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New Paradigms of Diabetes Classification: Implications for Complication

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Abstract

Background: The recent sub-classification of diabetes into five different subtypes or clusters, were known as 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). This new classification was based on six clinical variants: Age, body-mass index at diagnosis, glycosylated hemoglobin, glutamic acid decarboxylase antibodies, homeostasis model assessment 2 beta and IR.

This new classification helps i) reclassification of the accurate different forms and subtypes and their clinical characteristics, ii) better understanding of the pathophysiology of each type iii) drawing the prognosis and predict diabetic complications and iv) selecting the most suitable anti-diabetic treatments for each type based on the pathophysiology.

Objective: This review aimed to provide a short overview of new diabetes classification and rearrange of clinical characteristics, disease progression and treatment for each subtype.

Keywords: DM clusters; SAID; SIDD; SIRD; MOD; MARD

Introduction

Diabetes is a diverse range of disorders marked by persistent high blood glucose levels resulting from disturbances in carbohydrates, proteins, and fats metabolism, that leads to problems with insulin action, insulin secretion, or a combination of both [1].

Globally, diabetes mellitus is a prevalent metabolic disease. Approximately 10.5% of adults aged 20 to 79, which is more than 537 million people, have diabetes, and a significant portion, ranging from 30% to 80% are unaware of their condition. It's estimated that the total number of individuals with diabetes will reach 643 million by 2030. Furthermore, by 2045 about 783 million people will have diabetes, marking a 46% increase. Notably, three out of every four adults with diabetes reside in low- and middle-income countries [2].

Classification of Diabetes

In the 1960s, diabetes was categorized as either "maturity" or "growth onset" diabetes based on the age of diagnosis. The World Health Organization (WHO) Expert Committee (1980) [3] classified diabetes mellitus into several categories, including "insulin-dependent" (later referred to as type 1 diabetes, T1D), "non-insulin dependent" diabetes (later known as type 2 diabetes, T2D), gestational diabetes mellitus and specific types of diabetes caused by various factors.

These categories include T1D (identified by the presence of autoantibodies against pancreatic islet β-cell antigens and typically diagnosed at a younger age), T2D (characterized by insulin resistance and a relative lack of insulin and typically diagnosed at an older age), gestational diabetes mellitus (occurring during the second or third trimester of pregnancy and not pre-existing diabetes) and specific types of diabetes caused by other factors, accounting for 1% to 5% of cases. These other types encompass monogenic diabetes syndromes (such as neonatal diabetes and Maturity-Onset Diabetes of The Young, MODY) and secondary diabetes (resulting from conditions affecting the pancreas, drug or chemical interactions, and hormonal imbalances) [4].

The most common form of monogenic diabetes is MODY. It's characterized by diabetes typically diagnosed in young people, usually less than 25 years old, and it's inherited dominantly without the presence of autoantibodies. Various genetic abnormalities are associated with MODY. These genetic changes influence the development, function, and regulation of pancreatic beta cells, leading to

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problems in sensing glucose and releasing insulin, with little to no defect in insulin action [5].

T2D, which accounts for 94% of diabetes cases, shares some similarities with both T1D and Latent Autoimmune Diabetes in Adults (LADA). T1D and LADA, constituting 6% of cases, both result from the autoimmune destruction of beta cells, but LADA typically occurs later in life (usually after the age of 30) and may have some remaining beta-cell function [6] (Figure 1).

In 2018, Ahlqvist et al. [7] introduced a new diabetes classification system involving five subgroups or clusters based on six simple clinical factors: Age at diagnosis, Body-Mass Index at diagnosis (BMI), Glycosylated Hemoglobin (HbA1c), Glutamic Acid Decarboxylase Antibodies (GADA), beta-cell function (assessed through Homeostasis Model Assessment 2 beta, HOMA2-β), and insulin resistance (measured by HOMA2-IR, using fasting glucose and C-peptide levels). These five diabetes subgroups are known as 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).

After identifying these new diabetes clusters in the Scandinavian population, efforts were made to test their applicability in diverse populations with diabetes. While these subtypes were successfully replicated in some populations [8,9], in others, full replication could not be achieved.

Following the identification of new diabetes clusters in the Scandinavian population, these clusters were tested for replicability in various other populations to see if this classification is applicable to individuals with diabetes in other ethnic groups. While the Scandinavian subtypes were replicated in some populations [8,9] in others they could not be fully replicated [4,10].

Characteristics of Subtypes

Subtype 1: Severe Autoimmune Diabetes (SAID)

This kind of diabetes is marked by being diagnosed at a young age (early-onset diabetes), having a low BMI, very high HbA1c (indicating poor metabolic control), high Insulin Resistance (high HOMA-IR), high β-cell dysfunction (low HOMA-2-β), and positive Glutamate Decarboxylase Antibodies (GADA positive) [7,11].

Around 6% of adult individuals fit into this subtype. It's possible that the prevalence of this subtype could increase if additional autoantibodies are tested, as studies have shown that up to 7% of patients in GADA-negative clusters have antibodies against islet cells and/or insulin [12].

SAID shares some common traits with both T1D and LADA. T1D and LADA are both characterized by the presence of autoantibodies against pancreatic tissues in the blood, which can be used as a diagnostic marker. Detecting these antibodies strongly suggests that the patient will eventually require insulin therapy to manage blood glucose levels [13].

Subtype 2: Severe Insulin-Deficient Diabetes (SIDD)

This form of diabetes is identified by low age at diagnosis (early-onset diabetes), low BMI, very high HbA1c, high Insulin Resistance (HOMA-IR is high but lower than in SIRD), high β-cell dysfunction (low HOMA-2-β), and no Glutamate Decarboxylase Antibodies (GADA negative). Around 18% of adult individuals fall into this subtype, sharing similar characteristics with SAID but without the involvement of the immune system as the underlying cause of their condition [7,11].

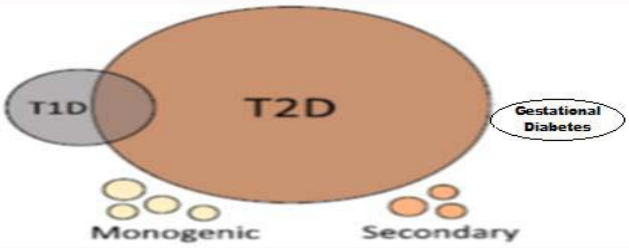

Figure 1: The traditional classification of diabetes where T1D, T2D and gestational diabetes are viewed as distinct subgroups but with an overlap including intermediate diabetes types such as LADA. Monogenic and secondary diabetes are rare.

Subtype 3: Severe Insulin-Resistant Diabetes (SIRD)

This type of diabetes is marked by high age at diagnosis (late-onset diabetes), a high BMI (overweight to obese), normal HbA1c, very high insulin resistance (very high HOMA-IR), high β-cell dysfunction (low HOMA-2-β, but higher than SAID & SIDD), and no Glutamate Decarboxylase Antibodies (GADA negative) [7,11]. In SIRD, β-cell function is less impaired, and HbA1c levels are lower compared to SAID and SIDD. This subtype represents about 15% of adult individuals [14].

Subtype 4: Mild Obesity-related Diabetes (MOD)

This kind of diabetes is associated with high age at diagnosis (late-onset diabetes), high BMI (obesity), normal HbA1c, high insulin resistance (high HOMA-IR but lower than SIRD), normal β-cell dysfunction (normal HOMA-Beta), and no Glutamate Decarboxylase Antibodies (GADA negative). About 22% of cases fall into this category, and it is thought to be linked to obesity [7,11].

Subtype 5: Mild Age-Related Diabetes (MARD)

This type of diabetes is characterized by a very high age at diagnosis (late-onset diabetes), normal Insulin Resistance (normal HOMA-IR), normal β-cell function (normal HOMA-Beta), normal BMI, normal HbA1c, and no Glutamate Decarboxylase Antibodies (GADA negative). The difference between MOD and MARD is primarily based on the age at diagnosis and BMI; MOD is characterized by a high BMI (obesity), while MARD is diagnosed at a later age [7,11].

This subtype is the most common form of diabetes, accounting for 39% of cases, and carries the lowest risk of diabetic complications [14].

Clinical Advantages of Clustering of Diabetes

An essential step in comprehending the causes of diabetes involves identifying its different forms and subtypes [7]. Subtyping also has a significant impact on selecting the most suitable anti-diabetic treatments. People with "milder" subtypes may require less intensive control of high blood sugar levels, especially if they are older individuals. Conversely, individuals with SIDD could benefit more from early initiation of insulin-based therapies, while those in the SIRD subtype might gain more from treatments targeting insulin resistance and weight loss [4]. Subtyping also aids in predicting outcomes and preventing diabetic complications, contributing to a reduction in mortality rates and a lighter burden of this condition [15] (Table 1).

Table 1: Representation of the characteristics of the new diabetes subgroups.

Subtype	%	Age at diagnosis	BMI	HbA1c	HOMA-IR	HOMA-2-β	GADA	Complications
SAID	0.06	Low age	Low	Very high	High	Low	Positive	Ketoacidosis
								Retinopathy
								Kidney diseases
SIDD*	0.18	Low age	Low	Very high	High but lower than SIRD	Low	Negative	Ketoacidosis
								Retinopathy
								Neuropathy
								CV diseases
								Erectile dysfunction
SIRD	0.15	High age	High	Normal	Very high	Low (but higher than SAID & SIDD)	Negative	Neuropathy
								Fatty liver
								Nephropathy
								CV diseases
								Erectile dysfunction
MOD	0.22	High age	Very high	Normal	High but lower than SIRD	Normal	Negative	Retinopathy
MARD**	0.39	Very high age	Normal	Normal	Normal	Normal	Negative	Low risk of complication but kidney and CV diseases may occur

*SIDD is similar to SAID but without GADA. **MARD is similar to MOD, but the MOD is characterized by a high BMI (obesity), while MARD has a higher age at diagnosis. CV: Cardiovascular; SAID: Severe Autoimmune Diabetes; SIDD: Severe Insulin-Deficient Diabetes; SIRD: Severe Insulin-Resistant Diabetes; MOD: Mild Obesity-Related Diabetes; MARD: Mild Age-Related Diabetes

Risk of Complications

Diabetes is responsible for over 1.5 million deaths annually. Diabetes mellitus brings about several complications, including microvascular disease, which impacts small blood vessels in the eyes, kidneys, nerves, and other organs, potentially leading to vision loss, kidney problems, nerve damage, and poor blood circulation. There's also macrovascular disease, affecting large blood vessels in the heart, brain, and limbs, which can result in heart attacks, strokes, peripheral artery disease, and even the need for amputations. Other related complications include Nonalcoholic Fatty Liver Disease (NAFLD) and erectile dysfunction [16].

Diabetic ketoacidosis is more common in people with T1D (70% to 90%), but it can occasionally occur in those with T2D (10% to 30%) and other diabetes types [17]. In the new classification, the risk of ketoacidosis is more closely associated with SAID and SIDD due to their very high HbA1c levels at diagnosis [7].

Over the first 20 years of living with diabetes, approximately 60% of people with T2D and nearly 100% of those with T1D develop diabetic retinopathy, a leading cause of vision loss among working-age adults worldwide. Retinopathy was more prevalent in SAID, SIDD, and MOD subgroups compared to SIRD and MARD subgroups, and the risk was found to be 2 to 5 times higher in individuals with long-standing diabetes (N=5580) compared to those with short-term diabetes (N=3455) [16].

Studies indicate that 10% to 20% of individuals with diabetes show objective signs of neuropathy, with this prevalence increasing as the disease progresses. Diabetes-related neuropathy was most common in the SIRD subgroup with short-term diabetes (N=3455) compared to other diabetes subtypes and was similar in all subgroups with long-standing diabetes (N=5580) [16]. Patients with SIDD also had a higher prevalence of diabetic sensorimotor polyneuropathy and cardiac autonomic neuropathy at diagnosis. These findings suggest that individuals with SIDD would benefit from early, intensive treatment, frequent complication monitoring, and sensitive diagnostic methods for early detection [12].

Approximately 25% to 30% of diabetics develop diabetic kidney disease. DM is the leading cause of Chronic Kidney Disease (CKD) worldwide and accounts for half of all patients with End-Stage Kidney Disease (ESKD). However, the incidence of ESKD among individuals with diabetes is relatively low due to high rates of cardiovascular-related mortality before the need for kidney replacement therapy [14].

Diabetes-related nephropathy was most prevalent in the SIRD subgroup with short-term diabetes compared to other diabetes subtypes [7], but it was more common in SAID, MARD, and MOD subgroups with long-standing diabetes compared to SIDD and SIRD. CKD was most prevalent in SAID, SIRD, and MARD subgroups, both in participants with short-term (N=3418) and long-standing diabetes (N=5502) [16]. SIRD had a significantly increased risk of kidney complications, emphasizing the link between insulin resistance and kidney disease. Insulin resistance has been associated with higher salt sensitivity, glomerular hypertension, hyperfiltration, and declining kidney function, all of which are hallmarks of diabetes-related nephropathy.

Gnudi et al. [18], reported that the increased incidence of kidney complications was observed despite relatively low HbA1c levels, suggesting that reducing blood sugar is not the sole method for preventing kidney complications.

Nearly 70% of patients with diabetes over the age of 65 die of heart disease, and 16% die of stroke. The majority of patients with type 2 diabetes are obese (>85%) and have comorbid hypertension (>70%) and dyslipidemia (>60%). Among people living with diabetes, nearly 30% have atherosclerotic cardiovascular disease, most often manifested as coronary artery disease, myocardial infarction, or angina. Approximately 15% of people with diabetes have concurrent heart failure, and another 8% have experienced a stroke [1]. High risk of cardiovascular, coronary event and stroke (dependent on age and

sex) were more common with SIDD, SIRD and MARD [19].

Nearly 70% of diabetes patients over the age of 65 die of heart disease, and 16% die from strokes. The majority of people with T2D are obese (>85%) and have concurrent hypertension (>70%) and high cholesterol levels (>60%). Among those living with diabetes, nearly 30% have atherosclerotic cardiovascular disease, most frequently presenting as coronary artery disease, heart attacks, or angina. Approximately 15% of individuals with diabetes experience heart failure, and an additional 8% have had a stroke [1]. A higher risk of cardiovascular events and strokes (depending on age and gender) was more common in SIDD, SIRD, and MARD [19].

The prevalence of Nonalcoholic Fatty Liver Disease (NAFLD) in T2D is considerably higher than in the general population, with an average prevalence of 47.3% to 63.7% [20]. SIRD patients also had the highest levels of liver fat and NAFLD-related indicators, including the fatty liver index, AST-to-platelet ratio index, and NAFLD fibrosis scores [12].

A high prevalence of erectile dysfunction is noted in individuals with SIDD and SIRD [21].

Treatment

Considering the documented effects of the currently available anti-diabetic drugs on β-cell function, insulin sensitivity, and metabolism, some medications may be more suitable for treating specific groups of patients [14].

For individuals with SIRD, MARD, and MOD, metformin is the recommended first-line therapy for controlling blood glucose levels. Metformin is an oral medication known as a biguanide, which helps prevent the liver from making excess glucose, reduces the absorption of glucose by the intestines, and enhances the body's response to insulin [22]. Metformin is favored as the initial treatment option due to its effectiveness and strong supporting evidence, including a reduced risk of major cardiovascular events as demonstrated in the United Kingdom Prospective Diabetes Study [23].

If metformin alone doesn't sufficiently manage a patient's blood sugar, if metformin isn't suitable due to contraindications or if specific patient characteristics necessitate additional treatment, several non-insulin second-line medications are available. These include Sodium-Glucose Cotransporter 2 Inhibitors (SGLT2is), Glucagon-Like Peptide-1 Receptor Agonists (GLP-1RAs), Dipeptidyl Peptidase-4 inhibitors (DPP-4is), and sulfonylureas [14].

SGLT2is directly targets SGLT2, a protein responsible for absorbing filtered glucose in the kidney's proximal convoluted tubules. Inhibiting SGLT2 leads to glucosuria, resulting in reduced HbA1c levels by 0.6% to 0.9% and fasting glucose by 1.1 mmol/L to 1.9 mmol/L compared to a placebo. SGLT2 is also associated with weight loss and lower blood pressure [24]. Moreover, they have positive effects on cardiovascular death, heart failure, and the progression of chronic kidney disease [25]. Several studies indicate that treatment with SGLT2 is improves the sensitivity of β-cells to glucose. For instance [26], reported a 25% increase in β-cell glucose sensitivity after just 48 h of SGLT2 is treatment in patients with T2D who were either treatment-naive or on metformin. Additionally, SGLT2 is can enhance insulin sensitivity by reducing plasma glucose levels and body weight [24].

GLP-1 is a hormone produced by the intestine's L-cells in response to food intake, particularly meals rich in fat and carbohydrates. This hormone aids in regulating glucose levels through various mechanisms, including glucose-dependent insulin secretion, reduced food intake, weight loss, and lowered glucagon levels [27]. found that a 12-week regimen of metformin combined with GLP-1RA significantly improved β-cell function, as measured by the disposition index, compared to a metformin-only or placebo group in a randomized, double-blind crossover trial. Furthermore, the impact of GLP-1RAs on body weight may explain their positive effects on hepatic and peripheral insulin sensitivity, as observed in other studies [28].

DPP-4is belongs to a class of glucose-lowering drugs that inhibit the enzyme DPP-4, which is found on the surface of various cells, including adipocytes, kidneys, the liver, and the small intestine. DPP-4is increases insulin secretion and decreases glucagon secretion [29].

Due to their overlapping mechanisms of action, it is not advisable to use GLP-1RAs and DPP-4is in combination, as both medications increase circulating GLP-1 levels and they are unlikely to exhibit greater efficacy when used together [14]. However, the final choice of treatment for T2D patients should also consider other diabetes-related factors. For instance, in the presence of cardiovascular disease, GLP-1RAs or SGLT2is are preferred options without regard to specific subgroups. Other factors such as the presence of kidney disease, the importance of weight loss alongside lifestyle changes, patient age, preferences, and potential side effects should also be taken into account [30].

Treatment of SAID is similar to those with T1D and LADA requires early introduction of insulin supplementation. SIDD subtype requires early introduction of insulin supplementation, but they also take oral medications [31]. They could benefit from most of the current second-line anti-diabetic treatments. Since the SIDD group is associated with a lower BMI, there is also no preferred type of medication for those patients to correct body weight. SIDD may also benefit from DPP4is or, when cost is a major issue, a sulfonylurea [14].

Patients with SIRD may benefit most from treatments that promote weight loss and improve insulin sensitivity, such as SGLT2 is or GLP-1RAs. These treatments may help enhance insulin sensitivity and lead to significant reductions in body weight, while also addressing the risk of cardiovascular disease or nephropathy. If safety and efficacy are established, new insulin sensitizers (e.g., peroxisome proliferator-activated receptor agonists) or anti-inflammatory drugs could also provide targeted treatment for SIRD [31]. Pioglitazone treatment is effective in improving insulin sensitivity and reducing NAFLD but should be considered only when no other treatment options are available due to the well-known side effects of weight gain and other adverse effects associated with pioglitazone use. DPP-4is do not seem to play a therapeutic role in this group as they have no established effects on insulin sensitivity, weight reduction, or NAFLD [14].

Lifestyle modifications, weight loss, increased physical activity, and metformin may suffice as the sole therapy for individuals with mild cases of MARD and MOD [32]. MOD patients might benefit most from GLP-1RAs and SGLT2is because both medications substantially reduce body weight. The use of pioglitazone should be avoided in this group due to its association with weight gain [33].

For patients with MARD, sulfonylureas and DPP-4 is could be viable additional therapies if metformin alone cannot adequately

control blood sugar levels. While sulfonylureas do not impact insulin sensitivity, they can initially enhance β-cell function [33]. However, SGLT2 is and GLP-1RAs may also be options for patients with established end-organ diseases such as cardiovascular disease and reduced kidney function. Since this population tends to be older, decisions regarding additional treatment should be made thoughtfully, taking into consideration the potential side effects associated with each medication type [14]. On the other hand, individuals with MARD should receive treatments that do not lead to weight loss and sarcopenia, such as protein-balanced diets and moderate resistance training [31].

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