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Is Type 2 Diabetes Mellitus one Disease?

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Abstract

This review aims to describe the four subtypes or clusters of Type 2 DM. We believe that differentiating these subtypes based on clinical and laboratory features—such as glutamic acid decarboxylase antibodies (GAD), age at onset, HbA1c, body mass index (BMI), and measures of insulin resistance and secretion—can help characterize them. The main goal of identifying these clusters is to improve treatment personalization and prevent complications that vary among these groups. The severe insulin-deficient group at diagnosis resembles Type 1 diabetes but lacks autoantibodies against beta cells and has different genetic markers. Microvascular complications like diabetic neuropathy and retinopathy are most common in this subtype, along with cardiovascular issues. Insulin therapy should be started early in this group. The insulin-resistant subtype is associated with the highest risk of diabetic nephropathy. Efforts to reduce insulin resistance and protect kidney function are essential in this cluster. The mild obesity-related and mild age-related subtypes usually have a lower risk of complications and respond well to lifestyle changes and weight loss. Recognizing these subtypes of Type 2 DM allows for a personalized approach to managing the disease.

Keywords: Type 2 Diabetes Mellitus, subtypes of type 2 DM, HOMA-IR, HOMA-IS, C-peptide.

Introduction

Until 2017, type 2 diabetes mellitus was mainly seen as a condition characterized by insulin resistance and initially a relative insulin deficiency that eventually progresses to complete insulin deficiency. It was regarded as a progressive disease that ultimately required insulin treatment. Over the past seven years, four subtypes or groups of type 2 diabetes mellitus (T2DM) have been identified, each with distinct risk factors and causes at diagnosis. This progress provides an opportunity to customize treatments based on the primary mechanisms of each subtype (Tuomi et al., 2014; Pearson, 2019; Ahlquist, et al., 2020). Additionally, the complications linked to different T2DM subgroups vary, allowing for more personalized care approaches. Clinical and laboratory markers reveal different pathways involved in disease development. Six parameters—such as glutamic acid decarboxylase antibodies (GAD), age at diagnosis, HbA1c, body mass index (BMI), and measures of insulin resistance and secretion—aid in distinguishing these groups.

Subtypes of type 2 DM

Type 2 DM is a complex disease with various presentations. The risk of developing insulin deficiency and related complications differs among patients. The concept of dividing type 2 DM into subtypes has rarely been studied. In Western countries, including both white and Black populations, many individuals with type 2 DM are obese. In contrast, Asian patients with type 2 DM often are not obese. Understanding the different subtypes of type 2 DM is important because their underlying causes are diverse and involve a wide range of predispositions.

In 2018, a study was carried out on patients with type 2 diabetes mellitus (DM) in Sweden. It was an observational cohort study called the New Diabetes in Scania (ANDIS) and included a group of 8980 patients. The study used six diabetes-related variables: age at diagnosis, insulin secretory capacity measured by homeostatic model assessment of insulin secretion (HOMA-IS), insulin resistance measured by homeostatic model assessment of insulin resistance (HOMA-IR), body mass index (BMI), HbA1c, and GAD antibodies. Four subtypes of type 2 DM were identified based on these six variables (Ahlquist et al., 2018; Ahlqvist et al., 2018).

Another study in 2020 by Kahkoska et al. confirmed these subtypes of Type 2 DM (Kahkoska et al., 2020). Together, these findings identified four subtypes of Type 2 DM at diagnosis. The subtypes or clusters are listed below (Ahlquist, 2020):

Subtype A: Severe insulin-deficient type 2 DM (SIDD); symptoms are quite severe, and GAD antibodies are negative. Patients usually have poor carbohydrate tolerance without

insulin treatment. Typically, the BMI is normal, with little or no insulin resistance. The later age of onset of Diabetes Mellitus and different genetic factors distinguish this subtype from type 1 DM without autoantibodies, which is very rare.

Subtype B: Severe insulin-resistant type 2 DM (SIRD). This subtype exhibits elevated beta-cell function, approximately 150-250% higher than usual. Patients typically have a high BMI. Blood glucose levels tend to rise later as pancreatic beta-cell function declines.

Subtype C: Mild obesity-related type 2 DM (MOD), where patients have moderate insulin resistance and slightly increased beta cell function, about 100-150% of normal, and respond well to weight loss. The typical age at diagnosis is 45-55.

Subtype D: Mild age-related type 2 DM (MARD) exhibits moderate insulin resistance and a slight increase in pancreatic beta cell function. The typical age at diagnosis for these patients is over 65 years. It is effectively managed with weight loss and physical activity.

Another study uses three cardiovascular outcomes trials (CVOTs) (Bilal & Pratley, 2018). These trials and their number of subjects were DEVOTE (n=7,637) (Bilal & Pratley, 2018), LEADER (n=9,340) (Marso et al., 2016; Verma et al., 2018), and SUSTAIN-6 (n=3,297) (Marso et al., 2016).Clustering parameters included HbA1c, baseline body mass index, and age at diabetes diagnosis. They analyzed the cumulative risk of a major adverse cardiovascular event (MACE), cardiovascular (CV) death, and all-cause death by cluster in the DEVOTE, LEADER, and SUSTAIN-6 trials. Using data from these three studies, subgrouping of T2DM was performed.

Together, these research findings indicate that four cluster labels match the ANDIS labels. The features of Clusters A-D are as follows:

- Cluster A, severe insulin-deficient diabetes; symptoms are pretty serious, and the GAD antibody is negative.
- Cluster B, severe insulin-resistant diabetes; usually linked with a high body mass index (BMI).
- Cluster C, mild obesity-related diabetes; more associated with obesity than insulin resistance.
- Cluster D, mild age-related diabetes; patients tend to develop the condition at an older age than those in Cluster C.

Among those studies, some important parameters were found as follows:

- The ratio of clusters A-D in DEVOTE (n=7546) is 18.7%, 23.7%, 21.1%, and 36.4%, respectively.
- HbA1c for A-D in LEADER is 11.05%, 8.17%, 8.49%, and 7.95%.
- The event ratio for MACE over 2.5 years in DEVOTE appears to be 14.4%, 10.6%, 11.4%, and 9.1%.
- The ratio of new or worsening nephropathy in LEADER appears to be 12.6%, 4.9%, 8.8%, and 6.7%, respectively (Marso et al., 2016).

When examining the results of HbA1c, BMI, and age at diagnosis, the median and 25%/75% quartile data were almost identical across three extensive studies. In contrast, data from four clusters displayed a divergent distribution. This pattern suggests potential clinical relevance for the existence of four distinct clusters in T2DM. Among these four clusters, (3-point MACE: non-fatal myocardial infarction, non-fatal stroke, cardiovascular death) was highest in cluster A.

Related to these clusters, Dennis and colleagues have replicated the clusters from ANDIS for the clinical trials of the ADOPT trial (n=4351) and RECORD (n=4447) (Dennis et al., 2019). The data obtained were similar to those of Ahlqvist et al., and these models based on simple clinical features appeared to be useful in stratifying diabetic patients.

Additionally, a clustering study was conducted within the German Diabetes Association involving patients with recent-onset diabetes (n=1105) (Zaharia et al., 2024). The results showed: i) mild age-related diabetes (MARD) at 35%, ii) mild obesity-related diabetes (MOD) at 29%, iii) severe autoimmune diabetes (SAID) at 22%, iv) severe insulin-resistant diabetes (SIRD) at 11%, and v) severe insulin-deficient diabetes (SIDD) at 3%. As a result, cluster analysis helps identify groups with different levels of insulin resistance in fat tissue and throughout the body. These methods could support targeted prevention and treatment strategies in diabetic precision medicine (Zaharia et al., 2024).We exclude autoimmune diabetes from the German study, which we believe relates to patients with type 1 DM.

These four subtypes of type 2 DM were identified in 2,652 Chinese patients by using Electronic Medical Records' data from a grade A tertiary hospital in Beijing, China, from 2000 to 2022 (Wang et al., 2024).

A total of 2,652 T2DM patients with complete clustering data were included. Among them, 466 (17.57%) were classified as severe insulin-deficient diabetes (SIDD), 502 (18.93%) as severe insulin-resistant diabetes (SIRD), 672 (25.34%) as mild obesity-related diabetes (MOD), and 1,012 (38.16%) as mild age-related diabetes (MARD). The risks of chronic kidney disease (CKD) and diabetic retinopathy (DR) varied across the four subtypes. Compared with MARD, SIRD had a higher risk of CKD (HR 2.40 [1.16, 4.96]), and SIDD had a higher risk of DR (HR 2.16 [1.11, 4.20]). There was no difference in the risk of stroke and coronary events. Some differences were observed in the MOD subtype among the European population and in patients with the Chinese MOD subtype; the latter had a lower BMI (Wang et al., 2024; Xing et al., 2021). Most type 2 DM patients in this study belonged to the MARD subtype, and individuals in this group had the oldest age at diagnosis. Compared with southern Chinese patients, northern Chinese patients had higher BMI in the SIDD, MOD, and MARD subtypes. Additionally, we found that the SIDD subtype accounted for a smaller proportion in this northern Chinese study than in the southern Chinese study (17.6% vs 27.6%; $P < 0.01$). The finding of a generally high BMI in northern Chinese aligns with a previous study that reported higher rates

of overweight and obesity in northern Chinese than in southern Chinese (Chen et al., 2023; Zhao et al., 2022).

However, there are some limitations. Several situations may arise, such as i) the same T2DM patients could have different characteristics based on race in Europe, America, and Asia, ii) the duration of diabetes might affect outcomes in addition to the age at onset, iii) assigning clusters B or C could be difficult in the case of a 50-year-old man with moderate obesity, and so on.

Clinical significance of subtyping patients with type 2 DM

The clinical importance of subtyping pertains to the complications linked to each subtype of type 2 DM and managing diabetes in the different subtypes with various antidiabetic medications. Clusters provide a better holistic view of type 2 diabetes than simple clinical features (Ahlqvist et al., 2019).

Type A – the SIDD subtype often presents with very high HbA1c levels at diagnosis, diabetic ketoacidosis, and rapid progression to insulin treatment compared to other subtypes (Kahkoska et al., 2020). These patients are typically younger and have a lower BMI. This subtype of type 2 DM has the highest incidence of diabetic retinopathy and neuropathy, with 23% experiencing at least mild retinopathy soon after diagnosis. The German Diabetes Study (GDS) further examined this group, confirming the low C-peptide secretory capacity of SIDD through an intravenous glucose tolerance test (Zaharia et al., 2019). In GDS, SIDD patients also exhibited the highest rates of diabetic sensorimotor neuropathy and cardiac autonomic neuropathy at diagnosis, along with an increased risk of cardiovascular events compared to other subtypes. Although blood sugar control was achieved after 5 years, neuropathy remained irreversible in these patients. These findings suggest that patients with SIDD should receive early, intensive insulin therapy, regular complication monitoring, and continuous glucose monitoring (CGM). Additionally, based on the DEVOTE trial, this subtype has the highest prevalence of MACE (Bilal & Pratley, 2018).

Based on patients with type 1 diabetes mellitus, many clinicians believe that microangiopathic complications such as diabetic retinopathy, neuropathy, and nephropathy also occur in patients with type 2 DM. However, while diabetic retinopathy and neuropathy tend to cluster in patients with SIDD, the Severe Insulin-Resistant Diabetic Patients (SIRD), which form the type B cluster, have the highest prevalence of diabetic kidney disease (DKD) (Ahlqvist et al., 2018). SIRD patients have the lowest estimated glomerular filtration rate (eGFR) at diagnosis. They also have the highest incidence of developing chronic kidney disease (CKD), macroalbuminuria, and end-stage renal disease (ESRD). In the SIRD subgroup, the incidence of CKD and macroalbuminuria was twice as high, and the incidence of ESRD was five times higher after adjusting for age and sex than in mild age-related diabetic (MARD) patients. The increased incidence of DKD in SIRD patients was also observed in GDS (Zaharia et al., 2019). The relationship between DKD and insulin resistance is complex, and insulin resistance is a common feature in patients with CKD and ESRD.

Additionally, patients with SIRD have the highest rate of Metabolically Dysregulated Steatotic Liver Disease (MASLD) (Zaharia et al., 2019).These patients benefit from early interventions such as lifestyle modifications, weight loss, and the use of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and sodium-glucose cotransporter 2 inhibitors (SGLT2i) (Veelen et al., 2020). Furthermore, in the ADOPT and RECORD trials, an insulin sensitizer (thiazolidinedione) was used, showing the greatest reduction in HbA1c among SIRD patients.

The C cluster-mild obesity-related diabetes (MOD) subtype—responds very well to lifestyle changes. In these patients, if weight loss is achieved, the HbA1c decreases more easily due to weight loss and improved insulin resistance. Additionally, GLP1-RAG, along with lifestyle interventions, might play a role in treatment (Veelen et al., 2020). Microvascular complications in this subtype are less common than in the first two subtypes.

In the D cluster – mild age-related Diabetes (MARD) subtype, weight loss and increased muscle mass help improve diabetes management. These patients experience only mild blood sugar control issues and have fewer microvascular complications.

Discussion

This article aims to describe the heterogeneity of patients with type 2 DM using clinical and laboratory parameters. We have identified four subtypes of the disease based on recent trials. These four subtypes have been confirmed in various studies and across different populations of patients with type 2 DM.

An essential laboratory measurement is the C-peptide. Estimating HOMA-IR and HOMA-IS helps identify different subtypes of patients with Type 2 DM. This assists clinicians in distinguishing between patients with SIDD, SIRD, and milder forms like MARD. These subtypes may initially receive similar treatments. Early recognition of the SIDD subtype emphasizes the need for prompt, intensive treatment focusing on insulin deficiency and close monitoring for microvascular and macrovascular complications. In MARD, treatment primarily aims to reduce insulin resistance and protect kidney function. For MOD, managing obesity becomes the main goal, and type 2 DM tends to be milder than in patients with SIDD. This subclassification provides clinicians with a valuable opportunity to tailor treatment strategies and monitor for specific complications related to each of the four subtypes. This personalized approach could improve understanding, enhance treatments, and lead to better outcomes for patients with Type 2 DM. The article has several limitations based on the studies cited above. There might be differences in the clusters depending on the race of the patients. Also, the studies available so far have not discussed in depth the ability to shift from one cluster to another over time. Additionally,

the duration of type 2 DM was not considered, which can influence the clustering approach. Furthermore, assigning patients to Cluster B or C and elderly populations above age 50 is challenging. We believe that future studies can achieve this, as well as the possibility of combining the subtypes of type 2 DM with one being predominant. The major strength of this review article is that it presents current scientific data on a prevalent disease like DM type 2 from different perspectives. Instead of a generalized approach, describing various subtypes within this disease allows clinicians to adopt an individualized approach in diagnosis and treatment, which can lead to better patient outcomes.

Summary

Describing the four subtypes of type 2 DM discussed in this article is crucial for physicians. This is because, instead of applying a one-size-fits-all approach to the disease, clinicians can adopt a more pathophysiologic perspective. Doing so can enhance the quality of care and outcomes for patients with different subtypes of type 2 DM, which was previously seen as a single, uniform disease with a standard treatment approach.

Disclaimer

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