active GLP-1 and GIP, stimulate glucose-dependent insulin secretion, reduce glucagon secretion, and lower blood glucose levels, particularly after meals. Compared to GLP-1 agonists and SGLT2 inhibitors, their blood glucose-lowering effect is more modest, and they do not produce significant weight loss; have not demonstrated the same significant cardiovascular and renal benefits. For this reason, they are used primarily when other options are unsuitable or contraindicated.

- Sulfonylureas (*e.g.*, glibenclamide, gliclazide, glimepiride), which stimulate insulin secretion but can cause hypoglycemia and weight gain.

- Insulin – indicated when blood glucose levels are very high, when HbA1c remains elevated despite oral treatment, when there are contraindications to other medications, or when severe complications or metabolic decompensation occur.

Treatment for gestational diabetes begins with an individualized diet, control of carbohydrate intake, and physical activity adapted to pregnancy.

* GLP-1 stands for Glucagon-Like Peptide-1, a hormone belonging to the incretin group that is naturally produced in the intestine after food consumption.

† SGLT2 – short for “Sodium-Glucose Cotransporter 2”, a protein in the kidneys responsible for reabsorbing glucose from primary urine and returning it to the bloodstream.

‡ DPP-4 is the abbreviation for “Dipeptidyl Peptidase-4”, an enzyme present in the body that rapidly degrades incretin hormones, particularly GLP-1 and GIP.

The patient must regularly monitor her blood glucose levels. If non-pharmacological measures prove insufficient, insulin is the treatment of choice, as it does not cross the placenta in significant amounts. Monitoring of fetal growth, amniotic fluid, and the fetus's general condition is required.

Treatment of monogenic diabetes (MODY) – Treatment varies depending on the identified mutation. Some forms require only monitoring and dietary management. Forms associated with HNF1A and HNF4A mutations respond excellently to sulfonylureas. Other subtypes require insulin therapy. Genetic diagnosis is essential for selecting the optimal treatment.

Treatment of secondary diabetes – Common causes of secondary diabetes include chronic pancreatitis, pancreatic resections, pancreatic cancer, Cushing's syndrome, acromegaly, and chronic glucocorticoid therapy. Therapeutic principles involve treating the underlying disease, controlling blood glucose levels with oral medications or insulin, and closely monitoring for complications. In cases of pancreatogenic diabetes, insulin requirements are often high due to the loss of pancreatic endocrine function.

CONCLUSIONS

In conclusion, diabetes mellitus represents one of the major challenges of contemporary medicine, due to both its steadily rising prevalence and the complexity of its pathophysiological mechanisms and consequences for individual and public health. The diversity of its forms – ranging from type 1 and type 2 diabetes to gestational, monogenic, and secondary types demonstrates that this condition cannot be approached as a monolithic entity; rather, it requires a deep understanding of each patient's specific characteristics and clinical context.

Advances in biomedical research have significantly contributed to elucidating the mechanisms underlying the onset and progression of the disease, enabling the development of modern, effective therapeutic strategies. Furthermore, the integration of new blood glucose monitoring technologies and innovative therapies has substantially improved metabolic control and the quality of life for individuals diagnosed with diabetes. Nevertheless, the medical, social, and economic burden of the disease remains significant, exacerbated by chronic complications affecting the cardiovascular, renal, neurological, and ocular systems.

In this context, emphasis must be placed not only on treating the disease but also on prevention, health

education, and early diagnosis. A multidisciplinary, patient-centered approach, supported by effective public health policies, is key to reducing the impact of diabetes mellitus on society. Understanding its various manifestations thus provides not only a scientific perspective on the disease but also the necessary foundation for developing therapeutic and preventive interventions tailored to the current and future needs of the population.

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