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# *Sadikot's International Textbook of*

# Diabetes



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*Managing Editor*
**Banshi Saboo**

*Executive Editor*
**Amit Gupta**

**2nd Edition**

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CHAPTER

3

# Clustering of Type 2 Diabetes

*Mohan Deepa, Ranjit Mohan Anjana, V Mohan*

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## INTRODUCTION

Worldwide, over 537 million people are affected by diabetes.[1] According to the recent publication from the Indian Council of Medical Research-India Diabetes (ICMR-INDIAB) study, India has over 101 million adults with diabetes.[2] Diabetes is identified based on the chronic hyperglycaemia that results due to irregularities in carbohydrate, protein and fat metabolism, by complex aetiological pathways, i.e., either by a defect in insulin secretion, action or both.[3] These pathways have an impact on the phenotype of the diabetes upon diagnosis as well as how it progresses, responds to medication and other related complications. Individuals with type 2 diabetes (T2D) can have a wide range of pathophysiology, ranging from severe insulin resistance with almost normal β-cell function to normal insulin sensitivity with severe β-cell secretory function defects. Due to this heterogeneity, it is difficult to provide exact information on the underlying pathologic causes or effects of T2D. In recent years, there have been new efforts to identify T2D clusters or subgroups that differ in terms of phenotypic behaviour, clinical manifestation, and complication risk. These subgroups or clusters could make it easier to predict clinical consequences and thereby determine specific treatments and ultimately help in our approach towards precision medicine.

## NEED FOR T2D SUBTYPES

There are various diagnostic tests including detection of pancreatic autoantibodies, identifying defects in single gene related to monogenic diabetes like MODY or neonatal diabetes. However, the diagnostic test for T2D is only by the exclusion of other causes. Consequently, additional T2D subtypes with distinctive clinical characteristics may not fit the standard classification of the disease.[4] Despite the known variation in patient characteristics and medication responses, T2D care strategies continue to be mostly impersonal. Thus, a well-defined T2D subtyping could help in increasing the knowledge of complex diseases and thereby might pave way providing patients with personalised diagnoses and treatment plans. Ultimately, this could assist patients, medical professionals, and administrators at the hospital in better managing the disease in terms of cost-effectiveness, prevention, and prediction. The subtyping also helps in bringing a shift towards customised disease management and improving the disease outcomes and is part of 'precision medicine' in diabetes.[5]

## EVIDENCE ON THE SUBTYPES OF T2D

An earlier study in 2003 by Maldonado et al.,[6] reported a classification of four groups of 103 diabetes individuals, across different ethnicities based on the presentation of islet autoantibodies (A+/–) and indication of β-cell functional reserve (B+/–). This has led to the identification of four groups: A–B+ (50%), A–B–(22%), A+B– (17%), and A+B+(11%). This classification has clinical implications for the evaluation and identification of people with diabetes who are at risk for ketosis although arguably this would largely pertain to type 1 diabetes. This information also showed that there are at least four etiologically distinct groups associated with ketosis-prone diabetes, which may be divided according to autoantibody status, β-cell functional reserve and HLA genotype. It has

also been shown that β-cell functional reserve at the time of diabetic ketoacidosis is the most reliable predictor of future metabolic control and helps to identify patients who are more likely to experience ketosis and enhance clinical outcome prediction.

In a 2015 study by Li et al.,[7] electronically collected medical records of more than 2000 T2D individuals were used that included 73 clinical features. This led to the detection of three clusters of T2D: 1) Subtype 1 (29.8%) built on 33 clinical variables significantly distinct to this subtype; 2) Subtype 2 (24.2%) based on three unique variables (weight, troponin and insulin) to other two subtypes; 3) Subtype 3 (43.0%) based on 11 variables including blood protein, systolic blood pressure. Subtype 1 was associated to diabetic retinopathy and nephropathy, subtype 2 to cancer and outcomes of cardiovascular disease, and subtype 3 to neurological and cardiovascular diseases, HIV infections and allergies. Further, the genetic associations to the subtypes were elucidated. This includes the 425, 322 and 437 genes specific to subtypes 1, 2, and 3 that had 1279, 1227, and 1338 single nucleotide polymorphisms, respectively. This study has shown that topological analysis of patient data in a high-dimensional clinical phenotypic space, combined with machine learning techniques, will make it possible to identify useful T2D subtypes. However, one notable limitation of this study is that the replication of the identified subgroups was not performed to validate the findings.

## RECENT ADVANCES IN IDENTIFICATION OF DISCRETE T2D CLUSTERS

The field of diabetes clustering really took off after the landmark study by Ahlqvist et al.,[8] who for the first time, performed clustering using variables like age of diagnosis of diabetes, glycated haemoglobin, body mass index, β-cell function (HOMA-B), insulin sensitivity (HOMA-S) and presence or absence of GAD antibodies in a Scandinavian (White Caucasian) population ($n$ = 8,980 individuals). By using hierarchical and k-means clustering of diabetes patients, five subtypes of T2D were identified. These were termed as Severe AutoImmune Diabetes (SAID) or type 1 diabetes, Severe Insulin-Deficient Diabetes (SIDD), Severe Insulin-Resistant Diabetes (SIRD), Mild Obesity-related Diabetes (MOD) and Mild Age-Related Diabetes (MARD). This study has also shown that patients assigned to clusters exhibit distinct characteristics. For example, the SIDD cluster responds swiftly to insulin therapy and is more likely to develop retinopathy, while the SIRD group is more likely to develop nephropathy. This study helped to map the individuals with T2D on a scale based on their key clinical and physiological characteristics performed at diagnosis of T2D. Using the k-means clustering, individuals are divided into a cluster, even though the likelihood of them being allocated to that cluster is only marginally higher than that of any of the other clusters. This clearly highlights that there is a need to ascertain the stability of assigning the clusters over time and the reproducibility across populations. A recent study by Dennis et al.[9] performed clustering in the ADOPT (A Diabetes Outcome Progression Trial) clinical trial data and replicated the clusters like those of Ahlqvist et al. The testing of the clinical utility in the ADOPT data suggest that the diabetes progression and treatment responses vary between clusters. However, the models based on continuous clinical parameters are more helpful in stratification of individuals with diabetes.

The relevance of the diabetes clusters developed in the Scandinavian population by Ahlqvist et al was confirmed in the Chinese and the US population and in a Brazilian population.[10,11] The study by Zou et al.[10] has reproduced the analysis in the cross-sectional studies conducted among 2,316 subjects with newly detected diabetes in the China National Diabetes and Metabolic Disorders Study (CNDMDS) and 685 subjects in the National Health and Nutrition Examination Survey (NHANES III). This led to the identification of four clusters of diabetes using five variables, viz. age at onset of diabetes, BMI, glycated haemoglobin (or mean plasma glucose if HbA1c not available), HOMA2-B and HOMA2-IR. The observed four clusters in both the studies CNDMDS and NHANES III, emphasized on the key phenotypes of the clusters identified in the Scandinavian population. The NHANES III included participants across the diverse race and ethnicity. Thus, the findings suggest generalizability of the European classification of diabetes across populations and ethnicities. Further, the diabetes clusters were also confirmed in Mexican cohorts[9] using data from four NHANES survey cycles: 1988–1994 (NHANES-III), 1999–2000, 2001–2002, and 2003–2004, which included individuals with previously diagnosed with T2D along with the newly diagnosed diabetes. This revealed that four reproducible clinical profiles (related to age, insulin resistance, insufficient insulin, and obesity) were produced using self-normalizing neural networks (SNNN) in the Mexican cohorts, thus, clearly showing its applicability to this population. In the Portuguese population[12] also, four clusters were replicable using three

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variables: age at diagnosis of diabetes, presence/absence of GAD antibodies and body mass index.

## T2D Clusters in Indians

The clusters developed in Western populations may not be applicable to Indians, as they have a different clinical phenotype of T2D referred to as the 'Asian Indian phenotype'. This phenotype is distinguished by having increased insulin resistance and abdominal fat, even at lower levels of body mass index.[13] According to recent evidence, β-cell dysfunction seems to be quite an earlier attribute of T2D in Asian Indians than other ethnicities.[14] It was thus clear that a large study was needed in Indians.

Anjana et al.[15] for the first-time attempted diabetes clustering in the Asian Indian population on a sample size of 19,084 patients with T2D utilizing eight clinically appropriate parameters, viz. age at diagnosis of diabetes, BMI, waist circumference, glycated haemoglobin, HDL cholesterol, serum triglycerides and fasting and stimulated C-peptide. The clustering of diabetes was performed using data from the Diabetes Electronic Medical Records (DEMR) of a tertiary care centre for diabetes in India (Dr. Mohan's Diabetes Specialities Centre). It was also replicated in the whole of India using a representative sample from the Indian Council of Medical Research-India Diabetes (ICMR-INDIAB) study.[8] This led to the identification of four unique phenotypic clusters of T2D in the Asian Indians, with highly significant implications for diagnosis and management. These clusters of patients identified in the Indian population varied in terms of clinical traits, disease progression, disease management and risk of complications. Two of the four Indian clusters that were found to exist[15] resembled those found in the Scandinavian population – SIDD and MARD of the patients and two were unique to the Indians – IROD (Insulin Resistant Obese Diabetes) and CIRDD (Combined Insulin Resistant and Deficient Diabetes). The clusters are described in detail below:

**Cluster 1—Severe Insulin Deficient Diabetes (SIDD):** 26.2% of T2D patients fall under this cluster. Low waist circumference, body mass index, C-peptide levels (fasting and stimulated), as well as the highest HbA1c levels in comparison to other clusters, are characteristics of this cluster. Low insulin resistance and diminished β-cell activity were present in this cluster. Individuals in this cluster compared to those in the other clusters, were more likely to need insulin, and had poor metabolic control. This cluster mimics the Scandinavian population's cluster.

**Cluster 2—Insulin Resistant Obese Diabetes (IROD):** About 25.9% of T2D patients exhibit this cluster. This is the first description of a novel cluster in this Asian Indian population. This group of patients had the highest waist circumference, BMI, and C-peptide levels. Additionally, this cluster has the highest insulin resistance and β-cell function. Individuals had moderate metabolic control which suggests that their β-cell function was sufficient to at least partially compensate for the insulin resistance due to obesity.

**Cluster 3—Combined Insulin Resistant and Deficient Diabetes (CIRDD):** 12.1% of T2D individuals belong to this cluster and this is another distinctive cluster among Asian Indians. The waist circumference, body mass index, β-cell function, and insulin resistance values in this subgroup were intermediate between SIDD and IROD, and the onset age was the youngest. The CIRDD cluster had the lowest levels of HDL cholesterol and the highest levels of triglycerides when compared to the other three clusters. Only 15% of this cluster were on insulin, and had poor metabolic control. Even though CIRDD only affects a lesser proportion of T2D patients, it has a more aggressive phenotype since it manifests earlier in life and has poor metabolic control similar to the group with SIDD.

**Cluster 4—Mild Age-Related Diabetes (MARD):** With a late age at onset as compared to other clusters, this cluster was the most prevalent in the Asian Indian cohort and was present in 35.8% of the T2D patients. This cluster had the highest levels of HDL cholesterol and preserved C-peptide in compared to the other three clusters, demonstrating the best metabolic management. This group had the lowest likelihood of using insulin. The individuals in this cluster matched the Scandinavian population's MARD subgroup.[8] **Figure 1** summarizes the 4 clusters in Asian Indians.

When the features of these four clusters were split depending on the duration of diabetes and by gender, it was shown that the four groupings in Asian Indians remained stable. When compared the clusters observed in the Asian Indian and Scandinavian populations, there were notable differences. While two clusters, SIDD and MARD, correspond to those seen in Scandinavian groups, the CIRDD and IROD clusters are specific to the Indian population and are thought to be novel.

## Diabetes Complications and T2D Clusters

Among Indians, diabetic retinopathy was more prevalent in the SIDD and CIRDD clusters.[15] The SIDD cluster

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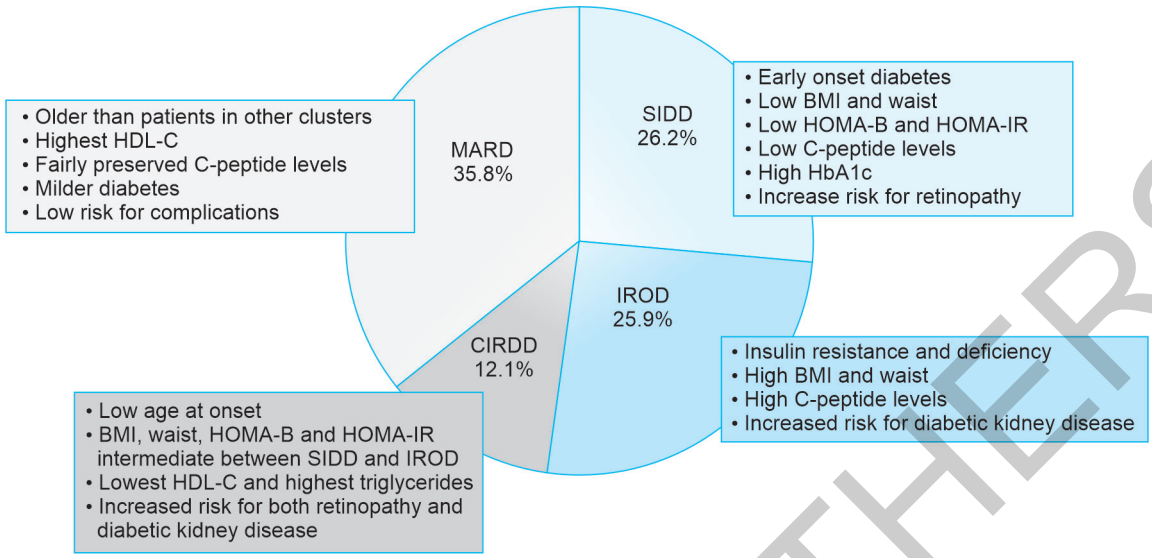


**Figure 1:** Novel clustering of type 2 diabetes in Asian Indians.

phenotype is comparable in the Asian Indian and Scandinavian populations, considering the fact that they had the poorest metabolic control and took the longest to attain the treatment objective among the four T2D clusters.[8] In Asian Indians, the risk of developing diabetic retinopathy was highest in the insulin deficient phenotype, similar to what has been observed in the Scandinavian population. This implies that, in addition to its involvement in insulin deficiency, hyperglycemia plays an important role in the development of microvascular complications. The CIRDD group was shown to have the highest prevalence of renal disease, which persisted even after age, sex, blood pressure, and glycated haemoglobin were taken into account. More aggressive treatment, which may include a mix of drugs that target different pathophysiology of T2D, may be suggested early at the time of diagnosis in order to aid these people avoid long-term consequences. The relationship between insulin resistance and increased salt sensitivity, hyperfiltration, and glomerular hypertension accounts for the higher risk of renal disease in the two insulin resistant phenotypes, namely CIRDD and IROD. The CIRDD has a higher chance of developing renal disease than the IROD, which is most likely caused by the CIRDD's concurrent insulin insufficiency and worse glycemic management.

## Validation of T2D Clustering in Asian Indian and South Asian Cohorts

The stability of the cluster is clearly demonstrated as cluster's features did not vary when divided by sex and duration of diabetes (<1 and < 3 years). Further, the identified clusters were also replicated in the countrywide representative population-based study, called the Indian Council of Medical Research-India Diabetes (ICMR-INDIAB) study[16] performed across 30 states/union territories of India. Data was used for validation purposes from 15 states (including 2,204 individuals with T2D). Data was used for validation purposes from 15 states (including 2,204 individuals with T2D). Age at onset of diabetes, waist circumference, body mass index, serum triglycerides, HDL cholesterol, and HbA1c were the six factors utilised for clustering. The MARD cluster included 34.8% of the overall INDIAB population, followed by the IROD at 30.3%, the SIDD at 24.7%, and the CIRDD at 7.6%. The validation results confirm that the that the clusters reported from the DEMR dataset and the ICMR-INDIAB population were comparable and thus the findings can be generalized to the individuals with diabetes belonging to the Indian population. The findings have indicated that the four clusters identified are truly reflective of the Asian Indian population.

A more recent study from the UK clustering of T2D was carried out in South Asians (Pakistanis and Bangladeshis living in UK).[17] The authors concluded that they were able to replicate the findings of the Indian study. Specifically, the presence of CIRDD was confirmed by these authors. Thus, it is clear that the unique forms of clusters of T2D identified in India are similar across South Asia also.

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## Heterogeneity of T2D—McCarthy's Palette Model

Type 2 diabetes is indeed a complex disease with extensive variation in the phenotypes of patients with T2D, led by lifestyle alterations and exposures to the environment. McCarthy[18] recently published a review that introduced the concept of the diabetes palette model, which has portrayed that the development of T2D is a consequence of defects in several aetiological pathways. This model indicated that a person develops T2D with an amalgamation of defects in these pathways. These processes have been labelled as beta cell function, beta cell mass, insulin action, glucagon secretion/action, incretin secretion/action and distribution of fat. Each pathway is assigned a colour in McCarthy's palette model, and when each patient is plotted with an axis representing the pathophysiological processes, the individuals would be represented by colour, reflecting the contribution of the pathophysiological pathways. Moving forward, it will be useful to subclassify a population of individuals with T2D into distinct clusters and deconvolute their aetiological processes. Thereby, this would help to predict the prognosis of the diabetes phenotype followed by its progression and deciding the management of treatment response and outcomes including high risk for developing complications. Due to the diverse contributions of the many pathophysiological processes that might cause diabetes, each individual is colour coded. By identifying the processes, evaluating the underlying genetic contribution, or measuring metabolites or gene expression, the underlying mechanism can be explained. These three approaches may then be combined in an integrative multi-omic method.

## CONCLUSION

Phenotypic clustering of T2D in Asian Indians provide understanding into the underlying pathophysiological processes and are believed to have important implications for development of a precision approach to treatment and prognostication. Individualized therapy will advance with the delineation of these clusters/subgroups. In the Asian Indians, of the four phenotypic clusters, the CIRDD represents the most aggressive phenotype with poor metabolic regulation and a noticeably increased risk of both renal and retinal diseases. Two of the clusters are unique and only found among Asian Indians. The Asian Indian population appears to have both insulin resistance and insulin insufficiency coexist, and this is linked with a higher risk of microvascular complications in this population. More crucially, because this clustering uses factors that are simple to assess, it can be applied in a variety of clinical settings across India. In summary, this clustering supports our approach to precision medicine by helping to accurately classify diabetes into multiple subgroups, organise treatment according to the pathophysiology, predict prognosis and thereby prevent complications.

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