REVIEW ARTICLE

Revisiting Diabetes Classification: Insights Challenges and Clinical Relevance of the ANDIS Framework in the Indian Context

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Abstract

Diabetes mellitus exhibits significant heterogeneity in clinical presentation, progression, and treatment response, rendering the traditional binary classification into type 1 and type 2 diabetes increasingly inadequate. The All New Diabetics in Scania (ANDIS) framework, introduced in 2018, proposed a novel data-driven classification system that stratifies adult-onset diabetes into five distinct subgroups based on clinical and biochemical characteristics. This manuscript critically examines the scientific rationale, methodology, and clinical implications of the ANDIS classification, while evaluating its utility through evidence drawn from Indian (INSPIRED and WellGen) and global validation studies (DEVOTE, LEADER, DD2, NHANES, and FoCus cohorts). Findings from these cohorts affirm the biological relevance of clusters like severe insulin-deficient diabetes (SIDD) and severe insulin-resistant diabetes (SIRD). However, their prevalence varies across ethnic and regional populations. Despite its theoretical strengths, the ANDIS model faces major implementation barriers, including diagnostic complexity, high costs, and limited therapeutic differentiation over existing guidelines. Furthermore, access to required diagnostics such as glutamic acid decarboxylase (GAD) antibody testing and homeostatic model assessment 2 (HOMA2) indices is limited even in high-income countries (HICs). The framework's real-world applicability can be simplified using accessible markers such as hemoglobin A1C (HbA1c), body mass index (BMI), and abdominal circumference. The manuscript emphasizes the need for dynamic, low-cost, and population-specific adaptations to make stratified diabetes care feasible and impactful globally.

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Introduction

Diabetes, a complex metabolic disorder with diverse clinical presentations and pathophysiological mechanisms, has traditionally been classified into type 1 and type 2 diabetes. This dichotomous classification has served as a functional framework for diagnosis and management, yet it fails to capture the variability in disease progression, complication risk, and therapeutic response among patients.[1] The heterogeneity within these broad categories is increasingly recognized, necessitating a more nuanced approach to classification.

In 2018, the All New Diabetics in Scania (ANDIS) study introduced a novel framework, segmenting diabetes into five subtypes: 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).[2] This model aims to advance precision medicine by stratifying patients based on clinical and pathophysiological characteristics, enabling personalized monitoring and treatment strategies.

Despite its theoretical promise, the clinical applicability of the ANDIS classification remains a topic of debate. This manuscript critically examines the rationale behind this reclassification, the methodology employed, and its implementation challenges. By exploring the model's strengths and limitations, we aim to provide insights into its relevance for clinicians, particularly in resource-constrained settings, while proposing strategies to bridge the gap between research and real-world practice.

Why a New Classification?[2]

The traditional diabetes classification system—primarily distinguishing between type 1 and type 2 diabetes—has been instrumental in simplifying diagnosis and management. However, it fails to reflect the inherent variability in clinical presentation, complications, treatment response, and underlying etiological mechanisms. This lack of granularity has significant implications for risk stratification, therapeutic efficacy, and the advancement of precision medicine.

Complication Risk

The development of diabetes-related complications varies widely among patients[2–4]:

- Microvascular complications: These include retinopathy, nephropathy, and neuropathy, which can occur early in patients with severe beta-cell dysfunction. For example, patients in the SIDD cluster, characterized by high hemoglobin A1C (HbA1c) levels and low beta-cell function, are at an elevated risk of these complications due to prolonged hyperglycemia.
- Macrovascular complications: Conversely, some patients primarily develop cardiovascular complications, often driven by persistent insulin resistance. The SIRD cluster represents these patients, characterized by obesity, dyslipidemia, and a higher propensity for cardiovascular events.

Traditional classifications do not differentiate between patients who are more likely to develop microvascular vs macrovascular complications, potentially delaying targeted preventive interventions. The ANDIS classification addresses this gap by stratifying patients into subgroups with distinct complication profiles, enabling more focused monitoring and preventive strategies.

Supporting evidence: Ahlqvist et al. demonstrated that SIDD patients had a significantly higher prevalence of microvascular complications, while SIRD patients exhibited elevated rates of cardiovascular events.[2] This association highlights the need for more precise risk-stratification tools.

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Therapeutic Response

Patients with diabetes exhibit significant differences in their response to glucose-lowering therapies, often resulting in suboptimal outcomes when treatments are selected based on traditional classifications.

- Insulin sensitivity vs insulin deficiency: While some patients respond well to insulin sensitizers like metformin or thiazolidinediones, others require early insulin therapy due to severely impaired beta-cell function. For example:
  - SIDD patients benefit most from insulin therapy, as their primary defect is severe beta-cell dysfunction.
  - SIRD patients respond better to insulin-sensitizing drugs due to underlying insulin resistance.

The traditional framework often relies on trial-and-error approaches, delaying optimal glycemic control by failing to distinguish between these pathophysiological differences. The ANDIS model enables personalized therapy by identifying each patient's dominant mechanism of dysregulation, guiding clinicians toward more effective treatments.[2]

Supporting evidence: Studies conducted in China[5] and India[6] have validated the ANDIS framework. This demonstrates that SIDD patients achieve better glycemic control with insulin, while SIRD patients respond well to metformin and other insulin-sensitizing therapies.

Disease Etiology

Diabetes is a heterogeneous condition influenced by genetic predisposition, environmental factors, and lifestyle. The traditional classification system does not account for these diverse etiological factors, instead grouping patients with distinct mechanisms of disease under broad categories[2]:

- Genetic predisposition: Variations in genetic factors affect beta-cell function, insulin secretion, and insulin sensitivity. The ANDIS model accounts for this heterogeneity by identifying subtypes like SIDD (severe beta-cell dysfunction) and SIRD (dominant insulin resistance).
- Environmental and lifestyle factors: Clusters such as MOD and MARD highlight the role of obesity and aging in the development of diabetes. These distinctions enable a more nuanced understanding of disease progression.

By incorporating these etiological factors, the ANDIS classification provides a comprehensive framework for understanding diabetes heterogeneity, advancing both clinical care and research.

Supporting evidence: Ahlqvist et al. reported that genetic and environmental risk factors differ significantly across the ANDIS subtypes, underscoring the value of this model in identifying population-specific diabetes phenotypes.[2]

The Goals of the ANDIS Classification

The ANDIS model aims to address these limitations through a data-driven approach to diabetes classification, with the following objectives[2]:

- Improve risk stratification: The model helps identify patients at high risk for complications (e.g., SIDD for microvascular complications and SIRD for cardiovascular disease), facilitating targeted monitoring and early intervention.
- Enable personalized therapeutic strategies: Treatments are tailored to the underlying pathophysiology of each subtype, optimizing therapeutic efficacy and minimizing delays in glycemic control.
- Support precision medicine: By leveraging advanced biomarkers [e.g., glutamic acid decarboxylase (GAD) antibodies, homeostatic model assessment of insulin resistance (HOMA2-IR), and homeostatic model assessment of beta-cell function (HOMA2-B)], the ANDIS model aligns with the principles of precision medicine, moving beyond one-size-fits-all approaches to diabetes care.

While the ANDIS classification represents a significant step forward in understanding diabetes heterogeneity, its real-world implementation poses challenges, including cost, complexity, and the need for specialized diagnostics.

How Does the ANDIS Model Work?

The ANDIS classification system emerged from the analysis of over 14,000 newly diagnosed adult-onset diabetes patients in Sweden. Using a combination of clinical and laboratory parameters, the cohort was stratified into five distinct subtypes, reflecting the heterogeneity of diabetes.[2]

Key Parameters

- Age of onset: Differentiates early-onset from late-onset diabetes, which often exhibit distinct pathophysiological mechanisms and progression rates.
- Body mass index: Indicates the contribution of obesity to disease etiology, with higher body mass indices (BMIs) often associated with insulin resistance.
- Hemoglobin A1C levels: Serves as a marker for chronic hyperglycemia, correlating with disease severity and complication risk.
- Glutamic acid decarboxylase antibodies: Detects autoimmune beta-cell destruction, identifying patients with SAID, akin to type 1 diabetes.
- Homeostatic model assessment of insulin resistance: Quantifies the degree of insulin resistance, a defining feature of the SIRD cluster.
- Homeostatic model assessment of beta-cell function: Assesses pancreatic beta-cell function, distinguishing patients with severe insulin deficiency (e.g., SIDD) from those with milder impairments (e.g., MOD).

Resulting Clusters

The analysis produced five clusters, each representing a unique pathophysiological profile[2]:

- Severe autoimmune diabetes: Autoimmune diabetes requiring insulin therapy.
- Severe insulin-deficient diabetes: SIDD with high HbA1c and microvascular complication risk.
- Severe insulin-resistant diabetes: SIRD, associated with obesity and cardiovascular complications.
- Mild obesity-related diabetes: MOD with a relatively stable metabolic profile.
- Mild age-related diabetes: MARD, often requiring minimal intervention.

By combining these parameters, the ANDIS model offers a more nuanced classification system that captures the complexity of diabetes, paving the way for personalized care. Figure 1 schematically represents the ANDIS subgroup classification overlapping the current international classification adopted by major international bodies.

Challenges in Clinical Implementation

Despite its potential to enhance our understanding of diabetes heterogeneity, the ANDIS classification system faces significant barriers to clinical implementation. These challenges stem from the complexity and cost of required diagnostics, limited therapeutic impact, and variability in diabetes phenotypes across global populations. Addressing these challenges is critical for

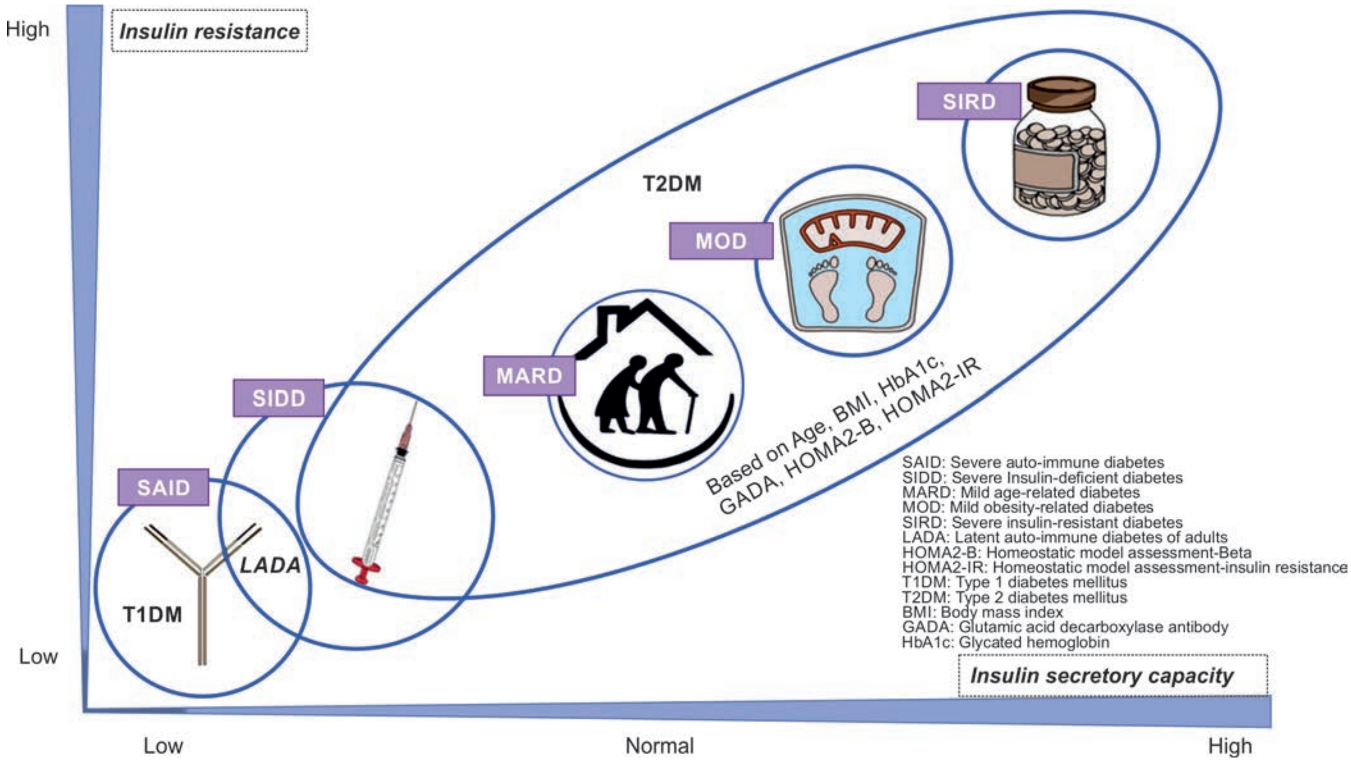

Fig. 1: ANDIS subgroup classification overlapping the current international classification of diabetes

translating this framework into routine clinical practice.

Diagnostic Complexity

The ANDIS classification relies on advanced laboratory diagnostics, which pose logistical challenges in routine healthcare settings, particularly in low-resource environments. Key diagnostic requirements include:

- Glutamic acid decarboxylase antibodies testing: Identifying autoimmune diabetes (SAID) depends on the detection of GAD antibodies, a test that is not universally available. GAD testing requires specialized equipment and trained personnel, limiting its feasibility in primary care or resource-limited settings.[7,8] Furthermore, antibody testing is costly, adding to the economic burden of implementing the ANDIS classification.
- HOMA2-IR and HOMA2-B calculations: These indices, which measure insulin resistance and beta-cell function, respectively, require fasting glucose and insulin levels.[9] The accurate calculation depends on specialized software, such as the HOMA2 calculator, which is not integrated into routine laboratory systems. Additionally, fasting insulin assays are not standard in many clinical laboratories, further complicating their accessibility.
- Dependence on high-quality laboratory infrastructure: The overall reliance on advanced diagnostic tools limits the scalability of the ANDIS model in regions where basic diabetes diagnostics, such as HbA1c or fasting glucose, are already underutilized. In many low- and middle-income countries (LMICs), even these basic tests remain unaffordable or unavailable to large segments of the population. Importantly, access to specialized diagnostics such as GAD antibody assays and HOMA2 calculations remains inconsistent not only in LMICs but also across certain healthcare systems in high-income countries (HICs), where these tests are often restricted to tertiary or academic centers due to cost, availability, or insurance limitations.

Implication: The diagnostic complexity restricts the practical application of the ANDIS model to research settings or well-funded healthcare systems, leaving the majority of global diabetes patients outside its scope.

Limited Therapeutic Impact

While the ANDIS classification refines our understanding of diabetes subtypes, its real-world impact on therapeutic decision-making is minimal. Treatment strategies remain largely unchanged for most patients, as current guidelines already address the primary pathophysiological mechanisms underlying diabetes:

- Severe autoimmune diabetes patients: This subgroup corresponds to traditional type 1 diabetes, managed with insulin therapy. The ANDIS classification does not alter this approach.
- Severe insulin-deficient diabetes patients: These individuals exhibit severe beta-cell dysfunction and require early insulin initiation, a strategy that mirrors current management of poorly controlled type 2 diabetes.
- Severe insulin-resistant diabetes patients: Patients in this group benefit from insulin sensitizers, such as metformin or thiazolidinediones, which are already the standard treatment for insulin resistance in type 2 diabetes.
- Mild obesity-related diabetes and mild age-related diabetes patients: These subtypes overlap significantly with mild forms of type 2 diabetes, which are often managed with lifestyle interventions and minimal pharmacological therapy.

Although the classification provides insights into the underlying pathophysiology,[2] it does not introduce new therapeutic pathways, nor does it significantly alter clinical outcomes in most cases.

Implication: The limited therapeutic impact raises concerns about the clinical utility of implementing the ANDIS framework, particularly when weighed against its logistical and financial costs.

High Cost

The financial burden of implementing the ANDIS classification represents one of its most significant challenges. The model requires multiple advanced tests, including the following:

- GAD antibody assays for autoimmune diabetes detection.[8]
- Fasting glucose and insulin measurements for calculating HOMA2-IR and HOMA2-B.[9]

The cumulative cost of these tests makes routine application of the ANDIS model impractical in many healthcare systems. For example:

- In LMICs, even basic tests such as HbA1c are often underutilized due to their expense.
- Introducing more complex and costly diagnostics, such as GAD antibody testing, would strain already limited healthcare budgets.

Furthermore, the model does not provide clear cost-benefit advantages, as it does not significantly change treatment outcomes for most patients.

Implication: The high costs associated with the ANDIS framework make it infeasible for widespread adoption, especially in healthcare systems with constrained resources.

Lack of Global Applicability

The ANDIS classification was developed based on data from a Swedish cohort, where the population is predominantly Caucasian with specific genetic, environmental, and lifestyle factors.[2] Subsequent studies in other populations have revealed significant differences in diabetes phenotypes, raising questions about the model's universal applicability:

- Asia: In Asian populations, beta-cell dysfunction is more prevalent, and insulin resistance plays a comparatively smaller role in diabetes pathogenesis. This makes clusters such as SIDD and MOD more common, while SIRD, which is strongly linked to obesity and insulin resistance, is less prominent.[6,10–12]
- Africa: In sub-Saharan Africa, diabetes often presents in younger patients with atypical phenotypes that do not align well with the ANDIS subtypes. Additionally, limited access to advanced diagnostics restricts the use of this classification model in the region.[13–15]
- Middle-income populations: In countries like India, where diabetes is characterized by both low BMI and high insulin resistance, the boundaries between subtypes become blurred, and the classification framework may lose its distinctiveness.

Supporting evidence: Wang et al. demonstrated that the prevalence and distribution of ANDIS subtypes vary significantly in Chinese cohorts, with a higher proportion of SIDD and MOD patients compared to Western populations.[5] Similarly, studies in India have reported high rates of beta-cell dysfunction, complicating the application of SIRD-focused therapies.[6]

Implication: The variability in diabetes phenotypes across populations limits the global relevance of the ANDIS classification, necessitating regional adaptations or entirely different frameworks to account for genetic and environmental differences.

The ANDIS classification system represents a significant advancement in understanding diabetes heterogeneity. However, its clinical implementation is hindered by diagnostic complexity, limited therapeutic impact, high costs, and lack of global applicability. For this framework to achieve broader adoption, future efforts must focus on simplifying diagnostic requirements, validating the classification across diverse populations, and demonstrating clear clinical and cost-benefit advantages. Without addressing these challenges, the ANDIS model risks remaining a valuable academic exercise with limited real-world relevance.

Validation of the ANDIS Framework in Indian Populations

Two pivotal studies—INSPIRED[12] and WellGen[6]—have critically evaluated the utility and adaptability of the ANDIS classification model in Indian populations, offering compelling evidence for both biological relevance and ethnic-specific variations in diabetes subphenotypes.

The INSPIRED study by Anjana et al. analyzed over 19,000 patients across 50 diabetes centers in India using k-means clustering with eight clinically relevant variables.[12] The study identified four distinct clusters[12]:

1. Severe insulin-deficient diabetes (26.2%): Marked by low BMI, severe insulin deficiency, and the highest HbA1c (10.7%), this group had the greatest hazard for diabetic retinopathy.
2. Insulin-resistant obese diabetes (25.9%): A novel cluster typified by obesity and severe insulin resistance, with the highest HOMA2-B and HOMA2-IR scores.
3. Combined insulin-resistant and deficient diabetes (12.1%): Another novel group featuring coexisting insulin resistance and deficiency, associated with elevated triglycerides and the highest hazard for nephropathy.
4. Mild age-related diabetes (35.8%): Characterized by older age at onset and best glycemic control.

These clusters were stable and reproducible in a nationally representative epidemiological dataset (ICMR-INDIAB), affirming the robustness of this framework in Indian clinical and community contexts.

In contrast, the WellGen study by Prasad et al. focused specifically on young-onset type 2 diabetes (diagnosed before age 45).[6] Applying both supervised (ANDIS-derived centroids) and unsupervised clustering to over 1,600 Indian participants, they found SIDD to be the dominant cluster (52.8%), significantly more prevalent than in European cohorts. This finding was corroborated across two other regional cohorts—Ahmedabad and PHENOEINDY-2—where SIDD ranged from 53 to 67%. Additionally, the SIDD group showed higher risks of nephropathy and retinopathy, while MOD (37.7%) was associated with neuropathy. SIRD and MARD were infrequent (<10%) in all Indian cohorts.[6]

Together, these studies demonstrate that insulin deficiency is the predominant driver of type 2 diabetes in Indian patients, especially those with young-onset disease, and emphasize the need for context-sensitive adaptations of the ANDIS framework that reflect the Indian population's unique metabolic phenotype and complication patterns.

Table 1 has depicted a detailed comparison that clearly underscores not only the pathophysiological divergence of Indian populations from the European ANDIS cohort but also the need for regional refinement of cluster-based diabetes management.

Global Replication and Expansion of the ANDIS Classification Framework

A growing body of global research has examined the generalizability of the ANDIS classification system, confirming its robustness while also identifying region-specific adaptations and insights. In a landmark analysis involving over 20,000 high cardiovascular risk patients from the DEVOTE, LEADER, and SUSTAIN-6 cardiovascular outcomes trials, Kahkoska et al. validated the ANDIS clusters using simplified variables—age at diagnosis, HbA1c, and BMI. Their study

Table 1: Comparative overview of the INSPIRED and WellGen studies on ANDIS subgroup validation in Indian populations[6,12]

Study	*Study design*	*Clusters identified*	*Unique features*	*Clinical implications*
INSPIRED[12]	Cross-sectional multicenter study; 19,084 adults with type 2 diabetes from 50 centers across India. Applied k-means clustering on eight clinical variables: age at diagnosis, BMI, waist circumference, HbA1c, triglycerides, HDL cholesterol, and fasting and stimulated C-peptide. Clustering was validated in a nationally representative cohort (ICMR-INDIAB)	SIDD (26.2%), insulin-resistant obese diabetes (IROD) (25.9%), combined insulin-resistant and deficient diabetes (CIRDD) (12.1%), and MARD (35.8%)	First study to define IROD and CIRDD—two novel Indian-specific clusters. CIRDD showed highest risk for nephropathy, while SIDD had highest risk for retinopathy. Cluster profiles were robust across clinical and community datasets	Demonstrates importance of ethnic-specific clustering for tailored clinical management. Use of stimulated C-peptide improves discrimination between insulin resistance and deficiency phenotypes
WellGen[6]	Observational study of 1,612 individuals with young-onset (<45 years) type 2 diabetes. Used both supervised clustering (ANDIS-derived centroids) and unsupervised k-means clustering based on five variables: age at diagnosis, BMI, HbA1c, HOMA2-B, and HOMA2-IR. Validation done in two additional Indian cohorts (Ahmedabad, PHENOEINDY-2)	SIDD (52.8%), MOD (37.7%), MARD (8.4%), and SIRD (1.1%)	Indian patients had a strikingly high prevalence of SIDD (53%) compared to Europeans. MOD and SIDD clusters were dominant. Minimal SIRD and MARD presence. Complications varied: SIDD had more nephropathy and retinopathy; MOD had higher neuropathy	Suggests insulin deficiency as the primary pathological driver in young Indians. Highlights limited generalizability of European ANDIS clusters to Indian cohorts without contextual adaptation. Calls for phenotype-guided treatment strategies

found that the SIDD-like cluster, marked by high HbA1c and low BMI, consistently exhibited the highest rates of cardiovascular mortality and nephropathy, reinforcing the framework's prognostic utility even in advanced-stage diabetes.[16] In a complementary US-based study, Xie et al. applied both standard ANDIS clustering and a simplified three-variable method (age, BMI, and HbA1c) to NHANES data. While the simplified approach adequately identified SIDD, MOD, and MARD clusters, it was less reliable for detecting the insulin-resistant (SIRD) phenotype, suggesting that although simplification is feasible for population-scale screening, key metabolic nuances may be lost without HOMA indices.[17] Meanwhile, Christensen et al. conducted a hybrid comparative study in the Danish DD2 cohort, juxtaposing the four canonical ANDIS clusters against a parallel classification based solely on HOMA2 indices (insulinopenic, classical, and hyperinsulinemic types). While the SIDD, MOD, and MARD clusters largely aligned with the "classical" phenotype, SIRD overlapped most distinctly with the hyperinsulinemic phenotype. Their data-driven approach indicated that only three clusters might be optimal for their cohort, suggesting the need for dynamic refinements of clustering models across populations.[18] Adding a novel dimension, Rohmann et al. examined the ANDIS framework in the German FoCus cohort and performed a broad characterization of each subtype, including metabolic, inflammatory, microbial, lifestyle, and psychosocial domains. Although metabolic biomarkers did not differ dramatically across subtypes, lifestyle factors (e.g., smoking, physical activity, and sleep), mental health, and educational status varied significantly—particularly for SIDD- and SIRD-like groups.[19] These findings suggest that subtype-informed care models should go beyond biochemical markers and incorporate social determinants of health.

Table 2 summarizes key global studies validating the ANDIS diabetes classification framework across diverse populations, highlighting differences in methodology, cluster detection accuracy, and implications for both clinical practice and health system adaptation.

The Five Subgroups: Key Insights

Table 3 summarizes the five subgroups the ANDIS classification system identified, highlighting their clinical profiles, key risk factors, and corresponding management strategies. Each cluster represents a distinct pathophysiological mechanism and complication risk, enabling targeted therapeutic approaches. For instance, patients in the SAID cluster require insulin therapy due to autoimmune beta-cell destruction. In contrast, SIDD patients, characterized by severe beta-cell dysfunction and elevated HbA1c, benefit from early to intensive glycemic control to reduce microvascular complications. Conversely, SIRD patients exhibit obesity-driven insulin resistance and heightened cardiovascular risks, necessitating insulin sensitizers like metformin. The MOD and MARD clusters, associated with milder disease progression, often require standard or minimal interventions, respectively. This classification framework offers a refined understanding of diabetes heterogeneity, though its clinical applicability is limited by diagnostic complexity and global variability in diabetes phenotypes.

Clinical Relevance for Physicians

The ANDIS classification represents an academic advance in understanding diabetes heterogeneity, yet its clinical impact remains limited. For practicing physicians, especially in resource-constrained settings, the model's utility is overshadowed by its cost and diagnostic complexity, making simpler tools and biomarkers a more practical focus for routine care.

No Major Paradigm Shift

Despite its innovative approach, the ANDIS classification essentially reinforces existing treatment principles without introducing substantial changes in therapeutic strategies.[2] For example:

- Severe autoimmune diabetes: This subtype aligns with type 1 diabetes and continues to require insulin therapy as the cornerstone of management.
- Severe insulin-deficient diabetes: Treatment mirrors that of poorly controlled

Table 2: Global validation studies of the ANDIS cluster classification framework

Study (year)	*Study population and design*	*Cluster variables used*	*Main findings*	*Implications*
Kahkoska et al. (2020)[16]	DEVOTE, LEADER, SUSTAIN-6 CVOTs (*n* = 20,274); high CV-risk T2D; clustering *via* nearest centroid	Age, HbA1c, and BMI (no HOMA)	ANDIS clusters replicated; SIDD-like cluster showed highest CV death and nephropathy risk	Validates ANDIS in advanced T2D settings; supports use of simplified models for risk stratification
Xie et al. (2022)[17]	NHANES 1999–2014 (n = 1,960); US adults; ANDIS clusters compared using five-variable vs three-variable methods	Age, BMI, and HbA1c ± HOMA2-IR/B	Three-variable model captured SIDD, MOD, and MARD well; SIRD identification was limited without HOMA indices	Simplified clustering useful for screening in low-resource settings; caution needed for SIRD-like phenotype detection
Christensen et al. (2022)[18]	Danish DD2 cohort (*n* = 3,529); newly diagnosed T2D; compared ANDIS with three HOMA-based phenotypes	Age, BMI, HbA1c, HOMA2-B, and HOMA2-IR	Best clustering fit was three, not four clusters; SIRD aligned with hyperinsulinemia; partial overlap with Danish HOMA-based classification	Calls for contextual refinement of clusters; hyperinsulinemic/ SIRD phenotype most distinct; phenotypic and HOMA models can be complementary
Rohmann et al. (2025)[19]	German FoCus cohort (*n* = 208 T2D + 208 controls); applied ANDIS model and analyzed metabolic, lifestyle, and social data	Age, BMI, HOMA-IR, HOMA-B, therapy, and lifestyle/psychosocial data	Subtypes replicated; metabolic differences minor; major subtype variation found in lifestyle factors, sleep, education, and psychological health	Emphasizes psychosocial and behavioral dimensions in diabetes subtyping; supports holistic, patient-centered, and subtype-specific care strategies

Table 3: Key characteristics and management of the five diabetes subgroups in the ANDIS classification[2]

Cluster	*Clinical description*	*Key risk factors*	*Management*
SAID	Autoimmune diabetes, insulin-dependent	Autoimmunity	Insulin therapy
SIDD	Severe beta-cell dysfunction, high HbA1c	High microvascular complication risk	Early insulin therapy, intensive glucose control
SIRD	Severe insulin resistance, high BMI	Cardiovascular disease	Insulin sensitizers (e.g., metformin)
MOD	Obesity-related, milder disease	Younger age, obesity	Standard type 2 diabetes management
MARD	Age-related diabetes, mild progression	Aging	Minimal intervention

type 2 diabetes, involving early initiation of insulin to address beta-cell failure.

- Severe insulin-resistant diabetes: Insulin resistance in this cluster is effectively managed with sensitizers like metformin and thiazolidinediones, already standard for many type 2 diabetes patients.
- Mild obesity-related diabetes and mild age-related diabetes: These subtypes correspond to milder forms of type 2 diabetes that typically require lifestyle interventions and minimal pharmacological treatment.

Thus, while the classification enhances our understanding of diabetes subtypes, it does not offer new therapeutic pathways or fundamentally alter management strategies.

Marginal Gains vs Costs

The ANDIS framework demands advanced diagnostics, including GAD antibody testing and HOMA2 calculations, which are often expensive and unavailable in routine care. These costs do not significantly enhance clinical outcomes compared to traditional metrics like:

- Body mass index and hemoglobin A1C: These simple, widely available markers are effective for guiding diabetes treatment decisions and assessing metabolic risk.
- Abdominal circumference: A practical, inexpensive measure of central obesity, abdominal circumference strongly correlates with insulin resistance and cardiovascular risk, making it a valuable alternative to more complex diagnostics like HOMA2-IR. Studies have shown that waist circumference can reliably predict type 2 diabetes onset and associated complications, particularly in patients with SIRD.

For physicians, especially in low-resource settings, prioritizing actionable, low-cost tools like abdominal circumference measurements ensures equitable access to care without compromising outcomes.

Real-world Feasibility

In many parts of the world, healthcare systems face resource constraints that make implementing the ANDIS classification impractical. Challenges include:

- Infrastructure limitations: Advanced diagnostic tests required for ANDIS clustering, such as fasting insulin and GAD antibodies, are unavailable in primary care settings.
- Time and cost barriers: Performing and interpreting the required diagnostics increases patient costs and clinic workload, limiting accessibility for underserved populations.
- Reliability of basic metrics: Practical and easily obtainable markers like abdominal circumference, BMI, and HbA1c are more suited for global healthcare settings. These metrics allow physicians to stratify patients by risk and tailor treatment without the need for complex or expensive tests.

Given these constraints, focusing on simplified approaches to diabetes management is more feasible and impactful for the majority of patients worldwide.

Looking Ahead: What should be the Focus?

To bridge the gap between advanced academic frameworks like the ANDIS model and real-world clinical care, future efforts should emphasize practical and scalable solutions.

Simplified Biomarkers

Replacing advanced diagnostic requirements with simpler, universally accessible biomarkers can make stratified diabetes care more feasible. For instance:

- Abdominal circumference: As a direct measure of central obesity, it provides a robust proxy for insulin resistance and cardiovascular risk, particularly in SIRD patients. This metric is inexpensive, noninvasive, and widely applicable.
- Fasting glucose and hemoglobin A1C: These markers remain critical for assessing glycemic control and overall diabetes risk, offering actionable insights without the need for advanced testing.
- Body mass index: While less specific than abdominal circumference, BMI remains a reliable and accessible measure for assessing obesity-related diabetes subtypes like MOD and SIRD.

Simplifying diagnostic requirements ensures that advanced frameworks can be adapted for broader use without excluding resource-limited settings.

Dynamic Risk Models

Rather than rigidly classifying patients into fixed subtypes, future approaches could incorporate dynamic algorithms that integrate basic clinical data, including:

- Age of onset.
- Abdominal circumference or BMI.
- HbA1c or fasting glucose levels. Such models could offer personalized treatment recommendations based on readily available information, eliminating the need for costly tests.

Validation in Diverse Populations

The ANDIS model was developed in Sweden, a predominantly Caucasian population with specific genetic and environmental factors. Broader studies are needed to assess its applicability across different ethnic and socioeconomic contexts.

- Asia: Beta-cell dysfunction predominates, making SIDD more common, while obesity-driven SIRD is less prevalent.
- Africa and South Asia: Atypical diabetes phenotypes, including lean diabetes, challenge the generalizability of the ANDIS framework. Population-specific adaptations, incorporating localized risk factors like abdominal obesity, could improve the relevance of stratified diabetes care globally.

Impact on Outcomes

Future research must evaluate whether applying the ANDIS classification improves long-term patient outcomes, such as:

- Complication rates: Does stratification reduce the incidence of microvascular or macrovascular complications?
- Treatment adherence: Can personalized approaches improve adherence to therapy?
- Quality of life: Does stratification lead to better patient-reported outcomes, such as reduced burden of treatment or improved well-being?

Without clear evidence of improved outcomes, implementing the ANDIS model's high costs and complexity may not justify its widespread adoption.

The ANDIS classification provides valuable insights into diabetes heterogeneity, but its clinical relevance remains limited due to high diagnostic costs, minimal therapeutic impact, and logistical challenges. Physicians must focus on actionable, cost-effective tools like abdominal circumference, BMI, and HbA1c, which can guide effective management without needing advanced diagnostics. Future efforts should aim to simplify stratified care and validate its applicability across diverse populations, ensuring equitable and impactful diabetes management for all.

Conclusion

The ANDIS classification significantly advances understanding of diabetes heterogeneity by identifying distinct subtypes with unique risk profiles and management needs. While it provides valuable insights into disease progression, its practical implementation is hindered by diagnostic complexity, high costs, and limited global validation. Simplifying diagnostic requirements and integrating cost-effective markers like abdominal circumference, HbA1c, and BMI can enhance its feasibility and relevance, especially in resource-limited settings. Future efforts should prioritize validating the model across diverse populations and demonstrating its ability to improve long-term outcomes, ensuring its transition from an academic framework to a clinically impactful tool.

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