

A new classification of diabetes mellitus – current approaches and challenges

Nowa klasyfikacja cukrzycy – aktualne podejścia i wyzwania

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- classification of diabetes
- hyperglycaemia
- diabetes mellitus type 1
- diabetes mellitus type 2
- other types of diabetes

ABSTRACT

Diabetes is a chronic metabolic disorder with a rapidly growing incidence worldwide. It is currently classified into two main types, type 1 and type 2 diabetes, based on status of the autoantibodies directed at the β -cell. However, it does not reflect the complexity of diabetes and the broad spectrum of the clinical manifestations, particularly in type 2.

In this review we present the evolution of the World Health Organization (WHO) classification of diabetes, with a focus on newly introduced categories – hybrid forms of diabetes and unclassified diabetes. We compare the WHO diabetes subgroups with the American Diabetes Association (ADA) approach to this issue. Since the current classification systems do not reflect all the factors leading to hyperglycaemia in type 2 diabetes, we present novel approach to phenotyping diabetes in adults based on six variables (age at diagnosis, body mass index [BMI], C-peptide based homeostasis model assessments of β -cell function and insulin resistance, haemoglobin A1c and glutamic acid decarboxylase antibodies [GADA] status) which allowed to distinguish five replicable groups of patients in Swedish cohort with different clinical presentations.

The understanding heterogeneity of diabetes helps to classify the patients more adequately, but none of classifications is optimal. Including combination of genetic, metabolomic and clinical factors into classification schemas will pave the way towards personalized medicine in diabetes and will presumably result in more effective treatment of the patients.

SŁOWA KLUCZOWE:

- klasyfikacja cukrzycy
- hiperglikemia
- cukrzyca typu 1
- cukrzyca typu 2
- inne typy cukrzycy

STRESZCZENIE

Cukrzyca jest przewlekłą chorobą metaboliczną, a liczba chorych na świecie stale rośnie. Obecnie, poza cukrzycą o znanej etiologii i cukrzycą ciężową, wyróżnia się dwa podstawowe typy cukrzycy (typ 1 i typ 2). Rozpoznanie opiera się głównie na oznaczeniu przeciwciał skierowanych przeciwko komórkom β trzustki. Jednak obowiązujący podział cukrzycy nie odzwierciedla złożonej patogenezy choroby i szerokiego spektrum manifestacji klinicznych, szczególnie wśród pacjentów z cukrzycą typu 2.

Artykuł przedstawia ewolucję klasyfikacji cukrzycy publikowanej przez Światową Organizację Zdrowia (WHO), ze szczególnym uwzględnieniem nowych kategorii – hybrydowych form cukrzycy oraz cukrzycy niesklasyfikowanej. Celem pracy jest także porównanie nomenklatury zaproponowanej przez WHO z obecnym podziałem cukrzycy według Amerykańskiego Towarzystwa Diabetologicznego (ADA). Pomimo licznych prób stworzenia optymalnej klasyfikacji cukrzycy, żadna z nich nie odzwierciedla złożonej patogenezy cukrzycy typu 2.

Artykuł prezentuje także nowy system podziału dorosłych ze świeżo rozpoznaną cukrzycą, oparty na sześciu zmiennych (wieku zachorowania, indeksie masy ciała [BMI], homeostaticznym modelu oceny funkcji komórki β oraz insulinooporności, odsetku hemoglobiny glikowanej i badaniu przeciwciał przeciwko dekarboksylazie kwasu glutaminowego [GADA]). Podział ten, w szwedzkim badaniu kohortowym umożliwił wyróżnienie pięciu grup pacjentów ze zróżnicowaną predyspozycją do rozwoju powikłań.

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Zrozumienie złożonej etiologii podtypów cukrzycy pomaga w lepszej klasyfikacji pacjentów, jednak nadal żaden podział cukrzycy nie jest optymalny. W przyszłości, uwzględnienie czynników genetycznych, klinicznych i metabolomicznych w schematach klasyfikacji cukrzycy, może stanowić ważny krok w drodze do medycyny spersonalizowanej i wyboru lepszej terapii dla pacjentów.

Introduction

Diabetes mellitus is a complex metabolic disease that has become an increasing health concern. Worldwide, the number of adults affected by diabetes has increased from 108 million in 1980 to 422 million in 2014. If the current trend continues, the number of adults with diabetes will surpass 700 million in 2025 (1). Available treatment options have not been efficient to stop the course of the disease and prevent the development of its complications. Early diagnosis and treatment initiation remain essential, since the epigenomic alterations of the target tissues due to poor glycaemic control may result in persistent vascular dysfunction years later (metabolic memory phenomenon) (2). The present classification of diabetes into type 1 and type 2, based on the status of autoantibodies against the pancreatic islets' β -cells antigens and the age at disease onset, does not reflect the broad spectrum of diabetes phenotypes (3). However, even the distinction between the main diabetes types may be challenging – 10-15% of young adults with diabetes are estimated to be incorrectly classified and wrongly treated, which may result in accelerated development of complications and the risk of ketoacidosis (4). Given the heterogeneity of diabetes manifestations, attempts to develop more adequate classification based on clinical features have been implemented.

Since 1965 the World Health Organization (WHO) has periodically published guidance on how to classify diabetes mellitus (5). First globally adopted classification of diabetes was published in 1980 and included two other than type 1 and type 2 diabetes subgroups of diabetes, namely "other types" and "gestational diabetes mellitus" (GDM) (6). The last update before 2019 was published in 1999 – twenty years ago.

The classification of diabetes published by WHO in 1999 introduced aetiological types which were distinguished from clinical stages (7). Previous diabetes classification and terminology (insulin dependent diabetes mellitus [IDDM] and non-insulin dependent diabetes mellitus [NIDDM]) were replaced by type 1 and type 2 since the patients with diabetes type 2 treated with insulin did not fit into single subgroup. The clinical staging distinguished the individuals who require the exogenous insulin from diagnosis. In 1999 latent autoimmune diabetes of the adults (LADA) was separated from heterogeneous group of the patients with diabetes type 1.

In the current classification of diabetes from 2019 the diagnostic criteria remained unchanged. However, the definition was extended as follows "the term diabetes describes a group of metabolic disorders characterized and identified by the presence of hyperglycaemia in the absence of treatment. The heterogeneous aetio-pathology includes defects in insulin secretion, insulin action, or both, and disturbances of carbohydrate, fat and protein metabolism. The long-term specific effects of diabetes include retinopathy, nephropathy and neuropathy, among other complications. People with diabetes are also at increased risk of other diseases including heart, peripheral arterial and cerebrovascular disease, obesity, cataracts, erectile dysfunction, and non-alcoholic fatty liver disease. They are also at increased risk of some infectious diseases, such as tuberculosis" (8).

Given that not all the cases of diabetes fall into established categories, the classification from 2019 introduces two new subgroups, namely hybrid forms of diabetes and unclassified diabetes. The form of diabetes, previously referred to as LADA, was distinguished from classic, rapid-onset diabetes type 1 and included into hybrid forms of diabetes. Despite recent calls to divide the cases of diabetes type 2 into categories (based on predominant pronounced insulin resistance or insulin secretion), subgroups considering specific aetiologies of diabetes type 2 were not reflected in the current classification. The WHO also updated and simplified the list of monogenic forms of diabetes.

In 2019 the WHO expert group also emphasized the limitations of the proposed classification of diabetes. "Classification systems should be used for three primary aims: 1. Guide clinical care decisions; 2. Stimulate research into aetio-pathology; 3. Provide a basis for epidemiological studies. However, at present there are so many gaps in understanding the causes of diabetes that the current classification cannot fulfil this triple role" (8).

Although assigning a type of diabetes to a patient may still not reflect all mechanisms leading to hyperglycaemia, new classification is important to better understand the pathogenesis of diabetes and to treat it more effectively. We aimed to present the WHO classification of diabetes published in 2019 and compare it with recent data-driven diabetes clustering of Swedish cohort and American Diabetes Association's approach to diabetes subgroups. Our objective was also to discuss heterogenic group of monogenic diabetes syndromes.

WHO diabetes mellitus classification (2019 update)

Due to the growing knowledge of diabetes pathogenesis, as well as the better understanding of the genetic basis of this disease, WHO decided to verify the previous classification of diabetes. The current revision of the diabetes classification system was published in 2019 (Table 1.) (8). The WHO panel of experts concluded that diabetes phenotypes represent a wide spectrum. In addition, classification is further influenced by the rapid changes in epidemiology among the young. Type 2 diabetes is diagnosed widely in younger people, including children and adolescents. Furthermore, obesity and insulin resistance become more common among patients with type 1 diabetes. Moreover, genetic studies allowed to identify new subtypes of diabetes.

A common feature of all forms of diabetes is the pathology of the pancreatic β -cell, its dysfunction or destruction (9). The mechanisms leading to this include genetic predisposition, epigenetic processes, insulin resistance, immunization, inflammation and environmental factors.

Unlike the previous classification, the current classification does not distinguish subtypes of type 1 diabetes and type 2 diabetes and introduce a "hybrid" category to describe atypical cases with features of both types. In addition, a new category – unclassified was proposed, to identify individuals that can be assigned to neither of the main diabetes subtypes.

Type 1 diabetes

The previous WHO classification of diabetes distinguished two subtypes among the patients with type 1, namely 1a (autoimmune) and 1b (non-immune), due to the unclear pathogenesis of non-immune diabetes, the current classification does not include subtypes of type 1 diabetes (7). In case of most patients, the autoimmune background of the disease may be confirmed by the presence of specific autoantibodies directed at glutamic acid decarboxylase (GADA), anti-insulin (IAA), anti-zinc transporter 8 (ZnT8), anti-islet antigen-2 (IA-2) (10). Genotypes with the highest risk of disease were also identified, i.e., HLA DQ8 and DQ2 (11). In type 1 diabetes, reduced secretion or lack of insulin is manifested by reduced or undetectable levels of C-peptide. Type 1 diabetes predisposes to ketoacidosis, but prevalence of this condition decreases with the age (12). The process of pancreatic β -cell destruction can differ among the patients.

Fulminant diabetes is mainly reported in East Asia, but it could be observed in people of European descent (13). Patients experience severe ketoacidosis which occurs abruptly after the onset of hyperglycaemic symptoms (usually <6 days), with near-normal HbA1c values at diagnosis. Pancreatic islet-related autoantibodies are negative and C-peptide level is undetectable, suggesting complete destruction of pancreatic β -cells. Findings suggest that the β -cells of patients with fulminant type 1 diabetes are damaged during an immune response against viral infection of the pancreas (14).

Type 2 diabetes

In the current classification, diabetes subtypes with predominantly insulin-resistant and predominantly insulin-secretory defects have been removed. It has been confirmed that the pancreatic cell dysfunction is necessary for the development of type 2 diabetes. Most patients with this type of diabetes have a relative insulin deficiency caused by different degrees of insulin resistance. In the early stages of the disease, there is usually an increase in absolute insulin levels (15).

Type 2 diabetes is the most common type of diabetes, accounting for 90-95% of all cases of this disease. It is associated with overweight and obesity, insufficient physical activity, an unhealthy lifestyle consisting of consuming highly processed food and sweetened beverages. It can also be a consequence of excessive exposure to hyperglycaemia in utero. Type 2 diabetes mainly affects people in adulthood and the elderly, it may be also diagnosed in children and adolescents (16).

Hybrid forms of diabetes

This newly proposed category of diabetes is an attempt to better differentiate between type 1 and type 2 diabetes. It introduces slowly evolving immune-mediated diabetes and ketosis – prone type 2 diabetes.

Slowly evolving immune-mediated diabetes was formerly called LADA and classified as subcategory of type 1 diabetes. This form of diabetes presents some hybrid features of both type 1 and type 2 diabetes – the evidence of autoimmune process with mainly GADA, longer retain of pancreatic β -cell function, metabolic syndrome features,

and association with TCF7L2 gene polymorphism (17). Three main criteria are used to diagnose this form of diabetes – age over 35 years on disease onset, presence of GADA, successful treatment with oral agents for the first 6-12 months.

The second distinguished subtype is ketosis-prone type 2 diabetes. It is relatively often observed in populations of African-Americans or sub-Saharan Africans, but very rarely reported in Caucasians. This phenotype is characterized by the presence of ketoacidosis and severe insulin deficiency at the time of diagnosis, but the further course of the disease is similar to type 2 diabetes (18). Presumably, the initial insulin treatment decreases glucotoxicity and the β -cells regain their function. These patients can be successfully treated with oral medications for many years, but ketoacidosis episodes can recur. No genetic markers or evidence of autoimmunity have been identified.

Other specific types of diabetes

Other specific types of diabetes include monogenic diabetes, diseases of the exocrine pancreas, endocrine disorders, drug- or chemical-induced diabetes, infections, and uncommon forms of immune-mediated diabetes or other genetic syndromes sometimes associated with diabetes. The panel of experts highlighted that developments in molecular genetics may allow clinicians to identify a growing number of subtypes of diabetes. Monogenic diabetes is now classified based on the mutated gene and the clinical syndrome (19).

A newly introduced subtype is diabetes associated with a pronounced hypertriglyceridaemia.

Unclassified diabetes

The WHO expert group has identified this subtype of diabetes, recognizing that it is not always possible to classify a definite category of diabetes, especially in the early stages of the disease. The diagnosis of unclassified diabetes should be temporary, until the final diagnosis is known. The increase in obesity in the group of patients with type 1 diabetes, the higher incidence of type 2 diabetes in adolescents, the cases of ketoacidosis in type 2 diabetes make it difficult to define a specific category of diabetes.

Hyperglycaemia first detected during pregnancy

The classification published by WHO in 2019 includes gestational diabetes, defined by the stricter metabolic criteria than other types of diabetes (20).

Table 1. Types of diabetes according to the WHO 2019 classification.

Type 1 diabetes
Type 2 diabetes
Hybrid forms of diabetes
Slowly evolving immune-mediated diabetes of adults
Ketosis prone type 2 diabetes

Type 1 diabetes
Type 2 diabetes
Other specific types (see Table 2)
Monogenic diabetes
<ul style="list-style-type: none"> • Monogenic defects of β-cell function • Monogenic defects in insulin action
Diseases of the exocrine pancreas
Endocrine disorders
Drug- or chemical-induced
Infections
Uncommon specific forms of immune-mediated diabetes
Other genetic syndromes sometimes associated with diabetes
Unclassified diabetes
This category should be used temporarily when there is not a clear diagnostic category especially close to the time of diagnosis of diabetes
Hyperglycaemia first detected during pregnancy
Diabetes mellitus in pregnancy
Gestational diabetes mellitus

Addressing the complexity of diabetes in adults – new subtypes of type 2 diabetes

The type 2 diabetes accounts for up to 95% of cases of diabetes and has a continuous spectrum of clinical manifestations since it includes both the patients with the predominant insulin resistance and relative insulin deficiency and the patients with the primary defects of β -cell function and mild insulin resistance (3). These differences are not reflected in the recent WHO classification of diabetes (8). However, there is an emerging need to develop more optimal tool to classify the patients with type 2 diabetes focusing on various aetio-pathological pathways.

In the recent study of Ahlqvist et al., a data-driven diabetes analysis based on six variables – age at diagnosis, body mass index (BMI), C-peptide based homeostasis model assessments of β -cell function and insulin resistance, hemoglobin A1c and GADA status – identified five replicable groups of patients with different clinical presentations (21). The five diabetes clusters, namely severe autoimmune diabetes (SAID), severe insulin-deficient diabetes (SIDD), severe insulin-resistant diabetes (SIRD), mild obesity-related diabetes (MOD) and mild age-related diabetes (MARD).

Since the proposed classification gives a closer insight into pathogenesis of diabetes clusters, it may help to adjust the treatment to the underlying cause. Therefore, for patients with evidence of islet autoimmunity (with SAID), insulin seems to be the optimal treatment. The patients with SIDD may be treated with insulin or sulphonylureas, while this cluster includes both patients with autoimmune diabetes with the absence of routinely assessed antibodies and patients with monogenic defects of β -cell function. In the study of Dennis et al., the participants in the A Diabetes Outcome Progression Trial (ADOPT) and the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia

in Diabetes (RECORD) trial with the pronounced insulin resistance (a distinctive feature for SIRD) had better response to thiazolidinediones (22). However, the SIRD cluster could include both patients from a wide spectrum of monogenic defects in insulin action (for instance, insulin receptor defects or familial partial lipodystrophy) and patients with uncommon specific forms of immune-mediated diabetes (23, 24). Given the proposed classification is aetiology-oriented, the patients with MOD could be treated with metformin, while for the patients with MARD, sulphonylureas may be recommended to ensure better glycaemic control.

Patients from new subtypes of type 2 diabetes showed also varying prevalence of diabetic complications. The risk of nephropathy was significantly increased in patients with SIRD, which may provide insight into close association between insulin resistance and kidney disease (25). The patients with SIDD, despite relatively young age at onset (56.7 years) and lean body status (BMI; 28.9 kg/m²), were characterized by poor metabolic control (Hb1Ac; 11.5%) and pronounced risk of retinopathy. However, the proposed classification does not identify the patients at high risk of cardiovascular events, which remains the main cause of mortality in patients with diabetes (26).

Whereas the new four subgroups provide better insight into diabetes type 2, SAID includes nearly exclusively the patients with diabetes type 1 or latent autoimmune diabetes in adults (LADA). These patients may be easily distinguished by the presence of GADA, the measurement of C-peptide may be omitted. In study of Ahlqvist et al. C-peptide was measured in all patients, but the cost-effectiveness of reclassification in patients with the presence of GADA is questionable. In 2014 half of adults with diabetes lived in five countries (namely China, India, the USA, Brazil and Indonesia), among which only the USA is classified as a high-income country (1). Therefore, in the developing world the measurement of C-peptide and GADA may not be available or well-standardised.

The study of Ahlqvist et al. provides better understanding of genetic background of diabetes. Among analysed genetic variants, none was associated with all clusters. A variant in the TCF7L2 gene (rs7903146), associated with diabetes type 2 through modifying the effect of incretins on insulin secretion, was associated with SIDD, MOD and MARD, but not with SIRD (27). While the variant in the TM6SF2 (rs10401969), which confers susceptibility to the non-alcoholic fatty liver disease, was associated with SIRD, but not with MOD, indicating that the correlation between insulin resistance and obesity is more complex (28).

The classification proposed by Ahlqvist et al. is an important step towards a better understanding of the complex nature of diabetes and more optimal therapy for the patients. Another approach to better define subgroups of diabetes is to use the combination of genetic, metabolomic and clinical factors (29, 30, 31). However, none of recently proposed diabetes subgroups have become widely used.

Monogenic diabetes

Monogenic defects resulting in diabetes include many heterogenous disorders. Depending on the dominant pathogenesis, they are divided into syndromes with genetically determined insulin deficiency [maturity onset diabetes of the young (MODY), mitochondrial, neonatal diabetes, transient neonatal diabetes] and disorders with genetically determined defective insulin action (32).

The latest update of the diabetes classification published by WHO includes advances in molecular genetics in the last 20 years. Monogenic diabetes is now classified based on mutated gene and the clinical syndrome. The updated nomenclature for monogenic diabetes is presented in Table 2. (8).

The current classification of ADA includes an updated list of monogenic forms of diabetes. Among them MODY and neonatal diabetes were distinguished, while the monogenic defects in insulin action (e.g., mutations of the insulin receptor and lipodystrophies) were omitted (Table 3.) (33).

Table 2. The WHO classification of monogenic diabetes published in 2019.

Monogenic defects of β -cell function (mutated gene followed by clinical syndrome)	Product of the gene
GCK MODY	Glucokinase
HNF1A MODY	Hepatic Nuclear Factor 1-Alpha
HNF1B RCAD	Hepatic Nuclear Factor 1-Beta
KCJN11 PNDM	Kir 6.2 subunit of the ATP-sensitive K ⁺ channel
KCNJ11 DEND	Kir 6.2 subunit of the ATP-sensitive K ⁺ channel
6q24 TNDM	PLAGL1, HYMA1
ABCC8 MODY	SUR1 subunit of the ATP-sensitive K ⁺ channel
INS PNDM	Insulin
WFS1 Wolfram syndrome	WFS1
FOXP3 IPEX syndrome	FOXP3
EIF2AK3 Wolcott-Rallison syndrome	Translation initiation factor 2-Alpha Kinase-3
Monogenic defects in insulin action (mutated gene followed by clinical syndrome)	
INSR Type A Insulin Resistance	Insulin Receptor
INSR Leprechaunism	Insulin Receptor
INSR Rabson-Mendenhall syndrome	Insulin Receptor
LMNA FPLD	Lamin A/C (nuclear protein)
PPARG FPLD	PPARG peroxisome proliferator-activated receptor gamma4 promoter gene
AGPAT2 CGL	AGPAT2 1-Acylglycerol-3-Phosphate O-Acyltransferase 2 gene
BSCL2 CGL	BSCL2 lipid droplet biogenesis associated, seipin

Abbreviations: FPLD – familial partial lipodystrophy; MODY – maturity-onset diabetes of the young; PNDM – permanent neonatal diabetes; RCAD – renal cysts and diabetes. DEND = developmental delay epilepsy and neonatal diabetes. TNDM = transient neonatal diabetes; FPLD = familial partial lipodystrophy; CGL = congenital generalized lipodystrophy.

Table 3. The classification of monogenic diabetes according to ADA, published in 2020.

MODY		
Diabetes subtype	Gene	Product of the gene
MODY 1	HNF-4 α	Hepatic nuclear factor 4 α
MODY 2	GCK	Glucokinase
MODY 3	HNF-1 α	Hepatic nuclear factor 1 α
MODY 4	IPF-1	Insulin promoter factor 1
MODY 5	HNF-1 β	Hepatic nuclear factor 1 β
MODY 6	NEUROD1	Neurogenic differentiation-1 transcription factor
MODY 7	KLF-11	Kruppel-like factor (transcription factor)
MODY 8	CEL	Carboxy ester lipase enzyme
Neonatal diabetes		
PNDM	KCJN11	Kir 6.2 subunit of the ATP-sensitive K ⁺ channel
	ABCC8	SUR1 subunit of the ATP-sensitive K ⁺ channel
	PTF-1 α	Pancreatic transcription factor-1
	EIF2AK3	Eucaryotic translation initiation factor-2 kinase-3
MIDD	A3243G	Leucine tRNA

Abbreviations: PNDM – Permanent Neonatal Diabetes Mellitus; MIDD – Mitochondrial Inherited Diabetes and Deafness.

Monogenic diabetes develops as a consequence of rare mutations in a single gene. The abnormal product could impair function of the pancreatic β -cell on any stage of the cascade of molecular events including the initial sensing, transport of glucose into the β -cell, biochemical pathways, and exocytosis of the insulin.

Monogenic forms are responsible for about 2% of all cases of diabetes, among them MODY remains a leading cause. At least fourteen MODY subtypes with distinct genetic aetiologies have been identified. Given the heterogeneity of the MODY, common features are high phenotypic penetration, early age of the disease – 15-35 years, occurrence in many generations of the same family with autosomal dominant model of inheritance, with equal incidence of the disease by women and men, absence of the ketoacidosis (34).

The two most common MODY subtypes are GCK MODY (MODY 2) and HNF-1 α MODY (MODY 3). Chronologically, the first MODY subtype described was GCK MODY. It is caused by a mutation in the gene of the enzyme – glucokinase. Glucokinase catalyses the first glycolysis reaction in liver cells and endocrine pancreas. Normally, it is activated when blood glucose concentration reaches 5 mmol/l (90 mg/dl). Heterozygous mutation affecting the GCK gene leads to reduced glucokinase activity and reduced hepatic and β -cell glucose sensing. Consequently, reduced β -cell glucose sensing leads to decreased insulin secretion. Other metabolic effects include reduced glycogen synthesis, higher hepatic glucon eogenesis, mild fasting hyperglycaemia (35). Moderate hyperglycaemia occurs mainly in the fasting state and chronic complications are rare. Other characteristic feature of GCK MODY (MODY 2) is low increase of glucose levels in oral glucose tolerance test – less than 4.6 mmol/l (83 mg/dl).

Other types of MODY are associated with mutations in the genes of transcriptions factors pivotal to β -cell development and functions. Frequent symptoms apart from hyperglycaemia include genitourinary abnormalities

HNF-1 α MODY (MODY 3) is the most common type of MODY, representing approximately 60% of all cases. It develops as a consequence of the mutation in HNF-1 α gene. HNF-1 α regulates genetic expression of insulin and GLUT-2. HNF-1 α mutations lead to β -cell dysfunction and result in hypoinsulinism, elevated fasting glycaemia and impaired glucose-stimulated insulin secretion. Other clinical features of HNF-1 α MODY are low renal threshold for glucose resulting in renal glycosuria, high sensitivity to sulfonylureas, and lower body mass index (BMI). Hyperglycaemia is usually progressive, which is probably connected to the progressive apoptosis of β -cells (36).

Neonatal diabetes belongs to rare conditions, usually diagnosed before the age of 6 months. Two forms have been recognised based on its clinical course – transient and permanent. Half of neonatal diabetes mellitus cases are transient (TNDM), require insulin treatment initially, and spontaneously resolve in less than 18 months. Two third of cases of TNDM results from a methylation abnormality on chromosome 6q24 region. Infants born with TNDM have a higher risk of developing type 2 diabetes later (37). The genetic causes resulting in permanent neonatal diabetes mellitus (PNDM) are relatively better understood than pathogenesis of TNDM. Approximately half of the infants with PNDM have activating mutations in genes KCJN11 and ABCC8 that encode subunits of ATP-sensitive potassium channel Kir 6.2 and SUR1 respectively. The hyperglycaemia develops due to persistent opening of the potassium channels preventing normal glucose sensing and insulin

release. However, defective channels retain the ability to bind and respond to sulphonylureas. Therefore, patients with mutations in genes KCJN11 and ABCC8 could be successfully treated by sulphonylureas. Other rare causes of PNDM include mutations in INS (insulin gene), EIF2AK3 (resulting in Wolcott-Rallison syndrome) and FOXP3 which is associated with immune dysregulation (37).

Maternally inherited diabetes and deafness (mtDNA 3243 MIDD) is a subtype of diabetes which results from a mutation in the gene encoding leucine tRNA in mitochondrial DNA. In addition to diabetes and sensorineural deafness, those affected also have pigmented retinopathy, myopathy, atrophy of cerebellum and glomerulosclerosis (38).

Other forms of monogenic diabetes result in defective insulin action or insulin receptor dysfunction. More than 70 mutations have been identified in the insulin receptor (INSR) gene in patients with insulin resistance. The INSR mutations may impair receptor function by decreased affinity of insulin binding or impaired cell signal transduction. There are three well-known clinical syndromes caused by mutations in the insulin receptor gene: type A insulin resistance, lepreuchanism and the Rabson-Mendenhall syndrome (39). The severity of clinical symptoms depends on the loci and type of the mutation. Some of the clinical features are shared by all the syndromes of extreme insulin resistance: hyperinsulinism, hyperandrogenism, hirsutism, virilization, acanthosis nigricans. Acanthosis nigricans, a hyperpigmented skin lesion found usually in the neck and the axillary areas, is strongly associated with insulin resistance. Although, this condition is not pathognomonic to monogenic defects in insulin action, it is present in all patients with congenital insulin resistance syndromes with a severity correlating with the degree of insulin resistance.

Lipodystrophies are heterogenous group of genetic syndromes where insulin resistance is associated with absence or deficiency of adipose tissue, which leads to accumulation of fat in unusual regions and pronounced insulin resistance. The most common genetic risk factor is mutation in the LMNA gene. However, multiple genes have been identified to cause partial and generalized lipodystrophy syndromes (PPARG, BSCL2, AGPAT2) (40).

Understanding of the molecular background of monogenic diabetes contributed to significantly increased knowledge of pathophysiological mechanisms leading to the hyperglycaemia. For instance, patients diagnosed with GCK MODY (MODY 2) have mildly progressive hyperglycaemia with a low risk of chronic complications, and usually the diabetic diet is the sufficient intervention. On the contrary, patients with HNF1 α gene mutation (as well with HNF4 α) have diabetes with more progressive course with the high probability of complications development. Therefore, the intensive treatment of hyperglycaemia is needed. Initially, sulfonylureas are effective, but after few years insulin is needed for glucose control. Since subtypes of monogenic diabetes vary in their treatment recommendation and prognosis, a molecular diagnosis is an important component of clinical management (41). Although monogenic forms of diabetes are rare it seems that genetic screening is cost-effective in individuals who have atypical diabetes and multiple family members with diabetes with atypical course (33).

Attempts to include genetic testing for the patients type 2 diabetes has been undertaken. However, this is not easy since type 2 diabetes is a consequence of interaction of many different factors, both environmental and genetic, which leads to two main disturbances: impaired insulin secretion and reduced sensitivity of peripheral tissues to insulin (42).

In the recent studies new polymorphisms associated with type 2 diabetes were identified. Examples of susceptibility variants that seem to predispose to type 2 diabetes include, among others: TCF7L2, CDKN2A, CDKN2B, FTO, PPARG, IRS1 (43). Despite the growing number of loci discovered there are obstacles in translating this knowledge into clinically useful information. Moreover, most susceptibility variants lie outside the coding regions of genes and are assumed to influence transcript regulation rather than gene function. Furthermore, allelic forms of the examined genes are common in the population of healthy people and have only a small impact on the individual risk of disease. Further studies on the molecular background of type 2 diabetes are necessary, which will allow to create further updates of the classification of this disease, proving that what was defined so far as type 2 diabetes phenotypes may turn out to be another genetic subtype of the disease, hopefully with both therapeutic and prognostic benefits for the patients (44).

Comparison of WHO 2019 and ADA 2020 classification of diabetes

In January 2020, ADA published "Standards of medical care in diabetes – 2020" (33). A group of experts updated the current classification of diabetes. The main categories of diabetes, namely type 1, type 2, gestational diabetes and other specific types of diabetes remain the same in both

ADA and WHO classifications. Exact differences between the two classifications are presented in Table 4.

The ADA experts distinguished subtypes of type 1 diabetes, i.e., immune-mediated and idiopathic diabetes. It was noted that the idiopathic type is very rarely diagnosed, mainly in African and Asian populations. It is characterized by varying degrees of insulin deficiency, susceptibility to ketoacidosis and no evidence of β -cell autoimmunity. This type of diabetes with new name "ketosis-prone type 2 diabetes" is classified as the hybrid diabetes in WHO classification. ADA also does not distinguish the LADA subtype or other slowly evolving form of immune-mediated diabetes. According to ADA the rate of progression is dependent on the age at first detection of autoantibody, number of autoantibodies, their titre and specificity. The presence of autoantibodies is sufficient to diagnose type 1 diabetes (45). ADA highlights that immune-mediated diabetes can occur at any age, even in the 8th and 9th decades of life, while WHO recognizes slowly evolving form of immune-mediated diabetes, as a separate type of diabetes with features of types, and assign it to hybrid diabetes. ADA classification also includes the pre-diabetes term for individuals with glucose levels above normal, but not high enough to meet the criteria of diabetes. It was noted that this state is associated with increased risk of cardiovascular complications.

When discussing other specific types of diabetes, ADA distinguishes diabetes associated with cystic fibrosis and post-transplant diabetes. It was noted that diabetes

Table 4. The comparison between the diabetes classification systems published by ADA (2020) and WHO (2019).

ADA Classification 2020	WHO Classification 2019
Type 1 diabetes Immune-Mediated Diabetes Idiopathic Type 1 Diabetes	Type 1 diabetes
	Hybrid form of diabetes Slowly evolving immune-mediated diabetes of adults Ketosis prone type 2 diabetes
Prediabetes	
Type 2 diabetes	Type 2 diabetes
Specific types of diabetes due to other causes	Other specific types
Diseases of the exocrine pancreas Cystic fibrosis – related diabetes (described as a separate subtype)	Diseases of the exocrine pancreas
Drug- or chemical induced Posttransplantation diabetes mellitus (described as a separate subtype)	Drug- or chemical induced
Monogenic diabetes syndrome MODY, Neonatal diabetes	Monogenic diabetes <ul style="list-style-type: none"> • defects of β-cell function • defects in insulin action
	Endocrine disorders
	Infections
	Uncommon specific forms of immune-mediated diabetes
	Other genetic syndromes sometimes associated with diabetes
	Unclassified diabetes
Gestational diabetes mellitus (diabetes diagnosed in the second or third trimester of pregnancy that was not clearly overt diabetes prior to gestation)	Hyperglycaemia first detected during pregnancy Diabetes mellitus in pregnancy Gestational diabetes mellitus

affects 20% of adolescents and almost half of adults with cystic fibrosis (46). In children with cystic-fibrosis older than 10 years old, ADA recommends an annual oral glucose tolerance. ADA highlights that major risk factors for development of posttransplantation diabetes mellitus (PTDM) are metabolic adverse effects of immunosuppressive drugs, post-transplant viral infections and hypomagnesaemia, in addition to the traditional risk factors seen in patients with type 2 diabetes mellitus (47). PTDM develops in 10-20% of patients with kidney transplants and in 20-40% of patients who have undergone other solid organ transplantation (SOT) (48). In the WHO classification, PTDM diabetes is intuitively assigned to drug- or chemical-induced diabetes.

Both ADA and WHO experts have different approach to the monogenic diabetes subgroups. ADA classifies monogenic diabetes into neonatal and MODY diabetes. Whereas, the WHO classification is more extensive, including monogenic defects of β -cell function or with a defect in insulin action. WHO also describes other genetic syndromes sometimes associated with diabetes like Down, Klinefelter's or Prader-Willi syndrome. ADA does not refer to diabetes related to endocrine disorders or infections and does not characterize genetic syndromes sometimes associated with diabetes.

ADA presents a slightly different view on gestational diabetes (GDM) that can be diagnosed in the second or third trimester of pregnancy that is neither pre-existing type 1 nor type 2 diabetes. Women diagnosed with prediabetes or diabetes by standard diagnostic criteria in the first trimester should be classified as having pre-existing pregestational diabetes or prediabetes.

The differences in both ADA and WHO classifications indicate that defining the mechanisms underlying common forms of diabetes remains challenging since they involve a complex interplay of genetic, epigenetic, proteomic and metabolomic processes. Ideally, a single, unified classification system of diabetes would facilitate clinical care of the patients.

Summary

Currently, there is no consensus on the classification of diabetes since the panels of experts of WHO and ADA approached differently that issue. The current WHO classification includes two new diabetes categories, namely hybrid forms of diabetes and unclassified diabetes.

The latter includes slowly evolving immune-mediated diabetes in adults and ketosis-prone diabetes. The term LADA was replaced by slowly evolving immune-mediated diabetes and distinguished from type 1 diabetes, since the genetic predisposition to this subtype of diabetes includes also polymorphisms associated with type 2 diabetes. Definition of slowly evolving immune-mediated diabetes is the same as LADA: patient with newly diagnosed diabetes, older than 35 years old, positive for GADA and initially hyperglycaemia could be corrected with oral agents. However, the prolonged treatment with oral drugs (especially with sulphonylureas) may lead to poor glycaemic control and rapid disease progression. In addition, progress of beta-cell loss in type 1 diabetes may varied in different persons as progress of hypothyroidism in patients with autoimmune thyroiditis.

Whether slowly evolving immune-mediated diabetes represents a separate subtype or should be classified as a specific subtype of type 1 diabetes remains controversial. It is questionable if separating slowly evolving immune-mediated diabetes from diabetes type 1 may add

clinical value, since insulin remains an essential treatment for all patient positive for GADA. Moreover, postponing the initiation of insulin treatment for 6 until 12 months after diagnosis may promote higher HbA1c level and more rapid development of complications.

Hybrid forms of diabetes also include ketosis-prone diabetes type 2. Before the diagnosis or by the treatment withdrawal those affected present with ketoacidosis. After the initial insulin treatment is introduced and glucotoxicity subsides, they can be effectively treated with oral agents. Despite the relatively low prevalence of that subtype of diabetes in the European population, the patients with that subtype may be identified in Poland. They are typically admitted to the hospital due to diabetic ketoacidosis, and later achieve remission and do not require insulin treatment. Whereas the patients with ketosis-prone diabetes type 2 remain negative for GADA, it is a challenge to distinguish them from the numerous individuals with diabetes type 2. The pathogenesis explaining the clinical course is unknown: either insulin secretion impairment is caused by glucotoxicity, or the ketoacidosis is also affected by alterations of sensitivity of ketogenic enzymes to low insulin concentrations. Further development of genome-wide association studies (GWASs) may provide relevant insights into disease aetiology. This may have practical clinical implications – the patients may be aware of the genetic predisposition which might help to avoid life-threatening ketoacidosis. According to the current WHO diabetes classification, ketosis-prone diabetes type 2 belongs to hybrid types diabetes, while ADA includes the patients with similar course of the disease into diabetes type 1. Given ketosis-prone diabetes type 2 combines the features of both main types of diabetes, it may be justified to include it into "unclassified diabetes".

To date, no classification of diabetes is optimal and reflects the heterogeneity of diabetes phenotype. Regarding the nomenclature of monogenic diabetes, in 2019 WHO experts proposed a new simplified system, while ADA did not distinguish monogenic defects in insulin action, namely the mutations of the insulin receptor and lipodystrophies. In case of patients with lean body status, pronounced insulin resistance and positive family history of diabetes, genetic testing should be considered.

The past decade has seen a rapid rise in global diabetes incidence as well as a better understanding of the diversity of the discrete types of this metabolic disorder. Despite recent attempts, we are still waiting for the ideal diabetes classification. Even if the current ones are not perfect, diabetes classifications help us to identify and treat adequately patients with rare causes of diabetes.

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