West Kazakhstan Medical Journal
Volume 66, Issue 2, DOI 10.18502/wkmj.v66i2.16460
Production and Hosting by KnE Publishing

KNE Publishing

Check for updates

Mini Review

Cluster-Based Diagnostic for Diabetes, Insights from Europe and Asia

Khatimya Kudabayeva[1], Yerlan Bazargaliyev[1], Galina Veklenko[2], and Bibigul Tleumagambetova[2]*

[1]Department of Internal Diseases No 1, West Kazakhstan Marat Ospanov Medical University, Aktobe, Kazakhstan
[2]Department of Propaedeutics of Internal Disease, West Kazakhstan Marat Ospanov Medical University, Aktobe, Kazakhstan

Abstract

Type 2 diabetes mellitus (T2DM) has emerged as a major global health challenge, with its prevalence steadily rising in recent decades. The International Diabetes Federation (IDF) Diabetes Atlas projecting that the number of individuals living with diabetes will reach 783 million by 2045. The Asian region is particularly affected, with over 157 million diagnosed cases in 2021, representing about 11% of the region's total adult population. This review aims to shed light on the heterogeneity within T2DM, emphasizing the importance on the diversity of disease and exhibits the different phenotypic characteristics. The focus of the review is to highlight the significance of understanding these variations in glycemic levels, insulin resistance, complications, heredity, lifestyle, and patient preferences to tailor effective prevention and management strategies. A comprehensive review of recent studies is presented, revealing the importance of personalized approaches in combating the multifaceted challenges related to T2DM. The key findings underscore the critical need for adapting treatment strategies to individual patient profiles, thus mitigating the burden of T2DM and its health consequences. This manuscript underscores the pressing need for additional research endeavors and the formulation of customized interventions to tackle the escalating prevalence of T2DM, both on a global scale and within the Asian region.

Keywords: diabetes mellitus, noninsulin-dependent, patient centered care, phenotypic variabilities, personalized medicine

Corresponding Author: Bibigul Tleumagamabetova; email: tleumagambetova@zkmu.kz

Received: 6 February 2024
Accepted: 10 March 2024
Published: 28 June 2024

Production and Hosting by KnE Publishing

OPEN ACCESS

1. Introduction

Type 2 diabetes mellitus (T2DM) is one of the fastest-growing global health challenges of the 21st century. The prevalence of this disease has been increasing dramatically over recent decades, as confirmed by the latest findings of the IDF Diabetes Atlas [1]. In 2021, 537 million people were living with diabetes, and it is expected that this number will rise to 643 million by 2030 and 783 million by 2045. Furthermore, impaired glucose tolerance was identified in 541 million individuals. According to estimates, more than 6.7 million people aged 20–79 will die from diabetes-related causes, accounting for approximately 9% of the adult population worldwide. The issue of T2DM is particularly acute in the Asian region, where, according to the IDF Diabetes Atlas, over 157 million adults were diagnosed with T2DM in 2021, representing about 11% of the region's total adult population.

Traditionally, T2DM has been presented as a homogeneous disease; however, an increasing number of evidence suggests its heterogeneity [2]. Research conducted in various countries has confirmed that T2DM consists of a complex array of subtypes, each characterized by unique genetic, clinical, and metabolic features [3–6]. This diversity among T2DM subtypes suggests that patients can significantly differ in glycemic levels, degree of insulin resistance, duration of the disease, presence of complications, genetic predisposition, lifestyle, and personal treatment preferences.

The importance of understanding T2DM heterogeneity cannot be understated, as it directly impacts treatment approaches [7]. Standard treatment strategies, applied universally, may be ineffective or even harmful for certain patient subgroups. Therefore, there is an urgent need to develop individualized treatment approaches that consider each patient's unique characteristics. These studies highlight the international recognition of the problem and the necessity for global collaboration to develop more effective methods of diagnosis and treatment for T2DM.

The aim of this article is to review the existing data on the heterogeneity of T2DM, with a special focus on the different subtypes of the disease. In this work, we will concentrate on analyzing the research conducted in various countries, dividing them into Europe and Asia. We seek to examine how this heterogeneity affects the choice of treatment strategies and which approaches may be most effective in adapting to the individual needs of patients, based on the most recent international research.

2. Materials and Methods

Three electronic databases were searched, alongside PubMed, Scopus, and Web of Science. We used the following keywords: "Diabetes Mellitus, Noninsulin-Dependent" and "Phenotypic Variabilities" and their combinations, by applying Boolean operators (AND, OR). The full-text articles in the English language, published within the last 10 years were included in the search. Studies focusing on type 1 diabetes mellitus or gestational diabetes, literature reviews, editorials, case studies, and opinion pieces were excluded.

3. Results

To comprehensively review the phenotypic characteristics of T2DM, we conducted a thorough analysis of the existing literature, focusing on studies conducted by European countries like Denmark [8], Germany [9], Sweden [10] and

Slovakia [11] in contrast to Asian regions, including China [12], India [13], Thailand [14] and where cluster analysis and phenotyping techniques were used to classify and characterize individuals based on specific clinical and metabolic criteria.

3.1. European region

E. Ahlqvist *et al*. identified five replicable clusters of individuals with diabetes in the All New Diabetics in Scania (ANDIS) cohort [15], focusing on six variables: glutamate decarboxylase antibodies, age at diagnosis, BMI, HbA1c, and estimates of β-cell function and insulin resistance [8]. The analysis identified five distinct clusters with significantly different characteristics and risks of diabetic complications. The risk of diabetic complications and genetic associations across clusters, reveal notable differences in complication risks and genetic markers when compared to traditional T2DM categorizations.

SAID: Severe Autoimmune Diabetes; SIID: Severe Insulin Deficient Diabetes; SIRD: Severe Insulin Resistant Diabetes; MOD: Mild Obesity-Related Diabetes; MARD: Mild Age-Related Diabetes (linked to age-related factors).

The proportion of individuals allocated to the same cluster at baseline and 5-year follow-up was on average 77% but varied by cluster (20% SIDD, 82% SAID, 51% SIRD, 79% MOD, and 82% MARD), suggesting some movement, particularly for individuals in the SIDD cluster. These findings not only illustrate the clinical heterogeneity of diabetes but also underscore the importance of individual approach strategies and risk management based on the specific cluster to which a patient belongs.

Similarly in Germany, the approach was conducted with 1105 patients newly diagnosed with T2DM who underwent extensive phenotyping and lab assessments. Insulin sensitivity was evaluated using hyperinsulinaemic-euglycaemic clamps, hepatocellular lipid content through magnetic resonance spectroscopy, hepatic fibrosis via noninvasive scores, and neuropathies through functional and clinical criteria[9]. At baseline, patients were grouped into four clusters: 386 (35%) with mild age-related diabetes (MARD), 323 (29%) with mild obesity-related diabetes (MOD), 121 (11%) with severe insulin-resistant diabetes (SIRD), and 28 (3%) with severe insulin-deficient diabetes (SIDD). After 5 years, 367 patients were reassessed, maintaining similar distribution percentages across the clusters.

Further supporting the heterogeneity of T2DM, the retrospective cohort in Sweden investigation examined clinical parameters related to diabetes, such as onset age, disease duration, HbA1c levels, BMI, HOMA2-β (assessing β-cell function), HOMA2-IR (measuring insulin resistance), and GAD65 autoantibodies among 2290 individuals with T2DM [10]. Through cluster analysis of initial patient data, five potential sub-groups were delineated, characterized by autoimmune β-cell failure (3%), short-duration insulin resistance (21%), nonautoimmune β-cell failure (22%), long-duration insulin resistance (32%), and metabolic syndrome presence (22%). Additionally, variations in the prevalence of cardiovascular disease, nephropathy, and neuropathy were observed across these subgroups.

Furthermore, findings of a study conducted in Slovakia, revealed that around 20% of the individuals formally diagnosed with T2DM showed signs of autoimmune insulitis. This was determined by the presence of at least one positive result from three tested diabetes-associated autoantibodies (DAA): glutamic acid decarboxylase antibodies (GADA), insulin autoantibodies (IAA), or insulinoma-associated-2 autoantibodies (IA-2A)[11]. The study

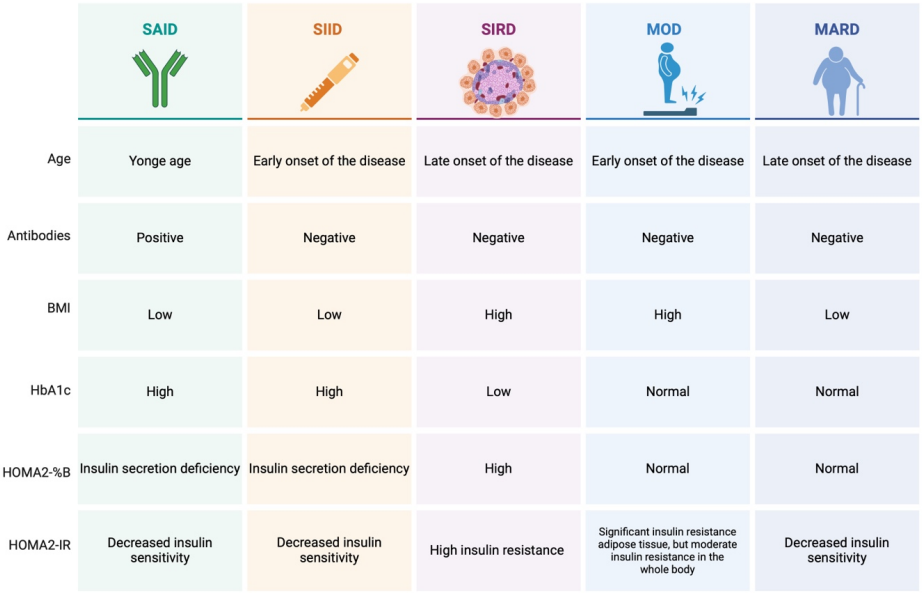

Figure 1: Clusters exhibited disparities in clinical parameters by six variables: age, antibodies, BMI, HbA1c, HOMA2-%B, and HOMA2-IR.

further delineated between individuals showing DAA positivity and those with DAA negativity, uncovering significant differences in various anthropometric measurements, biochemical markers, and clinical characteristics between the two groups.

3.2. Asian region

Chinese researchers utilized data-driven clustering methods to validate the diversity among individuals diagnosed with prediabetes and to assess their link with significant health conditions in 2023. The study aimed to dissect the cluster profiles of prediabetes by evaluating the connections between developing diabetes and its subsequent complications, employing 12 variables that cover aspects such as body fat composition, glycemic control, pancreatic beta-cell activity, insulin sensitivity, lipid concentrations, and hepatic enzyme levels16. Within the China Cardiometabolic Disease and Cancer Cohort (4C)[17–19], 55,777 prediabetic subjects were initially sorted into six distinct clusters, underscoring the heterogeneity within prediabetes. In this study, they identified five clusters among people with various conditions. The smallest cluster was defined with high HbA1c levels, indicating long-term blood sugar issues, yet normal in other tests, suggesting a distinct blood sugar pattern (cluster 1). Patient with high levels of HDL-c, or 'good' cholesterol, potentially lowering their risk of heart disease are in cluster 2. In cluster 2, patients with high fasting blood sugar but low HbA1c levels, hinting at an unusual response to blood sugar spikes. While, cluster 4 with high BMI, shows significant insulin resistance and poor insulin production, indicating serious insulin usage problems. Finally, in cluster 5 are individuals with high liver enzymes and blood fats.

In the research conducted in India, 19,084 participants with T2DM were analyzed, using eight important health factors, including age when diagnosed, body mass index (BMI), waist size, levels of glycated hemoglobin, triglycerides, HDL cholesterol, and C peptide levels (both fasting and after stimulation) [20]. They found four main types

of diabetes patients, each with different health characteristics and outcomes: one with severe insulin deficiency (SIDD), another with obesity and insulin resistance (IROD), a third combining both insulin resistance and deficiency (CIRDD), and a fourth with milder, age-related diabetes (MARD) [13].

The study conducted by researchers in Thailand involved 721 patients from the Siriraj Diabetes Registry and relied on five variables: age, body mass index (BMI), glycated hemoglobin (HbA1c), triglycerides (TG), and high-density lipoproteins (HDL) [14]. The findings of this study highlight the heterogeneity within the T2DM population in Thailand and the potential benefits of subclassification based on clinical variables [21]. Further research and validation of these subtypes could contribute significantly to personalized medicine approaches in diabetes care, not only in Thailand but potentially worldwide. They identified four distinct clusters of diabetes, differentiated by specific characteristics. The largest group, Cluster 4 (mild age-related diabetes: MARD), embrace 46.3% of cases, characterized by older individuals with lower HbA1c levels at diagnosis. Following this, Cluster 3 (mild obesity-related diabetes: MOD) accounts for 23.3% of cases, marked by higher BMI and younger age but with lower HbA1c. Cluster 1 (severe insulin-deficiency diabetes: SIDD) makes up 18.6% of the cohort, with high HbA1c and low BMI, indicating severe insulin deficiency. Lastly, Cluster 2 (metabolic syndrome diabetes: MSD) represents 11.8%, showing high triglycerides and low HDL-C, alongside average age and BMI, pointing towards metabolic complications.

4. Discussion

We analyzed the differences in T2DM found in studies from Europe and Asia, which show variations in its types and characteristics. In Europe, T2DM is categorized into five groups: one with severe immune reactions against insulin-producing cells (SAID), another with a significant lack of insulin without immune issues (SIID), a third facing major insulin usage problems (SIRD), a fourth linked to obesity but less severe insulin issues (MOD), and a fifth, milder form related to aging (MARD). Meanwhile, in Asia, T2DM is seen in four main types: one with a critical insulin shortage (SIDD), another involving obesity and difficulty in using insulin (IROD), a third showing both of these challenges (CIRDD), and a fourth, less severe type that generally affects older adults (MARD)[22]. Various mechanisms underlying the development and progression of T2DM can impact diagnostic approaches and individuals differently.

European studies, specially from Sweden [23], have explored the dynamics of five distinct clusters of T2DM. These clusters were identified based on an analysis of several factors: glutamate decarboxylase antibodies, age at diagnosis, body mass index (BMI), HbA1c levels, β-cell function, and insulin resistance. The findings suggest the importance of adopting an individualized treatment approach for each patient.

Indian study [24] classified patients with T2DM using cluster analysis with eight independent trends. Four clusters were identified, including two new ones: insulin-resistant obese diabetes and combined insulin-resistant and deficiency diabetes, indicating higher stages of severe insulin-deficiency diabetes and younger age at diagnosis in the Indian phase at the level of Europeans [25]. Moreover, cluster-based phenotype analysis conducted in China [13] noted a higher frequency

of severe insulin-deficient diabetes and a younger age at diagnosis, as well as lower beta-cell function, reduced insulin resistance, and lower BMI among the populations when compared to European individuals.

The Indian cohort showed a higher prevalence of SIDD (26.2%) compared to the Swedish cohort (17.5%). This divergence underscores potential disparities in the disease's presentation and prevalence between the two populations. Individuals with SIDD in India were diagnosed at a notably younger age (mean 42.5 years) compared to their Swedish counterparts (mean 56.7 years). This significant age gap suggests that diabetes onset in India tends to occur at a more youthful stage of life. The Indian SIDD group had a lower mean BMI (24.9 kg/m2) compared to the Swedish SIDD group (28.9 kg/m2). This discrepancy suggests variations in the relationship between diabetes and body weight in these populations. Within the Indian cohort, individuals in all subgroups exhibited lower levels of β-cell function and insulin resistance compared to the ANDIS cohort [22]. This indicates a potential disparity in the pathophysiological mechanisms underlying diabetes in Indian versus Swedish populations.

The Indian subgroup with severe insulin resistance also displayed low β-cell function [26] , a characteristic that differed from the Swedish subgroup with severe insulin-resistant diabetes mellitus. This highlights the complexity of diabetes subtyping and its variations in different populations. Individuals with obesity-related diabetes in India exhibited higher insulin resistance compared to their Swedish counterparts, further emphasizing variations in the disease's presentation across regions. A study in Slovakia [11] showed the presence of an autoimmune component in some patients with T2DM, which further complicates the classification and approaches to these individual diseases. In both regions, the prevalence and characteristics of T2DM may vary significantly, highlighting the global need to change regional-specific treatment approaches and specific patient characteristics.

5. Conclusion

Drawing from the experiences of other Asian countries and the research conducted within these regions, it becomes evident that implementing cluster analysis to classify phenotypes of T2DM in Kazakhstan represents a pivotal step in the development of personalized diagnostic and treatment approaches for this prevalent disease.

Cluster analysis holds the potential to unveil the diverse patient groups with T2DM in Kazakhstan based on clinical and epidemiological data. This valuable insight will greatly contribute to our understanding and assessment of T2DM phenotypes and their associations with various risk factors and complications. Moreover, it will enable the formulation of more precise and effective treatment and disease management strategies.

Integration of cluster analysis into the landscape of T2DM research in Kazakhstan represents a crucial step forward. By recognizing the individuality of each patient's condition and tailoring interventions accordingly, we pave the way for a future where the burden of T2DM is alleviated through personalized care strategies, ultimately benefitting the health and well-being of the Kazakhstani population.

References

[1] IDF_Atlas_10th_Edition_2021.

[2] Radtke MA, Midthjell K, Nilsen TIL, Grill V. Heterogeneity of patients with latent autoimmune diabetes

in adults: Linkage to autoimmunity is apparent only in those with perceived need for insulin treatment results from the nord-trondelag health (HUNT) study. *Diabetes Care*. 2009;32(2). doi:10.2337/dc08-1468

[3] Redondo MJ, Hagopian WA, Oram R, et al. The clinical consequences of heterogeneity within and between different diabetes types. *Diabetologia*. 2020;63(10). doi:10.1007/s00125-020-05211-7

[4] Gore MO, McGuire DK, Lingvay I, Rosenstock J. Predicting cardiovascular risk in type 2 diabetes: The heterogeneity challenges. *Curr Cardiol Rep*. 2015;17(7). doi:10.1007/s11886-015-0607-7

[5] Nair ATN, Wesolowska-Andersen A, Brorsson C, et al. Heterogeneity in phenotype, disease progression and drug response in type 2 diabetes. *Nat Med*. 2022;28(5). doi:10.1038/s41591-022-01790-7

[6] Silvia P, Simona Z, Ernesto M, Raffaella B. "H" for heterogeneity in the algorithm for type 2 diabetes management. *Curr Diab Rep*. 2020;20(5). doi:10.1007/s11892-020-01297-w

[7] Venkatasubramaniam A, Mateen BA, Shields BM, et al. Comparison of causal forest and regression-based approaches to evaluate treatment effect heterogeneity: An application for type 2 diabetes precision medicine. *BMC Med Inform Decis Mak*. 2023;23(1). doi:10.1186/s12911-023-02207-2

[8] 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(5). doi:10.1016/S2213-8587(18)30051-2

[9] 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(9):684-694. doi:10.1016/S2213-8587(19)30187-1

[10] Safai N, Ali A, Rossing P, Ridderstråle M. Stratification of type 2 diabetes based on routine clinical markers. *Diabetes Res Clin Pract*. 2018;141. doi:10.1016/j.diabres.2018.05.014

[11] Rončáková M, Davani A, Mikušová V, Ságová I, Novodvorský P, Martinka E. Prevalence of positivity for diabetes-associated autoantibodies in individuals with type 2 diabetes and their further characterisation: Cross-sectional study from Slovakia. *Diabetes Ther*. 2023;14(9):1537-1548. doi:10.1007/s13300-023-01440-2

[12] Qiu J, Xiao Z, Zhang Z, Luo S, Zhou Z. Latent autoimmune diabetes in adults in China. *Front Immunol*. 2022;13(August):1-14. doi:10.3389/fimmu.2022.977413

[13] Anjana RM, Baskar V, Nair ATN, et al. Novel subgroups of type 2 diabetes and their association with microvascular outcomes in an Asian Indian population: A data-driven cluster analysis: The INSPIRED study. *BMJ Open Diabetes Res Care*. 2020;8(1). doi:10.1136/bmjdrc-2020-001506

[14] Preechasuk L, Khaedon N, Lapinee V, et al. Cluster analysis of Thai patients with newly diagnosed type 2 diabetes mellitus to predict disease progression and treatment outcomes: A prospective cohort study. *BMJ Open Diabetes Res Care*. 2022;10(6). doi:10.1136/bmjdrc-2022-003145

[15] Dennis JM, Shields BM, Henley WE, Jones AG, Hattersley AT. 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(6):442-451. doi:10.1016/S2213-8587(19)30087-7

[16] Zheng R, Xu Y, Li M, et al. Data-driven subgroups of prediabetes and the associations with outcomes in Chinese adults. *Cell Reports Med*. 2023;4(3). doi:10.1016/j.xcrm.2023.100958

[17] Lu J, He J, Li M, et al. Predictive value of fasting glucose, postload glucose, and hemoglobin A1c on risk of diabetes and complications in Chinese adults. *Diabetes Care*. 2019;42(8). doi:10.2337/dc18-1390

[18] Zheng R, Li M, Xu M, et al. Chinese adults are more susceptible to effects of overall obesity and fat distribution on cardiometabolic risk

factors. *J Clin Endocrinol Metab*. 2021;106(7). doi:10.1210/clinem/dgab049

[19] Li M, Xu Y, Wan Q, et al. Individual and combined associations of modifiable lifestyle and metabolic health status with new-onset diabetes and major cardiovascular events: The China cardiometabolic disease and cancer cohort (4C) study. *Diabetes Care*. 2020;43(8). doi:10.2337/dc20-0256

[20] Unnikrishnan R, Anjana RM, Mohan V. Diabetes in South Asians: Is the phenotype different? *Diabetes*. 2014;63(1). doi:10.2337/db13-1592

[21] Anjana RM, Pradeepa R, Unnikrishnan R, Tiwaskar M, Aravind SR, Saboo B, Joshi SR, Mohan V. New and unique clusters of type 2 diabetes identified in indians. J Assoc Physicians India. 2021 Feb;69(2):58-61. PMID: 33527813.

[22] Roden M, Shulman GI. The integrative biology of type 2 diabetes. *Nature*. 2019;576(7785). doi:10.1038/s41586-019-1797-8

[23] Ahlqvist E, Storm P, Karajamaki A, et al. Clustering of adult-onset diabetes into novel subgroups guides therapy and improves prediction of outcome. *bioRxiv*. Published online 2017.

[24] Kumar A, De Leiva A. Latent autoimmune diabetes in adults in north Indian region: Assessment of β-cell function, metabolic and immunological features. In: *Metabolic Syndrome and Related Disorders*. Vol 15. ; 2017. doi:10.1089/met.2017.0103

[25] Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycaemia in type 2 diabetes: A patient-centered approach. Position statement of the american diabetes association (ADA) and the european association for the study of diabetes (EASD). *Diabetologia*. 2012;55(6). doi:10.1007/s00125-012-2534-0

[26] Cordiner RLM, Mari A, Tura A, Pearson ER. The impact of low-dose gliclazide on the incretin effect and indices of beta-cell function. *J Clin Endocrinol Metab*. 2021;106(7). doi:10.1210/clinem/dgab151