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REVIEW ARTICLE

New and Unique Clusters of Type 2 Diabetes Identified in Indians

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Abstract

Type 2 diabetes (T2D), the most common form of diabetes, is recognized as being a heterogenous disorder, and presents a universal threat to health. In T2D, the pathophysiology and phenotype differ significantly by ethnicity, particularly among Asian Indians, who are known to have the 'Asian Indian phenotype', which makes them more susceptible to develop T2D than white Caucasians. The recent sub-classification of T2D into different subtypes or clusters, which behave differently with respect to clinical presentation and risk of developing complications is a remarkable development. Five unique "clusters" of individuals with diabetes were described in the Scandinavian population [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)]. For the first time in India, identification of clusters of diabetes was done on 19,084 individuals with T2D, using 8 clinically relevant variables (age at diagnosis, BMI, waist circumference, HbA1c, triglycerides, HDL cholesterol and fasting and stimulated C-peptide). Four replicable clusters were identified [SIDD, MARD, IROD (Insulin Resistant Obese Diabetes) and CIRDD (Combined Insulin Resistant and Deficient Diabetes)], two of which were unique to the Indian population (IROD and CIRDD). Clustering of T2D helps i) to accurately subclassify diabetes into different subtypes, ii) plan therapies based on the pathophysiology, iii) predict prognosis and prevent diabetic complications and iv) helps in our approach to precision diabetes. Further studies would help us to refine the usefulness of these clusters of T2D particularly in the Indian population, with respect to selection of appropriate therapies and hopefully in the prevention of complications of diabetes.

Introduction

Diabetes is a heterogeneous group of disorders characterized by chronic hyperglycemia due to disturbances in carbohydrate, protein and fat metabolism, which result from either a defect in insulin action or secretion or a combination of the two.[1] Type 2 diabetes (T2D), the common form of diabetes, spans a spectrum of pathophysiology, from those with severe insulin resistance with near-normal beta-cell function at one end to those with normal insulin sensitivity with severe beta-cell secretory defect at the other.[2] The current management approaches have not been able to prevent the progression of diabetes and associated chronic complications. One of the reasons could be that T2D is diagnosed and treated as if it is one homogenous condition, although the disease is highly heterogeneous with respect to its clinical presentation, progression, treatment patterns and susceptibility to complications.[3] Over the past couple of years, attempts have been made to identify subgroups or "clusters" of individuals with T2D using metabolic traits, which behave differently with regard to phenotype, clinical presentation and risk of complications.[4-9] In addition, efforts to address diabetes heterogeneity have also been investigated using genetic markers.[10,11]

Evolution of Classifications of Diabetes

An important step in understanding the etiology of diabetes requires identification of its various forms and subtypes. While several sets of criteria have been proposed for diabetes, no systematic classification existed until the 1960s. A few decades ago, diabetes was classified as "maturity" or "growth onset" diabetes based on the age at diagnosis of the disorder. In 1980, the World Health Organization (WHO) Expert Committee classified diabetes mellitus as "insulin dependent" (later called type 1 diabetes) and "non-insulin dependent" diabetes (later called type 2 diabetes) depending on the need for insulin for survival or maintaining good health. Their classification system also included "other types of diabetes" and gestational diabetes mellitus (GDM).[12] The American Diabetes Association (ADA) classified the disorder into four major types based on presumed etiology.[13] The four major types include type 1 diabetes (presence of autoantibodies against pancreatic islet β-cell antigens and younger age at diagnosis); type 2 diabetes (absence of autoantibodies and characterized by insulin resistance with relative insulin deficiency and older age at diagnosis); GDM (diabetes diagnosed in the second or third trimester of pregnancy that was not clearly overt diabetes prior to gestation); and specific types of diabetes due to other causes, e.g., monogenic diabetes syndromes (neonatal diabetes and maturity-onset diabetes of the young), diseases of the exocrine pancreas (cystic fibrosis and pancreatitis), and drug- or chemical-induced diabetes (eg. glucocorticoid

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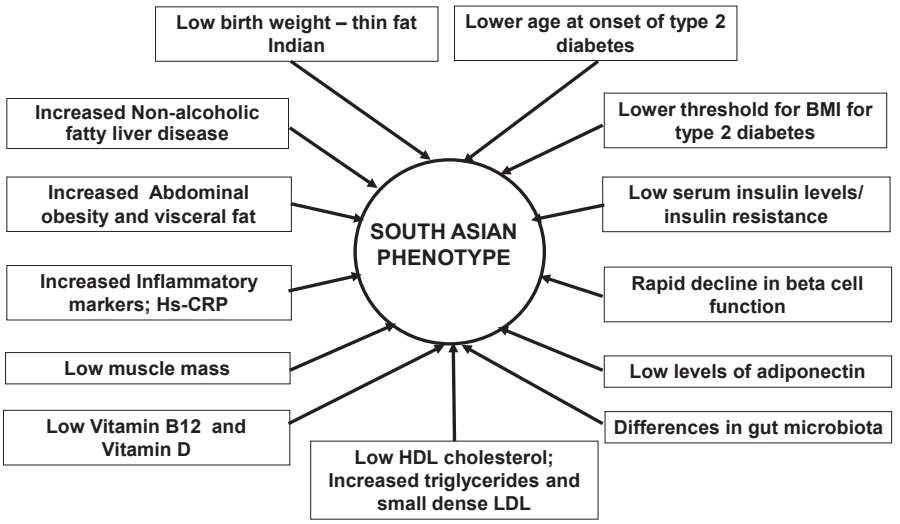


Fig. 1: 'Asian Indian Phenotype'[21-30]

use, in the treatment of HIV/AIDS, or after organ transplantation).[13]

Is Type 2 Diabetes One Diseases or Several Subtypes?

T2D is the most common type of diabetes present worldwide.[14] About 10% patients diagnosed to have T2D could actually have latent autoimmune diabetes of adults (LADA),[15] while another 1-5% may have autosomal dominant inherited forms of maturity-onset diabetes of young (MODY),[16] and 1%, rare genetic mutations. The majority (85% - 90%) however, have the common "garden variety" of T2D. T2D is caused by a combination of genetic and environmental factors.[17] The clinical features of this widely prevalent form of T2D shows marked heterogeneity. Hence, subclassification of individuals with T2D into distinct clusters could help in assessing prognosis and deciding management of individuals at high risk for developing complications.

Earlier Studies on Subtypes of Type 2 Diabetes

Maldonado et al[18] in 2003, reported on the classification of four groups of diabetic patients (n=103), of various ethnic groups, who presented with diabetic ketoacidosis (DKA) based on the presence or absence of islet autoantibodies (A+/−) and evidence of beta-cell functional reserve (B+/−). Based on these criteria, four groups: A^-B^+ (50%), A^-B^- (22%), A^+B^- (17%), and A^+B^+(11%) were identified. Another study undertaken by Li et al[11] in 2015, used electronic medical record data of T2D individuals (n= 2551) and 73 clinical features for topology-based patient-patient network generation. Three distinct subgroups of T2D were identified by this group which included i) Subtype 1 (29.8%), characterized by diabetic nephropathy and retinopathy; ii) Subtype 2 (24.2%), associated with cancer and cardiovascular diseases; and iii) Subtype 3 (43.0%), strongly associated with cardiovascular and neurological diseases, allergies and HIV infections. In addition, they also reported unique genetic associations to the subtypes, which included 1279, 1227, and 1338 SNPs that mapped to 425, 322, and 437 genes specific to subtypes 1, 2, and 3, respectively. This study provided an example of the potential use of large-scale data and machine-learning approaches to subtype complex disease; however, replication of these subgroups was not done to confirm these findings.

Identification of New Clusters Among Type 2 Diabetes

The field of clustering of T2D really took off after a novel diabetes subclassification was identified in a Scandinavian population by Ahlqvist et al.[4] They reported five unique "clusters" of individuals with newly diagnosed diabetes (n=8980) using a data-driven approach, and six clinical variables measured at the time of diagnosis, which included glutamic acid decarboxylase (GAD) antibodies, age at diagnosis of diabetes, body-mass index (BMI), glycated hemoglobin (HbA1c), homeostasis model assessment of insulin resistance (HOMA 2-IR) and beta-cell dysfunction (HOMA2-β). These five diabetes subgroups were termed as SAID (Severe Autoimmune Diabetes), SIDD (Severe Insulin Deficient Diabetes), SIRD (Severe Insulin Resistant Diabetes), MOD (Mild Obesity-related Diabetes) and MARD (Mild Age Related Diabetes).[4] The five clusters varied in clinical characteristics, progression and outcomes of diabetes. 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 clusters were replicated in some populations, in others they could not be fully replicated.[5-9]

Novel Clusters Identified in Indians

Why look for clusters in Indians?

T2D in Asian Indians differs from Caucasians in a number of significant ways. Asian Indians have several unique characteristics which are collectively called as the 'Asian Indian phenotype' such as younger age at diagnosis, less severe obesity, increased insulin resistance etc.,[19,20] which may account for their increased predisposition to develop T2D.

Figure 1 presents the characteristics of the 'Asian Indian phenotype'.[21-30] It is therefore possible (due to the above and the well-known younger age at diagnosis) that clusters of type 2 diabetes identified in Asian Indians based on parameters used in the Western population might not behave exactly in the same manner with respect to treatment outcomes and risk of complications. Hence, we wanted to look for clusters of T2D in Indians.

Indian Discovery Cohort

Using data from a tertiary diabetes centre in Southern India, clustering of diabetes was conducted in individuals with T2D (n=19,084), using 8 clinically significant variables (age at diagnosis, BMI, waist circumference, HbA1c, triglycerides, HDL cholesterol and fasting and stimulated C-peptide).[9] Four clusters of patients were identified in the Indian population, which varied in characteristics as well as disease outcomes with regard to the management of diabetes and risk of complications. Of the four clusters identified in Indians[9] two were similar to that identified in the Scandinavian population, while two were unique

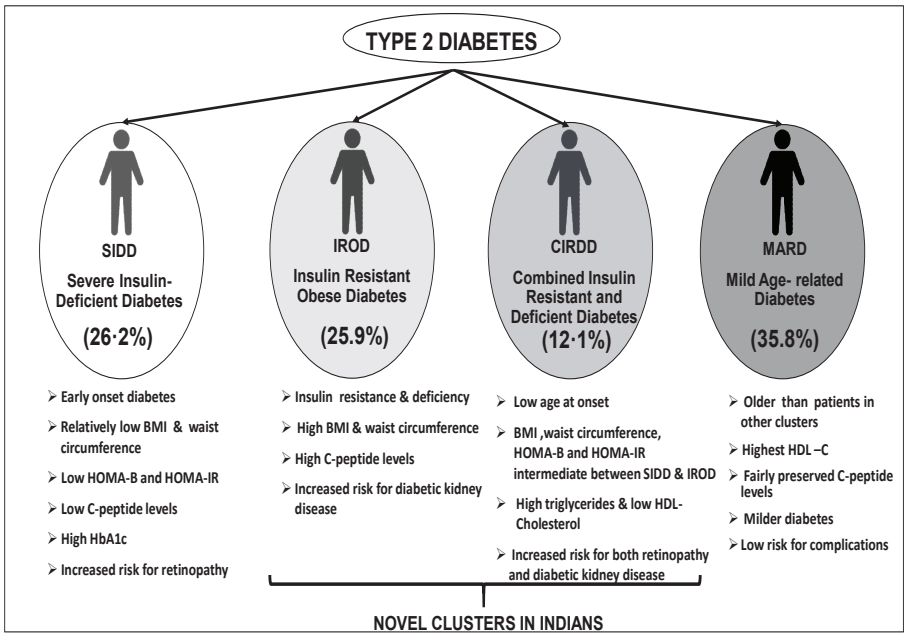
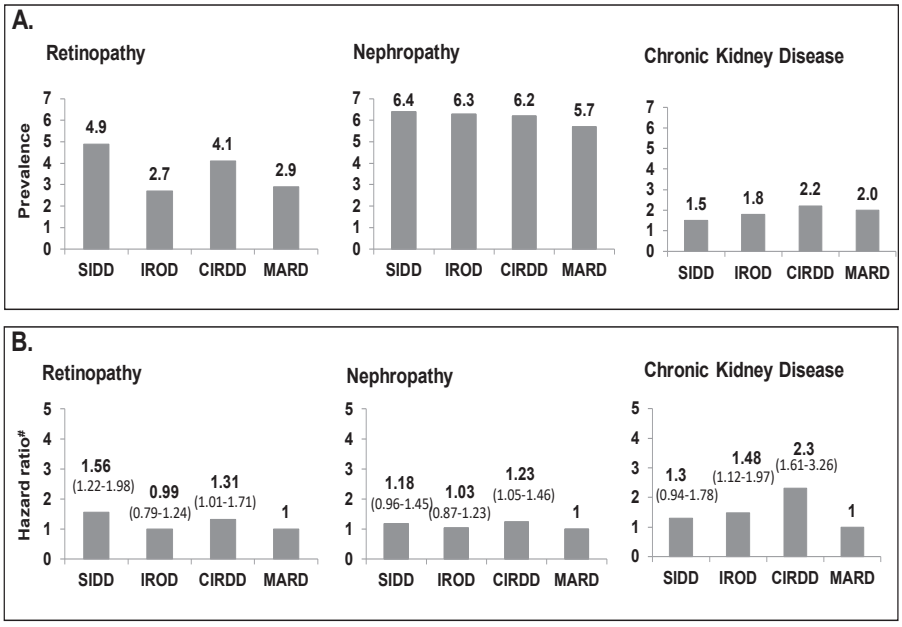


Fig. 2: Clustering of type 2 diabetes identified in Indians



Adjusted for age, sex, HbA1c and blood pressure, Using MARD as the reference group, HR=1.0

Retinopathy: Presence of at least one definite micro aneurysm; Nephropathy: Presence of either micro/macro albuminuria
Chronic Kidney Disease (CKD) : eGFR<60ml/min/1.73m^2

Fig. 3: Prevalence [A] and hazards ratios [B] for microvascular complications across different subgroups in the Indian population

to Indians. The two clusters similar to those in the Scandinavians, were **SIDD** and **MARD** which were present in 26.2% and 35.8% of the patients respectively. The two newly identified groups **IROD** (Insulin Resistant Obese Diabetes) and **CIRDD** (Combined Insulin Resistant and Deficient Diabetes) were present in 25.9% and 12.1% of the study population respectively. The phenotypic characteristics of the four clusters identified among Indians differed significantly from each other as shown in **Figure 2**. The characteristics of the clusters did not differ when split by gender and duration of diabetes (< 1 and < 3 years), which shows the stability of the clusters.

Indian Replication Cohort

The clusters identified in the Indian cohort were also replicated in the nationwide representative population-based ICMR-INDIAB study conducted across 15 Indian states/ Union territories,[31,32] showing that the four clusters identified are truly representative of the Indian population. In the INDIAB population, 34.8% of the population were in the MARD cluster, 30.3% in the IROD cluster, 24.7% in SIDD and 7.6% in the CIRDD cluster. Lowest BMI and waist circumference were observed in the SIDD group, who had the poorest glycemic control. IROD had the highest waist circumference and BMI, while the CIRDD cluster had the highest triglycerides, diastolic blood pressure, HbA1c, and lowest HDL. Highest age at diagnosis of diabetes, HDL levels and low diastolic blood pressure levels were observed in the MARD group. This group also had the mildest diabetes and therefore the best metabolic control.

This study also investigated the risk for microvascular complications of diabetes among the different subgroups **(Figure 3)** and reported that SIDD had the highest prevalence (4.9%) and risk for developing diabetic retinopathy [Hazard ratio (HR):1.6]. Conversely, CIRDD had the highest hazards for diabetic nephropathy (HR:1.2) while IROD (HR:1.5) and CIRDD (HR:2.3) had greater risk for chronic kidney disease after adjusting for confounding variables namely age, gender, blood pressure and HbA1c compared to MARD. The novel cluster CIRDD is of particular importance as it is characterized by difficult-to-control hyperglycemia and increased risk of both diabetic eye and kidney disease.

What is the Clinical Relevance of Identifying Clusters of Type 2 Diabetes?

Sub classification of individuals with T2D into distinct clusters has important implications for prognostication and management of patients. Individuals with the "mild" subtypes of T2D may require less aggressive management of hyperglycemia, particularly if they are in the elderly age group. On the other hand, individuals with a combination of severe insulin resistance and profound insulin deficiency appear to be the worst off when it comes to glycemic control as well as risk of complications. These patients will benefit from early aggressive treatment of hyperglycemia, using drugs that target a multitude of pathophysiologic

Table 1: Advantages of clustering of diabetes

Advantages
Helps to accurately subclassify diabetes into different subtypes
Helps to plan therapies based on the pathophysiology
Helps to predict prognosis and prevent diabetic complications
Helps in our approach to precision diabetes

targets, as well as early and regular screening for development of chronic vascular complications.

Identification of clusters also has an important bearing on the selection of the most appropriate anti-diabetic therapy. For instance, individuals with insulin-deficient diabetes (SIDD) which would benefit the most from early initiation of insulin-providing therapies while those in the IROD cluster would perhaps benefit more from therapies which tackle insulin resistance. Gan et al,[33] have shown that individuals of Asian Indian ethnicity respond differently to various classes of anti-diabetic medication compared to white Caucasians. This systematic review and meta-analysis concluded that the glucose-lowering efficacy of SGLT-2 and DPP-4 inhibitors, was greater in Asian Indians compared to white Caucasians.[33]

Conclusion

In summary, the classification of T2D in Indians into phenotypic clusters offers insights into the pathophysiological processes that drive diabetes in this ethnic group. This could aid in predicting the risk of diabetes complications. Identification of distinct subgroups of individuals with T2D could also have important implications for optimal management as well as prognostication, and this is an important initiative towards "Precision Diabetes". **Table 1** summarizes the benefits of clustering of T2D. Further studies along these lines would help us to refine the various clusters of T2D in the Asian Indian population, particularly with respect to selection of appropriate therapies and thus in the prevention of complications of diabetes.

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