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Оригинальная статья

Clustering of diabetes: implications for personalized treatment

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Abstract
Background. Diabetes mellitus traditionally classified into type 1, type 2, gestational, and other specific types. A novel five-cluster model 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 new classification was based on six clinical variants: age, body-mass index at diagnosis, glycosylated hemoglobin, glutamic acid decarboxylase antibodies, homeostasis model assessment 2 beta and insulin resistance. This model enhances personalized treatment and complication prediction.
Objective. This review evaluates the clinical and therapeutic implications of the five-cluster classification, synthesizing evidence from 2010–2023 to assess its impact on treatment efficacy and personalized care.
Methods. This review was limited to the last 15-years and was done using PubMed, Web of Science and Google Scholar. Terms used included "precision therapy," "diabetes sub-categories," "SAID," "SIDD," "SIRD," "MOD" and "MIRD." Only preclinical and clinical data in English were used.
Results. The five-cluster model highlights specific clinical trajectories: SIRD is associated with nephropathy, while SAID and SIDD clusters have more complications (e.g., neuropathy, ketoacidosis) severity. The metabolic and organ dysfunction (MARD and MOD) that is more common in obesity, is less severe. Validation studies have brought attention to regional and ethnic disparities in the distribution of SIRD and MOD; specifically, it seems that South Asians have a higher incidence of SIRD than African cohorts, where MOD is more prevalent.
Conclusion. By customizing therapeutic applications to metabolic profiles, the five-cluster method promotes precision medicine; therapy ought to be in line with biology.
Keywords: insulin resistance, diabetic complications, precision medicine, individualized therapy, diabetes clusters, SAID, SIDD, SIRD, MOD, MIRD.
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Original Article

Кластерный анализ диабета: значение для персонализированного лечения

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Аннотация
Введение. Традиционно выделяют сахарный диабет 1-го типа, 2-го типа, гестационный, а также ряд других специфических типов. В новой модели из пяти кластеров присутствуют тяжелый аутоиммунный диабет (SAID), тяжелый диабет, связанный с дефицитом инсулина (SIDD), тяжелый диабет, связанный с инсулинорезистентностью (SIRD), легкая форма диабета, связанная с ожирением (MOD), и легкая форма диабета, связанная со старением (MARD). Эта новая классификация основана на шести клинических параметрах: возраст, индекс массы тела на момент постановки диагноза, гликированный гемоглобин, антитела к декарбоксилазе глутаминовой кислоты, гомеостатическая модель 2 бета и инсулинорезистентность. Представленная модель облегчает персонализированное лечение и прогнозирование осложнений.
Цель. В обзоре представлена оценка клинических и терапевтических последствий применения системы классификации из пяти кластеров, полученная путем синтеза данных за 2010–2023 годы с целью оценить влияние на эффективность лечения и оказание персонализированной медицинской помощи.
Методы. Обзор публикаций за последние 15 лет выполнен с использованием баз данных PubMed, Web of Science и Google Scholar. Использованы термины: precision therapy, diabetes sub-categories, SAID, SIDD, SIRD, MOD и MIRD. Для обзора использовали исключительно данные доклинических и клинических исследований на английском языке.
Результаты. Модель из пяти кластеров демонстрирует определенные клинические траектории: SIRD ассоциирован с нефропатией, в то время как кластеры SAID и SIDD связаны с большей тяжестью осложнений (таких как нефропатия, кетоацидоз). Метаболическая дисфункция и нарушения функции органов (MARD и MOD), которые чаще встречаются при ожирении, отличаются меньшей тяжестью. Валидационные исследования привлекли внимание к региональным и этническим особенностям распределения SIRD и MOD; в частности, заболеваемость SIRD выше у жителей Южной Азии, чем в африканских когортах, где чаще встречается MOD.
Заключение. Подгонка терапевтических подходов к метаболическим профилям и применение модели из пяти кластеров способствуют развитию прецизионной медицины; лечение не должно противоречить биологии.
Ключевые слова: инсулинорезистентность, осложнения диабета, прецизионная медицина, персонализированная терапия, кластеры дибета, SAID, SIDD, SIRD, MOD, MIRD.
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Introduction

Diabetes impacts 537 million adults all over the world with estimates expecting this number to reach 783 million by 2045. They remain, however, overly simplified with their type 1 diabetes (T1D) and type 2 diabetes (T2D) classification systems because their categorization strategies are holistic and address the complexities of the disease heterogeneity poorly [1].

E. Ahlqvist et al. [2] performed a cluster analysis and was able to categorize subjects into five discrete clusters using age at diagnosis, body mass index (BMI), glycated hemoglobin (HbA1c), glutamic acid decarboxylase antibodies (GADA), homeostasis model assessment 2 beta (HOMA2-β), and homeostasis model assessment of insulin resistance (HOMA2-IR) as six variables. While T1D and T2D classifications remain foundational, their inability to capture diabetes heterogeneity often leads to suboptimal treatment [3]. The five-cluster model (severe autoimmune diabetes – SAID, severe insulin-deficient diabetes – SIDD, severe insulin-resistant diabetes – SIRD, mild obesity-related diabetes – MOD, mild age-related diabetes – MARD) addresses this gap by stratifying patients based on pathophysiology, enabling targeted therapies [4].

This review examines the clinical implications of a model paradigm for diabetes classification, based on previous studies. The model aims to reduce complications and improve treatment outcomes by combining clinical data from different geographic locations.

Methodology

This review has been conducted through the last 15 years utilizing PubMed, Google Scholar, and Web of Science. “Diabetes Clusters,” “SAID,” “SIDD,” “SIRD,” “MOD,” “MARD,” and “personalized treatment” were the search phrases used. The criteria for inclusion aimed at concentrating on the classification of diabetes and its traditional models versus the newly proposed classification system based on five groups. Exclusion criteria were applied to remove studies with small sample sizes, non-randomized designs, or those lacking clarity in the categorization of diabetes subtypes. Studies from Scandinavian, Asian, and African cohorts were prioritized to evaluate the model’s applicability across ethnicities, addressing potential biases in cluster prevalence.

Old classification of diabetes

Diabetes mellitus is traditionally divided into a number of types according to insulin dependency and etiology. These include insulin-dependent diabetes (T1D), "non-insulin dependent" diabetes (T2D), gestational diabetes mellitus, and other forms [5]. The forms that stem from secondary diabetes, such as those caused by pancreatic disorders, medication and chemical disorders, or hormonal imbalances, and monogenic diabetic syndromes like neonatal diabetes as well as maturity-onset diabetes of the young (MODY) are included [6].

The old classification of diabetes has weaknesses in pathogenesis, treatment, and diagnosis. The heterogeneity of patient responses to treatment makes this classification insufficient. So, this review argues for further classification steps by providing examples of situations that do not conform to traditional classification.

Characteristics of New Diabetes Clusters (table 1)

Measuring fasting C-peptide and GADA is the initial step in classifying diabetes. In step two, HOMA2-IR and HOMA2-β are calculated using the following formulas:

HOMA2-IR = fasting insulin × fasting glucose 22.5;

HOMA2-IR = 22.5 fasting insulin × fasting glucose;

HOMA2-β = 20 × fasting insulinfasting glucose - 3.5;

HOMA2-β = fasting glucose - 3.520 × fasting insulin.

Finding the patient's age and BMI upon diagnosis is the third stage [4]. According to E. Ahlqvist et al. [2], there are

New diabetes Cluster profiles

Cluster	%	Age at diagnosis	BMI	HbA1c	HOMA-IR	HOMA2-β	GADA	Complications
SAID	6	Low age	Low	Very high	High	Low	Positive	Ketoacidosis Retinopathy Kidney diseases
SIDD*	18	Low age	Low	Very high	High but lower than SIRD	Low	Negative	Ketoacidosis Retinopathy Neuropathy Cardiovascular diseases Erectile dysfunction
SIRD	15	High age	High	Normal	Very high	Low (but higher than SAID & SIDD)	Negative	Neuropathy Fatty liver Nephropathy Cardiovascular diseases Erectile dysfunction
MOD	22	High age	Very high	Normal	High but lower than SIRD	Normal	Negative	Retinopathy
MARD**	39	Very high age	Normal	Normal	Normal	Normal	Negative	Low risk of complication but kidney and cardiovascular diseases may occur

*SIDD is similar to SAID but without GADA. **MARD is similar to MOD, but the MOD is characterized by a high BMI (obesity), while MARD has a higher age at diagnosis.

five subgroups or clusters of diabetes: MOD, MARD, SIDD, SIRD, and SAID.

Cluster 1: severe autoimmune diabetes (SAID)

This kind of diabetes is marked by being diagnosed at a young age (early-onset diabetes), having a low BMI, very high HbA1c (indicating poor metabolic control), high insulin resistance (high HOMA-IR), high β-cell dysfunction (low HOMA2-β), and GADA positive [2, 4].

Approximately 6% of adults belong to this cluster. Studies have indicated that up to 7% of patients in GADA-negative clusters have antibodies against islet cells and/or insulin, suggesting that testing for additional autoantibodies may increase the prevalence of this Cluster [7].

Both T1D and latent autoimmune diabetes in adults (LADA) have certain characteristics in common with SAID. The existence of blood autoantibodies against pancreatic tissues, which can be utilized as a diagnostic marker, is a characteristic shared by T1D and LADA. The patient will eventually need insulin therapy to control blood glucose levels if these antibodies are detected [8].

Cluster 2: severe insulin-deficient diabetes (SIDD)

This form of diabetes is identified by low age at diagnosis (early-onset diabetes), low BMI, very high HbA1c, high insulin resistance (HOMA-IR is high but lower than in SIRD), high β-cell dysfunction (low HOMA2-β), and GADA negative. Around 18% of adult individuals fall into this Cluster, sharing similar characteristics with SAID but without the involvement of the immune system as the underlying cause of their condition [2, 4].

Because of their extremely high HbA1c levels at diagnosis, SAID and SIDD are more directly linked to the risk of ketoacidosis [2]. Diabetic sensorimotor polyneuropathy and cardiac autonomic neuropathy were also more common in SIDD patients upon diagnosis. According to these results, early, intense therapy, regular monitoring for complications, and sensitive diagnostic techniques for early diagnosis would all be beneficial for people with SIDD [7].

The greatest levels of liver fat and NAFLD-related markers, such as the fatty liver index, AST-to-platelet ratio index, and nonalcoholic fatty liver disease (NAFLD) fibrosis scores, were also found in SIRD patients [7]. Also, people with SIDD and SIRD are known to have a high prevalence of erectile dysfunction [9].

Cluster 3: severe insulin-resistant diabetes (SIRD)

This type of diabetes is marked by high age at diagnosis (late-onset diabetes), a high BMI (overweight to obese), normal HbA1c, very high insulin resistance (very high HOMA-IR), high β-cell dysfunction (low HOMA2-β, but higher than SAID & SIDD), and GADA negative [2, 4]. In SIRD, β-cell function is less impaired, and HbA1c levels are lower compared to SAID and SIDD. This Cluster represents about 15% of adult individuals [10].

According to studies, between 10% and 20% of diabetics exhibit objective neuropathy symptoms, and the prevalence rises as the condition worsens. In comparison to other diabetes clusters, diabetes-related neuropathy was most prevalent in the SIRD subgroup with short-term diabetes (n=3455) and was comparable across all subgroups with long-term diabetes (n=5580) [11]. According to E. Ahlqvist et al. [2], diabetes-related nephropathy was more common in the SIRD subgroup with short-term diabetes than in other diabetes clusters, although it was more common in the long-term diabetes SAID, MARD, and MOD subgroups than in SIDD and SIRD. Among participants with both short-term (n=3418) and long-term (n=5502) diabetes, chronic kidney disease was most common in the SAID, SIRD, and MARD subgroups [11]. SIRD had a significantly increased risk of kidney complications, emphasizing the link between insulin resistance and kidney disease. Insulin resistance has been associated with higher salt sensitivity, glomerular hypertension, hyperfiltration, and declining kidney function, all of which are hallmarks of diabetes-related nephropathy [12].

Cluster 4: mild obesity-related diabetes (MOD)

This kind of diabetes is associated with high age at diagnosis (late-onset diabetes), high BMI (obesity), normal HbA1c, high insulin resistance (high HOMA-IR but lower than SIRD), normal β-cell dysfunction (normal HOMA-Beta), and GADA negative. About 22% of cases fall into this category, and it is thought to be linked to obesity [2, 4].

Cluster 5: mild age-related diabetes (MARD)

This type of diabetes is characterized by a very high age at diagnosis (late-onset diabetes), normal insulin resistance (normal HOMA-IR), normal β-cell function (normal HOMA-Beta), normal BMI, normal HbA1c, and GADA negative. The difference between MOD and MARD is primarily based on the age at diagnosis and BMI; MOD is characterized by a high BMI (obesity), while MARD is diagnosed at a later age [2, 4]. This Cluster is the most common form of diabetes, accounting for 39% of cases, and carries the lowest risk of diabetic complications [10].

The E. Ahlqvist et al. [2] research (Scandinavian cohorts) found that those with high BMIs were more likely to have SIRD. According to further research in Asian populations [6], South Asians had a greater prevalence of SIRD, which was linked to an increased risk of NAFLD. The increased frequency of MOD in African cohorts is probably caused by inequalities in adiposity. While the Scandinavian clusters were replicated in some populations [13, 14] in others they could not be fully replicated [6, 15]. Depending on age and sex, SIDD, SIRD, and MARD were associated with a higher risk of cardiovascular events, coronary events, and stroke [16].

Clinical advantages of clustering of diabetes

While Scandinavian cohorts validated the original clusters, Asian studies [6] identified higher SIRD prevalence linked to NAFLD, underscoring the need for region-specific adaptations. Understanding diabetes's various forms and Clusters is a crucial first step in understanding its causes. This new classification helps:

1) improved reclassification based on clinical and metabolic profiles [2];

2) enhanced understanding of Cluster-specific pathophysiology [4];

3) better prediction of complications (e.g., nephropathy, cardiovascular disease) [17];

4) personalized treatment strategies aligned with Cluster characteristics [6].

Clustering can help predict complications from diabetes and inform treatment decisions, ultimately lessening the impact of the disease. To implement this approach, we need standardized diagnostic tests and effective treatment algorithms, which calls for a well-defined plan [6]. The five-cluster diabetes model encounters several challenges in practical use, such as technical and infrastructure issues, necessitating specialized diagnostic tools, uniform protocols, and extensive training [4]. The cost and availability of diagnostic procedures and treatments may limit the application of this paradigm, which might strain healthcare organizations' finances [6]. Therefore, a comprehensive assessment of cost-effectiveness is essential to provide fair access to treatment and successful integration.

Treatment strategies

The first-line treatment for regulating blood glucose levels in people with SIRD, MARD, and MOD is metformin. Metformin is a biguanide, an oral drug that helps stop the liver from producing too much glucose, decreases intestinal absorption of glucose, and improves the body's reaction to insulin [18].

Metformin is favored as the initial treatment option due to its effectiveness and strong supporting evidence, including a reduced risk of major cardiovascular events as demonstrated in the United Kingdom Prospective Diabetes Study [19].

If metformin alone doesn't sufficiently manage a patient's blood sugar, if metformin isn't suitable due to contraindications or if specific patient characteristics necessitate additional treatment, several non-insulin second-line medications are available. These include sodium–glucose cotransporter 2 inhibitors (SGLT2is), glucagon-like peptide-1 receptor agonists (GLP-1RAs), dipeptidyl peptidase-4 inhibitors (DPP-4is), and sulfonylureas [10].

SGLT2is directly targets SGLT2, a protein responsible for absorbing filtered glucose in the kidney's proximal convoluted tubules. Inhibiting SGLT2 leads to glucosuria, resulting in reduced HbA1c levels by 0.6-0.9% and fasting glucose by 1.1–1.9 mmol/L compared to a placebo. SGLT2 is also associated with weight loss and lower blood pressure [20]. Moreover, they have positive effects on cardiovascular death, heart failure, and the progression of chronic kidney disease [21]. Several studies indicate that treatment with SGLT2is improves the sensitivity of β-cells to glucose. For instance, E. Ferrannini et al. [22] reported a 25% increase in β-cell glucose sensitivity after just 48 hours of SGLT2is treatment in patients with T2D who were either treatment-naive or on metformin. Additionally, SGLT2is can enhance insulin sensitivity by reducing plasma glucose levels and body weight [20].

GLP-1 is a hormone produced by the intestine's L-cells in response to food intake, particularly meals rich in fat and carbohydrates. This hormone aids in regulating glucose levels through various mechanisms, including glucose-dependent insulin secretion, reduced food intake, weight loss, and lowered glucagon levels. C. Anholm et al. [23] found that a 12-week regimen of metformin combined with GLP-1RA significantly improved β-cell function, as measured by the disposition index, compared to a metformin-only or placebo group in a randomized, double-blind crossover trial. Furthermore, the impact of GLP-1RAs on body weight may explain their positive effects on hepatic and peripheral insulin sensitivity, as observed in other studies [24].

DPP-4is belongs to a class of glucose-lowering drugs that inhibit the enzyme DPP-4, which is found on the surface of various cells, including adipocytes, kidneys, the liver, and the small intestine. DPP-4is increases insulin secretion and decreases glucagon secretion [25].

Due to their overlapping mechanisms of action, it is not advisable to use GLP-1RAs and DPP-4is in combination, as both medications increase circulating GLP-1 levels and they are unlikely to exhibit greater efficacy when used together [10]. However, the final choice of treatment for T2D patients should also consider other diabetes-related factors. For instance, in the presence of cardiovascular disease, GLP-1RAs or SGLT2is are preferred options without regard to specific subgroups. Other factors such as the presence of kidney disease, the importance of weight loss alongside lifestyle changes, patient age, preferences, and potential side effects should also be taken into account [26].

Treatment of SAID is similar to those with T1D and LADA requires early introduction of insulin supplementation. SIDD Cluster requires early introduction of insulin supplementation, but they also take oral medications [27]. They could benefit from most of the current second-line anti-diabetic treatments. Since the SIDD group is associated with a lower BMI, there is also no preferred type of medication for those patients to correct body weight. SIDD may also benefit from DPP4is or, when cost is a major issue, a sulfonylurea [10].

Patients with SIRD may benefit most from treatments that promote weight loss and improve insulin sensitivity, such as SGLT2is or GLP-1RAs. These treatments may help enhance insulin sensitivity and lead to significant reductions in body weight, while also addressing the risk of cardiovascular disease or nephropathy. If safety and efficacy are established, new insulin sensitizers (e.g., peroxisome proliferator-activated receptor agonists) or anti-inflammatory drugs could also provide targeted treatment for SIRD [27]. Pioglitazone treatment is effective in improving insulin sensitivity and reducing NAFLD but should be considered only when no other treatment options are available due to the well-known side effects of weight gain and other adverse effects associated with pioglitazone use. DPP-4is do not seem to play a therapeutic role in this group as they have no established effects on insulin sensitivity, weight reduction, or NAFLD [10].

Lifestyle modifications, weight loss, increased physical activity, and metformin may suffice as the sole therapy for individuals with mild cases of MARD and MOD [28]. MOD patients might benefit most from GLP-1RAs and SGLT2is because both medications substantially reduce body weight. The use of pioglitazone should be avoided in this group due to its association with weight gain [29].

For patients with MARD, sulfonylureas and DPP-4is could be viable additional therapies if metformin alone cannot adequately control blood sugar levels. While sulfonylureas do not impact insulin sensitivity, they can initially enhance β-cell function [29]. However, SGLT2is and GLP-1RAs may also be options for patients with established end-organ diseases such as cardiovascular disease and reduced

kidney function. Since this population tends to be older, decisions regarding additional treatment should be made thoughtfully, taking into consideration the potential side effects associated with each medication type [10]. On the other hand, individuals with MARD should receive treatments that do not lead to weight loss and sarcopenia, such as protein-balanced diets and moderate resistance training [27].

Lastly, each subtype requires a different course of treatment due to its unique pathophysiology. The broad use of this new classification system in diabetes care will depend on pragmatic factors like customized treatment plans and suitable diagnostic equipment. The implementation of cluster-specific therapies is limited by the high cost of diagnostic tools (such GADA testing) and the need for clinical training, even when there are promising therapy alternatives. Ensuring that policy efforts may be implemented globally requires equitable access [4, 6].

Conclusion and future directions

The five-Cluster model is a precision medicine framework that helps physicians choose diabetic treatments and anticipate problems. It advocates for health policies incorporating cluster-based diabetes treatment into standard care. However, more study is needed to validate this strategy across age and ethnic groups and assess its long-term impacts on reducing diabetes-related complications.

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