



# Novel Classification of Diabetes of the Adults; Using METS-IR as a Metabolic Indicator for Insulin Resistance

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## Abstract:

Diabetes mellitus (DM) has been considered recently as a heterogeneous metabolic disorder. Numerous intricate etiological processes that can differ between people can contribute to hyperglycaemia. Clinical traits, progression, treatment response, and the emergence of complications are all impacted by these mechanisms. Unfortunately, current diabetes guidelines of treatment are unable to foretell which patients will need intensified or specialized treatment before the incidence of poor metabolic control and subsequent complications. As a result, the division of T2DM (Type 2 DM) patients into different unique subgroups (clusters) can aid in the development of our approach to precision diabetes, the planning of appropriate therapies based on their pathophysiology, and the prognosis of complications with methods of their prevention. Insulin resistance state (IR) is considered essential in new clustering system, however, using fasting C-peptide or fasting insulin to calculate HOMA-IR and HOMA-B is costly. Searching for alternative methods for assessing the level of insulin resistance or beta-cell activity is important for clustering of different populations.

A metabolic risk score called “The Metabolic Score for Insulin Resistance (METS-IR)” was prescribed to measure peripheral insulin sensitivity in mankind. It was initially introduced as METS-IR by Bello-Chavolla. et al in 2018(2). They reported that METS-IR is a new score that combines anthropometric measurements that can be performed easily during a brief evaluation with non-insulin fasting laboratory studies to assess insulin sensitivity and identify states of insulin resistance. In this paper we will try to give an overview on the use of METS-IR as an indicator for insulin resistance state and its importance in novel classification of diabetes in the adults.

**Keywords:** Diabetes mellitus, clusters, Insulin, C-peptide, Insulin resistance.

**DOI:** 10.21608/SMJ.2023.228434.1408

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Received: 10 August,2023.

Revised: 18September, 2023.

Accepted:27 August, 2023.

Published: 01September, 2023.

## Introduction

Diabetes mellitus (DM) is considered now one of the commonest non- communicable diseases all over the world. While the diagnosis of diabetes mellitus (DM) is now based on the abnormalities of a single metabolite (glucose), hyperglycaemia can develop as a result of numerous frustrating etiological mechanisms that can vary between individuals.<sup>(1)</sup> Clinical traits, progression, treatment response, and the emergence of complications are all impacted by these mechanisms. Based on the

linked etiology, the American Diabetes Association (ADA) classified (DM) into four main types.<sup>(1)</sup> These types include type1 diabetes (positive auto-antibodies against pancreatic islet  $\beta$ -cell antigens); type 2 diabetes (T2DM) (negative autoantibodies and characterized by insulin resistance with relative insulin deficiency); Gestational diabetes (GD-M) (diabetes diagnosed mostly from 20-24 weeks of pregnancy that was diagnosed diabetes before pregnancy); and special varieties of diabetes due

to others, e.g., monogenic diabetes cases (neonatal diabetes and MODY), exocrine pancreatic cells dysfunction, and drug-induced diabetes (eg. Glucocorticoid).

Worldwide, T2DM is the most prevalent form of diabetes.<sup>(3)</sup> It is a complex illness with complex etiopathogenesis and clinical presentation that is primarily brought on by an interaction of genetic and environmental agents.<sup>(1)</sup> The therapy and prognosis of patients with this illness are significantly impacted by this complexity. The clinical characteristics of this T2DM, which is extremely widespread, exhibit notable variations. From this point of view, the pressing need for a distinctive classification of people with T2DM into separate subgroups has been proposed. By planning appropriate therapeutics based on their pathophysiology and predicting the prognosis of complications with strategies for their prevention, this innovative sub-grouping will aid in our approach to precision diabetes. In recent years, efforts have been made for identifying "clusters" or subgroups of individuals with diabetes mellitus using different clinical and biochemical variables, which exhibit diverse phenotypic, clinical, and risk of complications behaviors.<sup>(4-7)</sup>

### **Trials for new classification of diabetes of the adults**

In 2015, Li.L et al. attempted to categorize various sub-types from diabetes mainly type 2 patients using topological analysis of patient cohort.<sup>(8)</sup>

This was the beginning of recent trials for discovering new categorizations of type 2 DM.

- 1) Group 1 (29.8%), with increased risk of diabetic microvascular complications.
- 2) Group 2 (24.2%), linked with malignant tumors and cardiovascular disorders.
- 3) Group 3 (46.0%), highly linked with cardiovascular and neurological disorders, and HIV infections."

They also prescribed entirely novel genetic relationships with these subtypes. This study is regarded as an instance study for the classification of a complicated disease into sub-types using large-scale data and machine-learning techniques;

nevertheless, further studies to confirm these findings failed to replicate these sub-types.

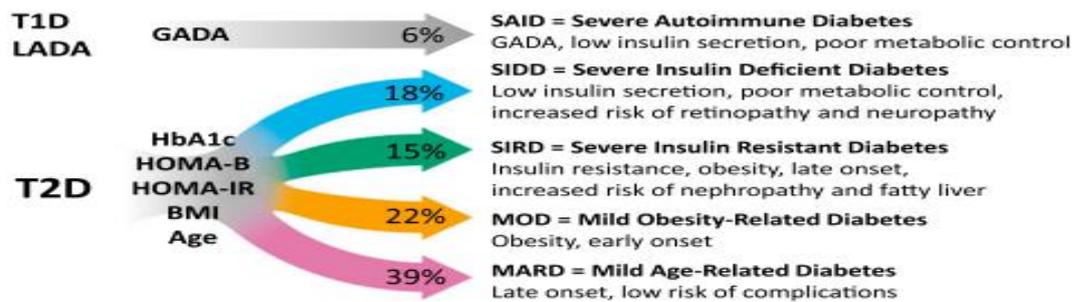
### **Scandinavian population new clustering of diabetes mellitus**

Diabetes is currently divided into type 1 and type 2 forms, although type 2 diabetes in particular is highly heterogeneous with variable aetiologies, according to Emma Ahlqvist et al.'s paper from 2018(4). From this perspective, Scandinavian population with newly discovered diabetes were investigated and they reported five unique subgroups using a data-driven method. Glutamic acid decarboxylase (GAD) antibodies, age at diabetes diagnosis, body mass index (BMI), HbA1c, homeostasis model assessment of insulin resistance (HOMA 2-IR), and beta-cell dysfunction (HOMA2-B) were some clinical parameters measured at the time of their diabetes diagnosis.

#### **"Resulted clusters were(4), Figure (1):**

- \*SAID (Severe Autoimmune Diabetes).
- \*SIDD (Severe Insulin Deficient Diabetes).
- \*SIRD (Severe Insulin Resistant Diabetes).
- \*MOD (Mild Obesity-related Diabetes).
- \*MARD (Mild Age-Related Diabetes).

The resulting sub-groups (clusters) differed in clinical characteristics, progression, and percentage of occurrence of complications. Risk of diabetes complications through follow up period of 3-9 years was found to be different between clusters. For example, individuals in sub-group 3 (most resistant to insulin with bad metabolic profile) had considerably higher incidence of diabetic kidney disease than individuals in sub-group 4 and 5. Sub-group 2 (insulin deficient and low BMI) had the highest incidence of retinopathy. Moreover, genetic associations in the sub-groups differed from those seen in conventional type 2 diabetes. Clustering individuals into these subgroups with different possibilities of disease progression and incidence of diabetic complications would help in justify and begin early management to diabetic individuals who would benefit more, so representing a first step towards better precision diabetes.



**Figure (1):** Novel diabetes sub-groups characteristics with definition of sub-groups resulted by clustering depended on clinical parameters in the ANDIS study.<sup>(4)</sup>

### Replication of the novel classification of diabetes in other populations

In order to determine whether this classification is applicable to people with diabetes in other ethnic groups, these clusters were investigated for replication in a number of populations after being shown to exist in the Scandinavian population. One of the largest replications done recently was performed by Anjana. et al.<sup>(9)</sup> They prescribed four sub-groups (clusters) of patients, with different phenotypic characteristics and disease subsequences:

- 1- Sub-group 1 (Severe Insulin Deficient Diabetes, SIDD).
- 2- Sub-group 2 (Insulin Resistant Obese Diabetes, IROD).
- 3- Sub-group 3 (Combined Insulin Resistant and Deficient Diabetes, CIRDD).
- 4- Sub-group 4 (Mild Age-Related Diabetes, MARD).

While IROD and CIRDD are entirely novel clusters, SIDD and MARD are similar clusters that observed in other populations. Age at diagnosis, BMI, waist width, HbA1c, serum triglycerides, serum HDL cholesterol, and C-peptide fasting and stimulated were the eight characteristics (variables) on which they were dependent. They did not include glutamic acid decarboxylase antibodies (anti-GAD) because they claimed that they were expensive and that a low number of type 2 DM adults had positive (anti-GAD) results, making it impossible for them to identify the SAID group. They also tried to apply this clustering on wider base when they applied it on the data base from the Indian Council of Medical Research-India Diabetes (ICMR-INDIAB) study. From this study, they took 3851 type 2 diabetics, and they divided them into smaller groups based on the following six variables: age at diagnosis, body mass index, waist circumference, HbA1c, serum triglycerides, and serum HDL cholesterol. Since they lacked

information on C-peptide in this sample, they eliminated it from the parameters. So, they applied to this sub-grouping without using HOMA-B or HOMA-IR). SIDD and CIRDD had the highest chances of developing retinopathy, according to Cox proportional hazards, whereas CIRDD had the highest risks of developing diabetic kidney disease (DKD).

Indian Replication by Anjana. et al.<sup>(9)</sup> was able to discover four subgroups of patients, with different clinical characteristics and also disease progression and risk of complications. While other subgroups (CIRDD and IROD) had unique phenotypic and investigatory parameters, two of these subgroups (SIDD and MARD) mimicked the clusters found in the Scandinavian populations by Ahlqvist et al.<sup>(4)</sup> A small number of type 2 diabetes patients were included in one of these novel subgroups, which they have named CIRDD. However, this group appeared to have a more aggressive pattern because their age of onset was earlier, and their metabolic profile was almost as bad as that of the severe insulin-deficient (SIDD) group.

Additionally, they took almost as long as those with SIDD to complete treatment goals. Due to the presence of dual aetiology, these patients are presumably more likely to develop diabetes at a younger age and to have worse glycemic control. Along with having the highest serum triglyceride levels out of all the other sub-groups, these people may have experienced rapid lipolysis as a result of insulin resistance. These individuals' insulin insufficiency may have been caused in part by beta-cell damage brought on by lipotoxicity. Additionally, patients with CIRDD had the second-highest prevalence of retinopathy and the greatest rate of developing renal disease. In order to help these patients develop a positive "legacy effect" and so help prevent more complications, more condensed therapy employing a combination of drugs that target many patho-physiologies of

type 2 diabetes may be recommended in these patients. Also, they require more extensive screening for complications, especially nephropathy and retinopathy. Naturally, randomized clinical trials with thoroughly carefully planned designs are required for the prospective evaluation of each of them.

Members of the second distinct subgroup, IROD, were found to have better metabolic control than either SIDD or CIRDD, indicating that they may have sufficient beta-cell function to compensate for the obesity-related insulin resistance at least partially. They were more susceptible to kidney disease, though. Due to the link between insulin resistance and greater salt sensitivity, glomerular hypertension, and over-filtration, the two insulin-resistant groups (CIRDD and IROD) have a higher incidence of kidney disease<sup>(10)</sup>. Less glycemic control and the existence of insulin insufficiency in the former can likely be attributed to the increased risk of diabetic kidney disease in CIRDD compared to IROD. The SIDD group resembles that of Ahlqvist et al. when compared to the other three groups. Additionally, it had the

worst metabolic control and took the longest to reach the treatment goal. This insulin insufficiency phenotype exhibited the highest prevalence of retinopathy, which is comparable to the Scandinavian population, emphasizing the crucial role that hyperglycemia brought on by insulin deficiency played in the emergence of this microvascular issue. To enable such people to take advantage of setting glycemic objectives, more intense insulin therapy use, instruction for patients, and implementation of technology would be required than has been done so far.

The most prevalent cluster in their community was made up of members of the MARD subgroup, and they exhibited behaviors similar to those of the Scandinavian population's corresponding cluster. Of the four groupings, they had the best metabolic control and the lowest risk of complications. However, compared to those in the Scandinavian MARD cluster (67.3 years), these people had a much lower age at which they first had diabetes (50.2 years). This is most likely explained by the Asian Indian population's overall lower age of diabetes onset., Figure (2).

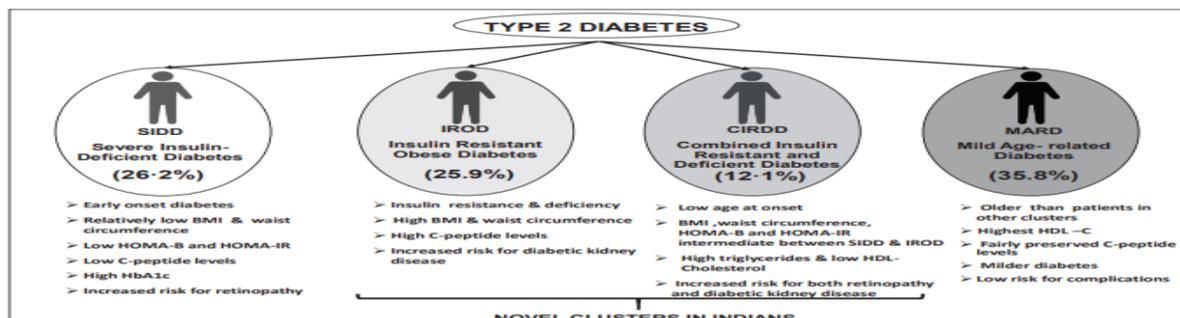


Fig (2): Novel sub-grouping of DM type 2 in Indian population.<sup>(11)</sup>

In Chinese inhabitants, “the National Diabetes and Metabolic Disorders Study (CNDMDS)” 2316 diabetic participants and “the National Health and Nutrition Examination Survey (NHANES III)” 685 participants in Chinese communities equally replicated the novel diabetes clustering<sup>(7)</sup>. Without usage of GADA, four sub-groups were obtained using age at diagnosis, BMI, HbA1c%, HOMA2-B and HOMA2-IR. The first sub-group (MARD) represented about fifty percent of the patients in both trials, then MOD, where SIRD and SIDD were least represented. Additionally, the prevalence of SIDD was higher in Chinese individuals than in Caucasian populations; this conclusion was confirmed in another Asian research.

**Clustering efforts using cheap variables:**

Clustering efforts using alternative approaches were extensively tried in the last few years. This was rendered achievable by the fact that the unique classification was dependent on GADA and C-peptide measurements, which are not prevalent among clinical trials and many existing research cohorts. This prompted replication attempts and subsequent research that classify subjects using surrogate measures. The parameters used and the ability to confirm that the produced groups indeed related to the categories indicated in Ahlqvist study determine the validity of such studies<sup>(4)</sup>. HOMA B and HOMA IR are usually calculated by usage of either fasting C-peptide or insulin. Usage of fasting insulin can be useful in drug naïve individuals but would be bad choice in those who treated with insulin. The HOMA meas-

ures seem to be important for the classification, mainly for determination of the SIRD sub-group. It is evident that some people could shift cluster since the cluster parameters can change over time (with the exception of age at diabetes diagnosis). The impact of such a change relies on the cause, which may include the fact that they were initially on the boundary of subtypes or that therapy and way of life had an impact on the cluster variables. Additionally, some studies have attempted to expand on clustering by including more variables. Depending on how relevant the additional parameters to the classification are, this could be a useful opportunity to increase classification accuracy.

Further subgrouping could be made possible by clustering with additional variables, but the usefulness of these groups depends on the clinical applicability of the parameters and resulting groups. Prediabetes, which is characterized by dysglycemia and is frequently undetected, precedes the

slow progression to diabetes. Early interventions and consequent preventive measures may be beneficial for some diabetic complications, such as DKD in SIRD. Additionally, prediabetes phenotyping may be significant in this case. A study by Wagner et al.<sup>(13)</sup> had been employing identical criteria, including hyperglycemia during the glucose tolerance test, insulin sensitivity, insulin secretion, waist circumference, fasting insulin, hip circumference, fasting triglycerides, BMI, and HDL cholesterol, was undertaken from the TUEF/TULIP trial and reproduced in the Whitehall II cohort. Six sub-groups, most of which correlate to the ANDIS clusters, with varying probabilities of developing diabetes were reported by Wagner et al. This would be very helpful in identifying people who are more likely to develop complications early on, so early prevention would be quite beneficial.<sup>(13)</sup> A comparison of different recent studies in novel diabetes clustering is shown in Table (1).

**Table (1):**Replications of the novel diabetes clusters in different nations<sup>(14)</sup>.

Population (cohort)	N	%SAID	%SIDD	%SIRD	%MOD	%MARD	PMID	Cluster variables	Inclusion/exclusion criteria	features
Sweden (ANDIS)	8980	6.4	17.5	15.3	21.6	39.1	29503172	GADA, Age at diagnosis, BMI, HbA1c, HOMA2-IR, HOMA2-B	Newly diagnosed, over 18 years	-
Sweden (ANDIU)	840	7.1	14.6	15.2	21.1	41.9	-	GADA, Age at diagnosis, BMI, HbA1c, HOMA2-IR, HOMA2-B	Over 18, longer duration	-
Finland (DIREVA)	3192	10.9	12.5	10.5	10.5	44.5	29503172	GADA, Age at diagnosis, BMI, HbA1c, HOMA2-IR, HOMA2-B	Newly diagnosed, 18-69 years	-
Germany (GDS)	1105	40	18	32	46	26	31345776	GADA, Age at diagnosis, BMI, HbA1c, HOMA-IR, HOMA-B	Newly diagnosed	Reference-based classification
Mexico	614	-	41.9	10.1	32.2	15.8	32699108	Age at diagnosis, BMI, HbA1c, HOMA2-IR, HOMA2-B, or surrogate variables	Newly diagnosed	Custom SNNN method, No GADA
China (CNDMDS)	2316	-	13.5	8.6	32.7	45.1	30577891	Age at diagnosis, BMI, HbA1c (or mean plasma glucose), HOMA2-IR, HOMA2-B	Newly diagnosed	No GADA
Japan	1520	5.4	19	7.2	28.9	39.5	32630741	Age at diagnosis, BMI, HbA1c, HOMA2-IR, HOMA2-B	Observational retrospective study	GADA, Insulin or C-peptide was used for HOMA
India	1612	-	52.8	1.1	37.7	8.4	-	Age at diagnosis, BMI, HbA1c, HOMA2-IR, HOMA2-B	Diabetes duration 10 years, age = < 18-45 years, age 45 <of diagnosis years, no T1DM	No GADA
Scotland (GoDARTS)	5509	-	13-17	9-22	18-23	29-35	34110439	Age at diagnosis, BMI, HbA1c, C-peptide and HDL	35, no T1DM>Age	No GADA
The Netherlands (DCS)	2953	-	13-17	9-22	18-23	16-19	-	Age at diagnosis, BMI, HbA1c, C-peptide and HDL	35, no T1DM>Age	No GADA

### **METS-IR as a metabolic indicator for insulin resistance:**

One of the important parameters in this novel classification is studying insulin resistance. Many ways are used in studying insulin resistance among individuals. Euglycemic-Hyperinsulinemic Clamp (EHC) is considered the gold basic standard method; however, its clinical usage has decreed nowadays due to invasive technic used in its performance. Alternatively, fasting insulin-based methods, which include the homeostatic model assessment for insulin resistance (HOMA-IR) and the quantitative insulin sensitivity check index (QUICKI), have been indicated previously as the basic methods for evaluation of insulin resistance.<sup>(15)</sup> However, due to the low practicality and inconsistency of insulin-based indices, non-insulin-based fasting insulin resistance indices have been established to replace insulin measurements for fasting glucose, triglyceride, and lipoprotein measurements. “The Metabolic Score for Insulin Resistance (METS-IR)” is one of several non-insulin-based techniques for assessing insulin resistance state.

METS-IR is a metabolic index introduced to determine peripheral insulin sensitivity in humans; it was first introduced by METS-IR by Bello-Chavolla. et al in 2018.<sup>(2)</sup> They proposed METS-IR, a novel score that determines insulin sensitivity and identifies cases of insulin resistance by combining non-insulin fasting laboratory tests and conveniently obtained anthropometric data. They believed that their index had a good association with the Euglycemic-Hyperinsulinemic Clamp (EHC), fasting insulin levels, and HOMA-IR which makes it a good indicator of overall insulin resistance. According to this study, METS-IR is considered a good substitute for insulin-based methods for the determination of insulin resistance like HOMA-IR.<sup>(2)</sup>

METS-IR can be calculated through fasting laboratory investigations including glucose in (mg/dL), triglycerides (mg/dL) and high-density lipoprotein cholesterol (HDL, mg/dl), BMI. The index can be calculated using the following formula:

**(Ln [2×fasting blood glucose+ fasting triglyceride level]×body mass index)/(Ln [high-density lipoprotein cholesterol])”(2).**

All values are easily obtained from the patients and all of them are cheap and can be used in low-income populations. In 2020, Bello-Chavola. et al utilized “self-normalizing neural networks (SNNN)” for classification using easily obtained

variables in Mexican population.<sup>(16)</sup> They used four SNNN models to obtain a classification for diabetes subgroups:

- ▶ Model 1: HOMA-IR, HOMA-B, BMI, HbA1c%, years of diagnosis.
- ▶ Model 2: HOMA2-IR, HOMA-B, BMI, HbA1c%, years of diagnosis.
- ▶ Model 3: HOMA2-IR, HOMA-B, BMI, FPG and years of diagnosis.
- ▶ Model 4: Substituting HOMA for METS-IR , METS-VF (a visceral fat estimator, metabolic score for visceral fat)(5), HbA1c%, BMI and age at diagnosis”. So, they used METS-IR and METS-VF instead of HOMA in their fourth model. This method was ideal for this classification when c-peptide-based HOMA and HbA1c were absent, but still had less performance for the SIRD group.

### **Conclusion**

Simple clinical parameters seem to be easily used to categorize individuals suffering from T2DM into subgroups with variable clinical traits and progression of the disease. These clusters have been demonstrated to be repeatable in several populations and to be comparatively stable over time. The utility of this approach is substantially increased by the ability to classify individuals and special cohorts using a reference population, providing novel options for individualized and targeted therapy. HOMA calculations seem to be critical for accurate clustering and identification of the SIDD cluster and so, no alternative parameters have been able to replace C-peptide or insulin measurements. Searching for alternative, less costly methods for determining insulin resistance and/or insulin deficiency is essential especially in low socio-economic populations. It seems that METS-IR is considered a good substitute for insulin-based methods for the determination of insulin resistance like HOMA-IR.

The higher expense of utilizing c-peptide and GADA measures could make it difficult for low-income regions of the world to apply this classification. Yet because C-peptide is an independent predictor of conditions like kidney disease.<sup>(18)</sup> In comparison to the expense of managing issues, this expenditure would be deemed minimal. Furthermore, clustering opens up fresh research directions that allow for more precise characterization of the pathogenic flaws in action. Despite considerable replication, the classification as it currently should not be taken as conclusive. By adding other cluster factors, like biomarkers, genes, or

genetic risk factors, it might be possible to further optimize the ANDIS classification in the future. A possible approach towards a clustering process with even higher quality and better prediction values can also be found in more recent technologies utilizing artificial intelligence. This new sub-classification could nevertheless be an important beneficial tool for supporting clinical judgments.

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