Editorial

Type 2 Diabetes : One Disease or of Many Subtypes?

It is now well known that diabetes mellitus is of different types. The main classification of diabetes is as Type 1 Diabetes, Type 2 Diabetes, gestational diabetes and other types of diabetes. Under 'other types' are included various genetic forms of diabetes, secondary diabetes, endocrine forms of diabetes, drug induced diabetes and many other forms. Unfortunately, once such classifications are published, there is a tendency to consider Type 2 Diabetes as a homogenous entity. Based on this, till recently, various guidelines for treatment of diabetes have suggested algorithms whereby metformin is used first for all patients with Type 2 Diabetes and then, subsequently, various choices of antidiabetic drugs were prescribed including sulfonylureas, DPP4 inhibitors, Glitazones (Pioglitazone), SGLT2 inhibitors, GLP1 analogs and insulin. More recently, due to the increasing evidence of benefits for the heart and the kidney, the SGLT2 drugs have been considered as the drug of choice, particularly for those with heart failure or with high risk of cardiovascular disease. The GLP1 receptor analogs have also been suggested for those in whom weight reduction or prevention of heart disease is a priority. While these changing guidelines point to the increasing role of precision medicine in the diagnosis and treatment of diabetes, it still considers Type 2 Diabetes as one single entity.

During the last few years, scientists have been trying to subclassify Type 2 Diabetes in several ways. However, the early attempts to segregate Type 2 Diabetes into different subtypes, did not really take off.

In 2018, Ahlqvist, *et al*[1] published their seminal paper in Lancet Diabetes Endocrinology, classifying Type 2 Diabetes into 5 different subtypes.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 paper was a turning point for sub dividing Type 2 Diabetes into various clusters. The paper was based on 3 Scandinavian registries and indeed in that population these subtypes seemed to have worked very well. However, the SAID variety is a form of autoimmune diabetes and one could argue that it either represents a variant of Type 1 Diabetes or that it is nothing but what was earlier called as Latent Autoimmune Diabetes of Adults (LADA). The replication of these subtypes soon followed and many countries, including China, Mexico, Portugal and others described clustering of Type 2 Diabetes in their respective populations with some getting exactly the same results as was obtained in Sweden by Ahlqvist, *et al*[1] and others reporting some variations in the clustering.

What about India? For many years we have known that Type 2 Diabetes in Indians (and in South Asians) differs considerably from that seen in Europeans. Some of the characteristics of 'Asian Indian Phenotype'or 'South Asian Phenotype' are that Type 2 Diabetes occurs at least 10-15 years earlier in Indians compared to that seen in Europeans and that a rapid decline in beta cell function in this ethnic group thereby leaving to a faster progression to pre-diabetes to diabetes in South Asians and in Indians[2-4]. Moreover Indians have a major dyslipidemia characterized by very low HDL (good) cholesterol and high serum triglycerides.

Given the differences in phenotype of Type 2 Diabetes, we looked at the clustering of Type 2 Diabetes in Indians, in collaboration with the University of Dundee by taking up the India-Scotland Partnership for Precision Medicine in Diabetes (INSPIRED) project. Specifically, we looked at the type of Type 2 Diabetes clusters in our population[5]. The study was done on 19,084 patients with Type 2 Diabetes using simple clinical parameters which included age at diagnosis, body mass index, waist circumference, glycated hemoglobin, HDL cholesterol, serum triglyceride and fasting and stimulated C-peptide. The clustering was initially performed using data of patients seen at Dr Mohan's Diabetes Specialities Centres (DMDSC) across the country. Later it was also replicated in a representative sample of the whole of India, through the ICMR-INDIAB study. We found that 4 clusters were present in Indians :*Severe Insulin Deficient Diabetes* (SIDD), *Insulin Resistant Obese Diabetes* (IROD), *Combined Insulin Resistant and Deficient Diabetes* (CIRDD) and *Mild Age-Related Diabetes* (MARD). The SIDD and the MARD varieties were similar to that described in Scandinavia, although there were some differences here also. The SIDD variety, for example appeared to have more severe insulin deficiency than in Europeons and the MARD variety seemed to develop diabetes at a younger age group than in Europeons. eg, the mean age at the diagnosis of the Scandinavian MARD patients were 67 years compared to 50 years in the Indian population. The characteristics of four subtypes of Type 2 Diabetes in Indians is shown in Fig 1[5].

It was gratifying to note that the clusters were validated in the whole of India through the ICMR-INDIAB population. Subsequently, in another study, the prescribing patterns of treatment at different diabetes centres was looked at and was confirmed in a larger sample size of 32,867 patients that the same four clusters were identified across different clinic populations across India[6].

More recently, these Indian clusters have also been replicated in South Asians in the UK (Pakistani's and Bangladeshis)[7]. It is notable that the CIRDD variety appears to be unique to South Asians and they also have the lowest HDL cholesterol and highest serum triglycerides among the four subtypes.

What is the significance of the clusters of Type 2 Diabetes ?

The clustering of diabetes has several clinical implications :

(1) In terms of the time taken for individuals to reach the HbA1c target of 7%, the MARD variety was easiest group to treat, followed by the IROD variety. The most difficult to control group was the SIDD variety, not unexpectedly, because they have the lowest insulin secretion. The CIRDD variety behaved similar to the SIDD variety, because they also have insulin deficiency.

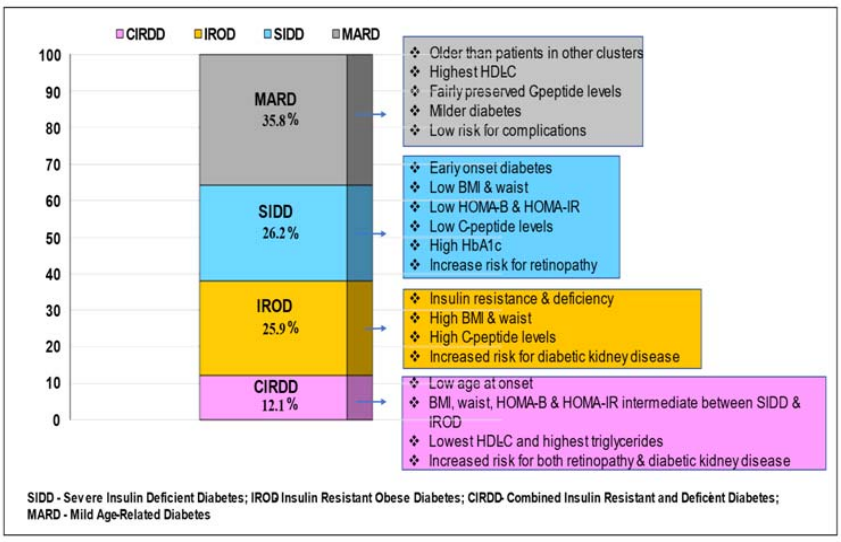
(2) With regard to the risk of complications, it was shown that the SIDD variety is more prone to retinopathy and neuropathy, whereas the IROD variety is more prone to nephropathy. These findings were similar to what was reported by the Ahlqvist, *et al*[1].

(3) A novel finding of our study was that the CIRDD variety was more prone to both retinopathy and nephropathy[5].

How does one subclassify Type 2 Diabetes as a Clinician?

Using the simple clinical characteristics described above, it is possible to make a mental diagnosis of the subtype of diabetes that we are treating, even as the patient walks into our consultation room. For example, if a young, thin individual walks in (and Type 1 and Fibrocalcific Pancreatic Diabetes have been ruled out in them) it is most likely that they have the SIDD variety. If an obese individual walks in, most likely this individual has IROD. If in some of these individuals whom we suspect to have IROD, the HDL cholesterol is very low and the triglyceride levels very high, and the insulin secretion is on the lower side, they have the CIRDD variety. Finally, if an older person, say above 60 years of age, who has just been diagnosed, walks in, most likely this individual has MARD type of diabetes.

Figure 1: Novel clustering of type 2 diabetes in Indians



SIDD - Severe Insulin Deficient Diabetes; IROD Insulin Resistant Obese Diabetes; CIRDD- Combined Insulin Resistant and Deficient Diabetes; MARD - Mild Age-Related Diabetes

What about the Therapeutic Approach to Individuals in these Various Categories ?

Till date we do not have a randomized clinical trial to prove that a particular group of drugs will work better in a particular subtype of Type 2 Diabetes. However, the hypothesis is that the SIDD variety will respond better to insulin secretagogues like sulfonylureas or DPP4 inhibitors, or

may need insulin early. The IROD variety on the other hand, would respond better to insulin sensitizers, and thus, metformin and SGLT2 drugs would be more suitable. In the CRIDD variety, we can speculate, that they would need an insulin secretagogue as well as a sensitizer. Finally, the MARD variety is the easiest to treat and most likely all that they would need is metformin. This hypothesis is currently being tested at our centre through a randomized clinical trial (CITR No. CTRI/2021/11/037753), The control group in each of the subtypes would start with metformin and then go on to one of the other drugs as we conventionally treat now. In the intervention arm in each of the subgroups, the specific drugs based on the pathophysiological defect would be given. This RCT, when completed, should throw more light on whether the classification of Type 2 Diabetes into clusters could translate into better control of diabetes by using the appropriate antidiabetic drugs.

We have also recently developed an App called '**Dia**betes **N**ovel subgroup **A**ssessment **(DIANA)** of we feed in the basic clinical characteristics, the App will tell us which type of Type 2 Diabetes that particular patient is likely to have, ie, SIDD, IROD, CIRDD or MARD. It will also suggest the first line drugs which can be used for that patient. Finally, it will also inform us about the risk of developing the retinopathy or nephropathy within the next five years. The App is just being launched and this could help the clinician to offer individualized or personalized care to diabetes.

The era of precision medicine in diabetes has finally dawned. Besides classifying patients into Type 1 or Type 2 Diabetes, or Monogenic forms of diabetes, or other specific forms of diabetes, with the further refinement into subclasses of Type 2 Diabetes, the field is now moving on at a rapid pace.It is hoped that this will set the scene for precision diabetes diagnosis and treatment in India and elsewhere.

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