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The new Scandinavian Five-Point Classification of Diabetes Applied to an Indian Population: A Pilot Study from Eastern India

Rudrajit Paul, Kunal Som**, Dipanjan Bandyopadhyay****

Abstract

Background: Diabetes is a major public health problem all over the world. It is a heterogeneous disease and the patients have different degrees of metabolic control and other complications. Recently, there have been attempts to classify diabetes into further sub-groups which can give better prognostic information. The present study is aimed to test one such classification in a sample Indian population.

Material and methods: Diabetic adult patients coming to medicine department were the subjects for this cross-sectional pilot study. Parameters like HbA1C %, Body Mass Index (BMI), HOMA-2 IR and HOMA-2B scores were collected. Then, the patients were classified into clusters according to the scheme proposed by Ahlqvist et al in 2018. Appropriate India/South Asia specific cut-offs were used to define obesity and insulin resistance. Presence of specific complications like fatty liver and microalbuminuria in different clusters was studied.

Results: There were 64 diabetic patients with male: female ratio 41: 23. According to this classification system, 10.9% of the subjects had SIDD, 26.6% had SIRD, 31.3% had MOD and 4.7% had MARD. 26% of the patients remained unclassified and there was no SAID. Average HbA1C of SIDD and SIRD groups were higher than study average. In the unclassified group, HbA1C was lower (p = 0.013). Urine ACR was higher in the MOD group.

Conclusion: This study gives an idea of the relative percentage of different clusters in Indian diabetic subjects. A higher percentage of MOD was found in this study, compared to other European data. However, the classification may need some modification in the Indian context to account for the unclassified section.

Keywords: Diabetes; cluster; HbA1C; insulin resistance; HOMA.

Introduction:

Diabetes is a complex metabolic disorder with multi-organ involvement[1]. By some accounts, diabetes is the fastest increasing disease worldwide and the economic impact of the disease will adversely affect all health systems[1]. The management of diabetes involves managing the metabolic parameters as well as dealing with the long-term complications like blindness or nephropathy.

Diabetes has been traditionally classified broadly into type 1 and type 2[2]. There are also other types like MODY, pancreatic diabetes and gestational diabetes. However, this classification system may sometimes look inadequate as newly diagnosed diabetics can't always be put into a definite box. Also, among patients of type 2 diabetes, there are wide variations in complications, metabolic control, and prognosis[1]. The same treatment algorithm may not benefit all type 2 diabetes patients and a nuanced approach may be necessary. Some authors have expressed an opinion that type 2 diabetes is not a single disease entity but a heterogeneous combination of different syndromes. Thus, the present classification of diabetes is not always appropriate in correctly prognosticating all patients after diagnosis and there is scope of revision.

In this background, in 2018, Ahlqvist *et al* proposed a new classification of diabetes[1]. Based on certain variables in addition to blood glucose, they attempted to classify diabetes phenotypically into five types[1]. Later, they used independent cohorts to replicate the clusters and found that the classification is robust. This classification can give a better idea of the prognosis and various systemic complications.

This new classification is just two-years-old. Thus, it is still early days to comment on its usefulness. But in general, there are attempts to reclassify diabetes[3]. For example, with the availability of continuous glucose monitoring, there is a new concept of "glucotypes"[3]. Improved use of statistical methods and genetics will probably lead to more such attempts in the future. In 2019, the German diabetes study group published a study on this novel classification[4]. They reported that the phenotypic classification, as proposed by

Associate Professor, Department of Critical Care Medicine, IPGMER and SSKM Hospital, Kolkata - 700 107; **Associate Consultant, Department of Medicine, Desun Hospital, Kolkata; ***Professor and HOD, Department of Medicine, North Bengal Medical College. Corresponding Author: Dr Kunal Som, Associate Consultant, Department of Medicine, Desun Hospital, 720, Eastern Metropolitan bypass, Sector-1, Kolkata - 700 107. Tel: 9433606056, E-mail: kunalsom8@gmail.com.

Ahlqvist *et al* was, in fact, able to predict systemic complications in their cohort too[4]. Thus, this new classification can be the first step in precision medicine for diabetes.

There are no published studies on this new classification of diabetes from India. However, India is experiencing a rapid rise in the number of diabetics (probably the highest in the world) and this will be a significant burden on the health system in the future[5]. Thus, there is an urgent need of research into the biological characteristics of diabetics in India so that better management decisions can be made. The present study is a small attempt in this regard.

The aim of this study is to analyse the metabolic parameters of diabetic patients and classify them according to the novel classification system as mentioned above.

Material and methods

This was a cross-sectional observational study conducted in a tertiary care private hospital of Eastern India. Diabetic patients coming to the medicine OPD were screened for inclusion in the study. Exclusion criteria included anyone with drug-induced diabetes, genetic form of diabetes, pregnancy, anyone below 18 years of age, autoimmune diseases, on-going steroid or other immunosuppressive therapy, known haemolytic disorders and cirrhosis of liver. Also, anyone with an active infection like tuberculosis was excluded.

The patients were explained about the study in their native language and written informed consent was obtained. Necessary approval for the study was obtained from the medical superintendent.

The aim of the study was to classify the diabetic patients according to scheme suggested by Ahlqvist *et al*[1]. For this, the parameters as mentioned in this Scandinavian study, were analysed.

To characterise insulin resistance, the HOMA-2 scoring system was used. Software for this scoring system has been developed by the Diabetes Trials Unit of the University of Oxford[6]. This software is freely downloadable.

The HOMA-2 IR score cut-off to define insulin resistance in different populations is a matter of intense research. In a study from Iran, the cut-off points for HOMA-2 IR was determined to be 1.4 (men), 1.18 (women) and cut-off for HOMA-2B was found to be 72 - 74% respectively[7]. In another recent study from Asia (China), the HOMA-2 IR cut-off point has been determined to be 2[8]. The optimum HOMA-IR score cut-off must be calculated for each population separately. In India, there are not many studies on the HOMA-2 scoring. In a 2013 study from North India, the optimum HOMA-2IR cut-off for adolescents of both sexes was determined to be 2.5[9]. But adolescents have higher insulin resistance than adults. In the present study, adolescents were excluded. In another recent study from India, the HOMA-2 IR cut-off for insulin resistance has been taken as 2[10]. Thus, considering the Chinese and Indian study methodology, the HOMA-2 IR cut-off in the present study has also been taken as > 2. A recent Venezuelan study has also proposed the same cut-off value[11]. However, whether there are grades of insulin resistance with higher IR scores, indicating higher resistance, is again a matter of debate.

According to this study, diabetes has been divided into five types[1]:

Cluster	Characteristics					
	BMI	Age of onset	GAD antibody	Insulin secretion	HbA1C	Insulin resistance
Cluster 1: SAID: Severe Auto-immune diabetes	Low	Early	Positive	Low	High	None
Cluster 2: SIDD: Severe insulin-deficient diabetes	Low	Early	Negative	Low	High	None
Cluster 3: SIRD: Severe insulin-resistant diabetes	High	Variable	Negative	Normal	Variable	High
Cluster 4: MOD: Mild Obesity-related diabetes	High	Variable	Negative	Normal	Moderate	None
Cluster 5: MARD: Mild age-related diabetes	Normal	Delayed	Negative	Normal	Moderate	None

To define obesity, body mass index has been used. For this purpose, the Asian/Indian population specific standards have been used[12]. Thus, BMI $\geq$ 25 kg/m^2 has been considered as obese.

To define beta cell failure and low insulin secretion, the HOMA-2B score was used. This reflects the release of insulin under basal conditions. Any exogenous insulin or insulin secretagogues would falsely change the serum insulin levels and thus, the HOMA scores. Thus, patients on sulfonylurea or basal insulin treatment were excluded from this study. However, there is no single cut-off for HOMA-2B score which can define beta cell failure. So, in this study, to define insulin deficiency or beta cell failure, we considered the lowest quartile of the HOMA-2B scores.

To define age-related diabetes, a cut-off age of 60 or above was considered.

Blood glucose was checked by the hexokinase method, HbA1C was checked according to NGSP standards, fasting insulin was checked by Chemiluminescence and urine ACR was checked by Immunoturbidimetry (urine microalbumin) and Modified Jaffe method (urine creatinine). The GAD-65 antibody in serum was calculated only for patients with low HOMA-2B scores.

Since this was a pilot study with no Indian precedence, there was no reference value to determine sample size. Hence, a sample size of at least 50 was targeted. Consecutive sampling technique was used. The data was entered into Microsoft Excel worksheet and standard statistical tests were used. The data is expressed as percentage with 95% confidence interval (CI). $P < 0.05$ was considered significant.

Results

We had a total of 64 diabetic patients in this pilot study. Male: female ratio was 41: 23. Average age was 58.6 ± 11.1 years. In HOMA-2B score, the median was 42.65, first quartile was 23.3.

Based on the methodology described above, the patients were classified (Fig. 1). It is seen that there were no patients with severe autoimmune diabetes. SIDD was present in 7 (10.9%; 95% CI: 4.5 - 21.2%), SIRD was present in 17 (26.6%; 95% CI: 16.3 - 39.1%), MOD was present in 20 (31.3%; 95% CI: 20.2 - 44.1%) and MARD was present in 4.7% (95% CI: 1 - 13%). But 26.6% of the patients could not be classified into any of the 5 categories. These were the subjects who had BMI below 25, HOMA-2IR score below 2, age of diagnosis between 30 and 50 and HOMA-2B score in the 2nd or 3rd quartiles. They are hereby referred to as "unclassified".

The average HbA1C% of the SIRD group was higher than other subjects (8.8 ± 1.9 vs 8.2 ± 2.5%) but the difference was not statistically significant ($p = 0.2$). In the unclassified group, average HbA1C was 7 ± 1.1%, which was lower than the average HbA1C of study population (8.3%; $p = 0.013$; $t = -2.26$). In the SIDD group, average HbA1C was 9.5%, which was higher than the study average ($p = 0.11$).

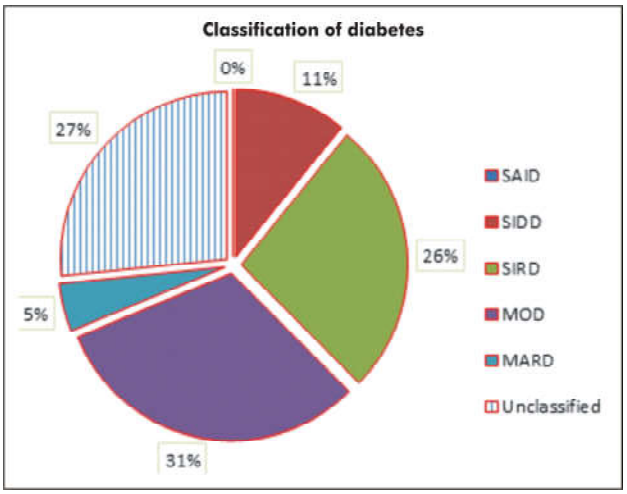

Fig. 1: *Pie chart showing the various categories of diabetic patients in the study.*

Average urine ACR of study subjects was 125.9 ± 326.1 µg/mg. But in the unclassified group (n = 17) it was 45 ± 42.4 ($p = 0.17$) and in the MOD group (n = 20) it was 256.3 ± 579 ($p = 0.13$). Thus, obese patients tended to have higher degree of proteinuria. Fatty liver by ultrasonography was found in 12 subjects (18.8%). There was no difference among the categories regarding occurrence of fatty liver.

Discussion

In this pilot study, we have attempted to apply the recently published Scandinavian classification of diabetes on a sample adult Indian population. It was found that 26% of the diabetic subjects remained unclassified. This unclassified group had better metabolic control (as determined by the HbA1C%) and lower incidence of proteinuria.

In the Scandinavian study mentioned in "introduction", the relative percentage of diabetic subjects in each category was as follows: SAID: 6.4%, SIDD: 17.5%, SIRD: 15.3%, MOD: 21.6%, MARD: 39.1%[1]. In the present study, SIDD was 10.9%, SIRD was 26.6% and MOD was 31.3%. We did not find any SAID and MARD was only 4.7%. We may have missed the SAID cases as our study population involved only adult subjects (> 18 years) and autoimmune diabetes cases are usually diagnosed at younger age. Also, our study area was medicine OPD and indoors; but autoimmune diabetes cases tend to attend the endocrinology speciality clinics.

Recently, the classification system of Ahlqvist *et al* was applied to a UK population[13]. Here, it was found that SIRD was 20%, MOD was 22% and MARD was 34%[13].

Ahlqvist *et al* identified that the different clusters had different prognosis and occurrence of diabetic complications. For example, they found that clusters 1 and 2 had higher HbA1C and cluster 3 had the highest incidence of fatty liver[1]. In the UK study, some difference in treatment response was also seen among the clusters[13]. In the present cross-sectional study, treatment response was not assessed.

Thus, there seems to be some evidence that this cluster-driven approach in diabetes may be useful for clinical purposes also, like deciding on therapy. But the specific elements which make up the clusters, like HOMA2 scores are not meant for clinical use and are difficult to interpret for an individual patient. Thus, how this clustering will become clinically applicable is a matter of future research.

Another similar classification of diabetic subjects based on this model was done in Germany recently[4]. They found that the SIRD cluster had the highest prevalence of fatty liver and also, hepatic fibrosis on follow-up[4]. This group also had the highest fasting adipose tissue-insulin resistance index. Diabetic polyneuropathy was more prevalent in SIDD[14]. In

the current study, the number of fatty liver cases was too small for any comment or inference.

As this present study shows, the cluster-driven classification of diabetes may not be the same in Indian patients. We found that about a quarter of our patients did not fulfil the criteria for any cluster. This unclassified group also had metabolic parameters like urine ACR different from other diabetics. There are two possibilities here. One is: for Indian patients, the description of clusters may have to be changed or a new cluster introduced. The second is, on longitudinal follow up, these patients may show new features and thus, may become eligible for one of the existing clusters. Also, this Scandinavian classification has "severe" for the first three clusters and "mild" for the last two clusters. There is no "moderate" category. May be some of these unclassified patients of the present study will fall into that moderate grade. Some Indian authors are quite sceptical of this new classification[14]. They raise a lot of issues like lack of availability of suitable tests in this country and lack of inclusion of South Asian variety of diabetes like Flat-bush diabetes[14]. Also, since this new clustering cannot predict cardiovascular mortality, they are not hopeful about its prognostic role. Some authors have proposed that this new classification of diabetes should also include parameters like family history and lipid profile.

However, this novel classification of diabetes is just in its infancy. These are early days and it is difficult to comment on their merits with the current meagre data. There is need of more data from different ethnic groups.

Limitations

The present study is limited by small number of subjects. But this was meant mainly as a pilot study. A larger study is planned in the future. Also, a cross-sectional study is not appropriate to assess parameters like treatment response or progression of specific complications like neuropathy. For that, a cohort study would be appropriate.

Secondly, there is much controversy regarding the cut-off for HOMA scores. This study has used a certain cut-off based on available literature. But there are other proposed values also. The whole idea of division into clusters is based on these cut-offs and thus, the relative percentage of subjects in each category will change significantly if cut-off references are changed.

Finally, the present study also did not study genetic markers in the different sub-groups for want of funds.

Conclusion

Diabetes is a major public health problem of modern times. There is need of newer research into the types of diabetes and their prognostic value. However, whether novel classification systems proposed from other parts of the world will be applicable in the Indian context is a matter of further deliberation.

References

1. Ahlqvist E, Storm P, Käräjämäki A *et al*. Novel subgroups of adult-onset diabetes and their association with outcomes: a data-driven cluster analysis of six variables. *Lancet Diabetes Endocrinol* 2018; 6: 361-9.
2. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2014; 37 (Suppl. 1): S81-90.
3. Hall H, Perelman D, Breschi A *et al*. Glucotypes reveal new patterns of glucose dysregulation. *PLoS Biol* 2018; 16: e2005143.
4. Zaharia OP, Strassburger K, Strom A *et al*. Risk of diabetes-associated diseases in subgroups of patients with recent-onset diabetes: a 5-year follow-up study. *Lancet Diabetes Endocrinol* 2019; 7: 684-94.
5. Dey S. Nearly 12% of Indians above 50 have diabetes, finds new survey. *The Times of India*. (Updated 2019 Oct 11; Cited 2020). Available online from https://timesofindia.indiatimes.com/india/nearly-12-of-indians-above-50-have-diabetes-finds-new-survey/articleshow/71531884.cms.
6. HOMA2 Calculator. Diabetes Trials Unit. University of Oxford. (Cited 2020 Jan 15). Available online from https://www.dtu.ox.ac.uk/homacalculator/
7. Ghasemi A, Tohidi M, Derakhshan A *et al*. Cut-off points of homeostasis model assessment of insulin resistance, beta-cell function, and fasting serum insulin to identify future type 2 diabetes: Tehran Lipid and Glucose Study. *Acta Diabetol* 2015; 52: 905-15.
8. Lee CH, Shih AZ, Woo YC *et al*. Optimal Cut-Offs of Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) to Identify Dysglycaemia and Type 2 Diabetes Mellitus: A 15-Year Prospective Study in Chinese. *PLoS One* 2016; 11: e0163424.
9. Singh Y, Garg MK, Tandon N *et al*. A Study of Insulin Resistance by HOMA-IR and its Cut-off Value to Identify Metabolic Syndrome in Urban Indian Adolescents. *J Clin Res Pediatr Endocrinol* 2013; 5: 245-51.
10. Ray S, Bairagi AK, Guha S *et al*. A simple way to identify insulin resistance in non-diabetic acute coronary syndrome patients with impaired fasting glucose. *Indian J Endocrinol Metab* 2012; 16 (Suppl 2): S460-4.
11. Bermudez V, Rojas J, Martinez MS *et al*. Epidemiologic Behaviour and Estimation of an Optimal Cut-Off Point for Homeostasis Model Assessment-2 Insulin Resistance: A Report from a Venezuelan Population. *International Scholarly Research Notices* 2014; Article ID 616271.
12. World Health Organisation. Appropriate Body Mass Index for Asian populations and its implications for policy and intervention strategies. *Lancet* 2004; 363: 157-63.
13. Dennis JM, Shields BM, Henley WE *et al*. Disease progression and treatment response in data-driven subgroups of type 2 diabetes compared with models based on simple clinical features: an analysis using clinical trial data. *Lancet Diabetes Endocrinol* 2019; 7: 442-51.
14. Dutta D, Mukhopadhyay S. Novel diabetes subgroups. *The Lancet Diabetes and Endocrinology* 2018; 6: 438.