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Clinical and Metabolic Parameters Across Different Clusters of Diabetes Mellitus: A Comparative Analysis

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ABSTRACT

Background: *In recent years, new strategies for diagnosing and treating diabetes mellitus have been developed, with novel diabetes stratifications emerging from the perspective of predicting metabolic disorders and complications to facilitate a personalized treatment approach. One particularly interesting approach is a classification based on five parameters (glycated hemoglobin - HbA1c, BMI, age at diagnosis, HOMA-IR and HOMA-β indices), which identifies five clusters. Three of these clusters include patients with type 2 diabetes: Severe Insulin-Resistant Diabetes (SIRD); Mild Age-Related Diabetes (MARD); and Mild Obesity-Related Diabetes (MOD) [1]. However, the practicality and clinical applicability of this logical classification system require further investigation.*

Objectives: *To conduct a comparative analysis of laboratory parameters characterizing carbohydrate and lipid metabolism in patients with different diabetes phenotypes, categorized according to cluster analysis criteria.*

Materials and Methods: *A retrospective analysis was conducted on data from 83 patients with type 2 diabetes mellitus (T2DM) who were hospitalized at the endocrinology department of the Federal State Budgetary Institution "Central Clinical Hospital of Civil Aviation" between 2024 and 2025. The characteristics of the course of diabetes (age of onset, combination of complications, BMI, etc.), glycemic and lipid profile indicators, insulin, and C-peptide in patients of clusters were assessed. SIRD (39 people), MARD (18 people) and MOD (26 people).*

The study was approved by the Ethics Committee of the Patrice Lumumba Peoples' Friendship University of Russia. – protocol No 8 of 14.10.2025

Results: *Postprandial blood glucose levels were significantly higher in the SIRD cluster (8.44 ± 2.93 mmol/L) compared to the MOD cluster (6.66 ± 1.78 mmol/L). Target HbA1c levels were achieved by 66.7% of patients in the MARD cluster, compared to 25.6% in the SIRD cluster and 26.9% in the MOD cluster. HDL cholesterol levels were significantly higher in the MARD cluster (1.29 ± 0.37 mmol/L) than in the MOD cluster (1.08 ± 0.24 mmol/L; $p<0.01$).*

The timing of type 2 diabetes manifestation differed across clusters. Earlier disease onset was observed in the MOD cluster, with a mean age of 47.62 ± 7.14 years, compared to 50.15 ± 9.79 years in the SIRD cluster and 66.53 ± 5.49 years in the MARD cluster. Diabetes duration was longest in the SIRD cluster at 16.70 ± 8.50 years, compared to 6.92 ± 4.85 years in the MARD cluster and 12.96 ± 7.57 years in the MOD cluster.

Conclusions: *Cluster-based classification shows promise for implementing a personalized treatment approach. The study established that glycemic control was least effective in the SIRD cluster, which also had the longest overall disease duration. Patients in the MARD cluster achieved diabetes compensation more frequently and demonstrated lower cardiometabolic risks. An earlier disease onset (MOD) did not consistently correlate with a more severe disease course. Cluster differentiation enables the personalization of treatment strategies.*

Keywords
Type 2 diabetes, T2DM, Clusters, Cardiometabolic risk, Diabetes complications.

Background
Type 2 diabetes mellitus represents one of the major challenges in modern medicine, primarily due to the high risk of complications. The progressive increase in the number of patients with diabetes and the high mortality rate among them necessitate further research into the causes and mechanisms of the disease. Despite the availability of modern diagnostic methods and the development of new treatment and preventive measures, the number of cases of early disability and mortality among working-age patients with diabetes continues to rise. Evaluating contemporary aspects of the etiology and pathogenesis of carbohydrate metabolism disorders will enable the development of more effective methods for diagnosis, treatment, and prevention of complications in diabetic patients.

In recent years, priority directions in diabetology have included both fundamental scientific research—such as studying genetic forms of diabetes, including relatively rare ones, and identifying key pathogenetic mechanisms for each—and practical aspects, which remain highly relevant. Despite all scientific advancements, diabetes remains a severe disease and is ranked among the top four pathologies leading to high population mortality. A natural prospect for further combating diabetes is the development of methods for early diagnosis and complication prevention, which requires reliable tools for prognosis assessment and risk stratification. In recent years, attempts have been made worldwide to develop new stratifications of diabetes. Therefore, it is crucial to conduct cluster analysis across different diabetes durations and in diverse cohorts to identify phenotypic groups of T2DM and validate them through cluster reproducibility [2]. Using topological analysis based on patient-patient networks, three subgroups of T2DM have been identified [3]. However, such classification requires patient genotype data, which is difficult to implement in real-world clinical settings. In the studies by E. Ahlqvist et al., based on key features—namely, patient age at disease onset, body mass index (BMI), GAD autoantibody testing, glycated hemoglobin (HbA1c) level, insulin resistance index (HOMA2-IR), and basal β-cell function (HOMA2-β)—five distinct groups (clusters) of diabetes have been proposed: 1.Severe Autoimmune Diabetes (SAID), 2.Severe Insulin-Deficient Diabetes (SIDD), 3.Severe Insulin-Resistant Diabetes (SIRD), 4. Mild Obesity-Related Diabetes (MOD), 5. Mild Age-Related Diabetes (MARD) [1].

The identification and study of diabetes clusters contribute to a better assessment of the clinical course of T2DM, the risk of cardiovascular complications, and will optimize treatment and preventive measures. Since insulin-independent forms of diabetes are significantly more common, and methods for a differentiated approach require further refinement, we compared the characteristics of clinical manifestations, including metabolic control parameters, specifically in patients from these groups.

Objectives
To conduct a comparative analysis of laboratory parameters characterizing carbohydrate and lipid metabolism in patients with different diabetes phenotypes, categorized according to cluster analysis criteria.

Materials and Methods
A retrospective analysis was conducted on data from 83 patients with type 2 diabetes mellitus (T2DM) who were hospitalized at the endocrinology department of the Federal State Budgetary Institution "Central Clinical Hospital of Civil Aviation" between 2024 and 2025. The characteristics of the course of diabetes (age of onset, combination of complications, BMI, etc.), glycemic and lipid profile indicators, insulin, and C-peptide in patients of clusters were assessed. SIRD (39 people), MARD (18 people) and MOD (26 people).

Results
According to the clinical data, it was revealed that patients in the MARD group were older and had the highest age at disease onset 73.44±7.25. Analysis of clinical data showed that patients from this group had the worst indicators for the following parameters: arterial hypertension - 18 patients (100%); chronic heart failure - 3 patients (16.7%); ischemic heart disease - 7 patients (38.9%); post-infarction cardiosclerosis - 3 patients (16.7%); angiopathy of the lower extremities - 17 patients (94.4%). However, patients from the MARD group had the lowest incidence of some forms of diabetic neuropathy: urogenital, gastrointestinal, cardiovascular autonomic neuropathy and peripheral neuropathy. They also had a lower body mass index compared to other patients.

The MOD group (n = 26) was characterized by the youngest age of participants (60.58 ± 9.44 years) and the highest body mass index - 34.75 kg / m2. Participants in the MOD group had a low level of macrovascular complications. Arterial hypertension (HTN) was diagnosed in 88.5% of patients, which is a high rate, but lower than in the SIRD (97.4%) and MARD (100%) groups.

The percentage of participants with chronic heart failure was 3.9%, which is the lowest rate among all the study groups. Post-infarction cardiosclerosis was detected in 3.9% of patients, which corresponds to the minimum level. Lower extremity angiopathy (LEA) was diagnosed in 84.6% of participants in the MOD group, however, these rates are lower than in the SIRD (92.3%) and MARD (94.4%) groups. Chronic kidney disease (CKD) was diagnosed in 3.9% of participants in the MOD group, indicating an extremely low rate of renal complications. Despite the high frequency of lower extremity angiopathy, the prognosis in the MOD cluster is more favorable compared to the MARD cluster (due to the absence of severe macroangiopathy) and the SIRD cluster (due to a lower burden of microvascular complications).

Table 1: Clinical characteristics of the compared groups.

Criteria	SIRD (n=39)	MARD (n=18)	MOD (n=26).
Middle age	66.85±9.33	73.44±7.25	60.58±9.44
Age of patients at the onset of the disease	50.15±9.79	66.53±5.49	47.62±7.14
BMI (kg/m^2)	32.50±5.90	31.58±7.78	34.75±6.97
Complications			
Diabetic retinopathy	35 (87.5%)	14 (77.8%)	20 (76.9%)
Cataract	27 (69.2%)	11 (61.1%)	14 (53.9%)
CKD	28 (71.8%)	7 (38.9%)	1 (3.9%)
Lower extremity angiopathy	36 (92.3%)	17 (94.4%)	22 (84.6%)
Coronary heart disease	9 (23.1%)	7 (38.9%)	9 (34.6%)
PICS	2 (5.1%)	3 (16.7%)	1 (3.9%)
CHF	3 (7.7%)	3 (16.7%)	1 (3.9%)
AG	38 (97.4%)	18 (100%)	23 (88.5%)
Peripheral polyneuropathy	39 (100%)	17 (94.4%)	26 (100%)
CAN	14 (35.9%)	2 (11.1%)	5 (19.2%)
DAN gastrointestinal form	7 (17.9%)	0 (0%)	3 (11.5%)
DAN urogenital form	6 (15.4%)	1 (5.6%)	2 (7.7%)

Note: BMI – body mass index, CKD – chronic kidney disease; IHD – ischemic heart disease; PICS – post-infarction cardiosclerosis; CHF – chronic heart failure; AG – arterial hypertension; CAN – cardiac autonomic neuropathy; DAN – diabetic autonomic neuropathy.

The SIRD group (n = 39) was characterized by a mean age of 66.85 ± 9.33 years and an age at diabetes onset of 50.15 ± 9.79 years. Body mass index (BMI = 32.50 ± 5.90 kg/m²) confirmed the presence of obesity, but did not reach the level observed in MOD. Patients with SIRD were found to have the most pronounced microvascular pathology: diabetic retinopathy (87.5%), chronic kidney disease (71.8%), and cataracts (69.2%). Peripheral polyneuropathy was diagnosed in 100% of patients, indicating severe damage to the peripheral nervous system. The frequency of cardiac autonomic neuropathy (35.9%) was the highest among all the studied clusters, which is associated with an increased risk of cardiovascular events. Macrovascular complications are also significant: arterial hypertension (97.4%), lower extremity angiopathy (92.3%), and post-infarction cardiosclerosis (23.1%). The obtained data suggest that SIRD is the cluster with the highest risk of developing micro- and macrovascular complications (Table 1).

The mean age of type 2 diabetes onset also varied between clusters. The earliest disease onset was observed in the MOD cluster (47.62 ± 7.14 years), consistent with its pathogenetic association with obesity and metabolic syndrome, which develop in young and middle age. In the SIRD cluster, the mean age of onset was 50.15 ± 9.79 years, while in the MARD cluster it was 66.53 ± 5.49 years, confirming its association with age-related metabolic changes and decreased β-cell function.

The longest duration of type 2 diabetes mellitus (T2DM) was observed in the SIRD cluster (16.70 ± 8.50 years), which may explain the more pronounced disorders of carbohydrate metabolism and the difficulties in achieving compensation. Patients in the MARD cluster had a significantly shorter diabetes duration (6.92 ± 4.85 years), while in the MOD cluster, it was 12.96 ± 7.57 years. The conducted analysis of metabolic and clinical parameters of patients with type 2 diabetes mellitus (T2DM) revealed significant differences between clusters of patients (Table 2).

Thus, the postprandial glycemia level in the SIRD cluster was significantly higher (8.44 ± 2.93 mmol/L) than in the cluster MOD (6.66 ± 1.78 mmol/L). This indicates more pronounced postprandial hyperglycemia and, likely, a more severe degree of insulin resistance in patients with SIRD.

Glycemic control efficacy also differed between clusters. Target glycated hemoglobin levels (HbA1c < 7%) were achieved in 66.7% of patients in the MARD cluster, while in the SIRD and MOD clusters this figure was significantly lower—25.6% and 26.9%, respectively. These data indicate that, despite the advanced age of patients in the MARD cluster, diabetes is milder and more responsive to treatment.

Table 2: Metabolic control indicators in patients with diabetes mellitus in the compared clusters.

Indicator	3 SIRD (39)	4 MARD (18)	5 MOD (26)	P1	P2	P3
Postprandial glycemia (mmol/L)	8.44±2.93	8.26±4.07	6.66±1.78	0.861	0.006	0.098
Target HbA1c (%)	7.51±0.33	7.44±0.34	7.23±0.35	0.481	0.001	0.043
HbA1C (%)	9.13±2.08	7.72±2.20	7.94±1.58	0.013	0.009	0.718
HDL cholesterol(mmol/l)	1.17±0.25	1.29±0.37	1.08±0.24	0.183	0.129	0.028
Onset of type 2 diabetes	50.15±9.79	66.53±5.49	47.62±7.15	<0.001	0.279	<0.001
Duration of the disease	16.70±8.50	6.92±4.85	12.96±7.57	<0.001	0.052	0.006
HbA1c target achieved	10 (25.6%)	12(66.7%)	7(26.9%)	0.004	0.944	0.009

Note: Data is presented as M±SD, P1-reliability of the difference in clusters SIRD vs MARD, P2 -reliability of the difference in clusters SIRD vs MOD, P3 clusters reliability of the difference in clusters MARD vs MOD.

Cardiometabolic parameters also varied across clusters. High-density lipoprotein cholesterol (HDL-C), an important marker of cardiovascular risk, was significantly higher in the MARD cluster (1.29 ± 0.37 mmol/L) compared with the MOD cluster (1.08 ± 0.24 mmol/L, $p < 0.01$). This indicates a more favorable lipid profile and a reduced risk of atherosclerotic complications in patients with age-related diabetes.

Discussion

The development of diabetology as a science has led to the emergence of new methodological approaches. Some scientists believe that modern approaches certainly deepen the understanding of SD, but a radical rejection of the proven classification is still premature. Proponents of the new system (e.g., Ahlqvist et al., 2018) argue that it better reflects pathogenetic mechanisms and allows for more precise treatment selection. However, despite the obvious pathophysiological logic and prognostic value of this classification, its application in everyday clinical practice faces several limitations. First, accurate assignment of a patient to a particular cluster requires several laboratory tests (including HOMA indices), which are not always available in practice. Second, the boundaries between clusters can be blurred, especially in patients with intermediate parameter values, requiring additional validation and standardization of criteria. Third, long-term treatment outcomes and the effectiveness of personalized approaches for each cluster have not yet been adequately studied in large randomized trials.

Nevertheless, even in its current form this classification serves as a valuable tool for understanding disease pathophysiology, predicting complication risks, and choosing patient management strategies. This is particularly significant in the context of the growing global prevalence of type 2 diabetes mellitus.

Conclusions

A study that performed cluster-based stratification of patients with type 2 diabetes mellitus revealed significant differences in clinical, metabolic, and prognostic characteristics among the groups. The SIRD cluster demonstrated the most severe disease course, characterized by high postprandial glycemia, low achievement of target HbA1c levels, the longest diabetes duration, and the highest risk of developing micro- and macrovascular complications. In contrast, patients in the MARD cluster demonstrated better glycemic compensation and a more favorable lipid profile, indicating reduced cardiometabolic risks. In the MOD cluster, early age of onset of type 2 diabetes mellitus did not lead to worsening glycemic control compared with other clusters, highlighting the ambiguous relationship between age of onset and disease severity.

Thus, clustering patients with type 2 diabetes mellitus represents a promising tool for personalizing diagnosis, prognosis, and treatment strategy selection, which may lead to improved outcomes and reduced risk of complications [4].

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