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DIABETES MELLITUS TYPE 5 (MALNUTRITION-RELATED DIABETES): PATHOPHYSIOLOGY, CLINICAL CHARACTERISTICS, AND THERAPEUTIC CHALLENGES

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ABSTRACT

Type 5 diabetes mellitus (T5DM), historically referred to as malnutrition-related diabetes mellitus (MRDM), represents an emerging and underrecognized subtype of diabetes that predominantly affects individuals in low- and middle-income countries (LMICs). Unlike type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM), T5DM is characterized by severe insulin deficiency in the absence of autoimmune destruction or significant insulin resistance, reflecting a distinct pathophysiological mechanism linked to chronic undernutrition and impaired pancreatic development. Despite increasing recognition, variability in terminology, diagnostic criteria, and clinical characterization has limited its identification and management in both clinical practice and research settings. This narrative literature review aims to synthesize current evidence on the epidemiology, pathophysiology, clinical features, and therapeutic approaches of T5DM, as well as to evaluate its distinction from classical diabetes subtypes and its implications for global health. A structured literature search was conducted across major electronic databases, including PubMed, Scopus, EMBASE, and Google Scholar, covering publications from January 2020 to March 2026. Relevant studies were selected based on predefined inclusion criteria encompassing epidemiological data, mechanistic insights, clinical characteristics, and treatment outcomes. Due to heterogeneity in study design, populations, and reported outcomes, findings were synthesized descriptively. The available evidence indicates that T5DM typically presents in young, underweight individuals with preserved insulin sensitivity, detectable but reduced C-peptide levels, and minimal risk of ketosis despite significant hyperglycemia. Pathophysiological mechanisms involve early-life nutritional deprivation leading to reduced β-cell mass, epigenetic modifications, and impaired insulin secretion. Therapeutically, patients often require lower insulin doses and may respond to selected oral antidiabetic agents, although evidence remains limited. Significant diagnostic challenges persist, particularly in resource-limited settings, where misclassification as T1DM or T2DM is common.

Keywords: C-peptide; insulin deficiency; malnutrition-related diabetes; type 5 diabetes; undernutrition

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INTRODUCTION

Diabetes mellitus is a chronic metabolic disorder encompassing multiple subtypes, including type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM), gestational diabetes mellitus, and other specific forms resulting from genetic, environmental, or pancreatic causes. Globally, T2DM accounts for approximately 90% of all diabetes cases, while T1DM contributes a smaller but

steadily increasing proportion (Saeedi et al., 2019; Ogle et al., 2025). The global prevalence of diabetes has risen markedly over recent decades, exceeding 400 million individuals worldwide, driven by population aging, urbanization, and lifestyle-related factors.

Beyond these classical categories, atypical forms of diabetes such as latent autoimmune diabetes in adults (LADA), maturity-onset diabetes of the young (MODY), and malnutrition-related diabetes are increasingly recognized, particularly in non-European populations. However, conventional classification systems often fail to adequately capture these heterogeneous phenotypes, resulting in diagnostic ambiguity and suboptimal therapeutic approaches (Bavuma et al., 2019). Malnutrition-related diabetes mellitus (MRDM), first described in 1955 as "J-type diabetes" in Jamaica, is characterized by young-onset diabetes in undernourished individuals and was formally recognized by the World Health Organization (WHO) in 1985 as a distinct category, including subtypes such as fibrocalculous pancreatic diabetes (FCPD) and protein-deficient pancreatic diabetes (PDPD). Despite this recognition, MRDM was removed from the WHO classification in 1999 due to insufficient consensus. In recent years, emerging evidence has renewed interest in this entity, now increasingly referred to as type 5 diabetes mellitus (T5DM), with the International Diabetes Federation (IDF) acknowledging its clinical relevance and initiating efforts to establish clearer diagnostic criteria (Wadivkar et al., 2025).

Clinically, a subset of patients typically lean, non-autoimmune, and insulin-sensitive do not conform to traditional T1DM or T2DM classifications, instead exhibiting primary insulin deficiency resulting from impaired pancreatic development associated with chronic undernutrition rather than autoimmune destruction or insulin resistance (Prajitno & Sutanto, 2025). Misclassification of these patients frequently leads to inappropriate management, including excessive insulin administration or inadequate therapy, thereby increasing the risk of hypoglycemia, poor glycemic control, and inefficient use of healthcare resources. Furthermore, such misclassification distorts epidemiological data and hampers the development of targeted public health strategies, particularly in low- and middle-income countries (LMICs), where the burden of both diabetes and malnutrition remains high (Prajitno & Sutanto, 2025). Despite growing recognition, T5DM remains insufficiently defined, with no universally accepted diagnostic criteria and limited high-quality evidence.

Therefore, this review aims to synthesize current evidence on the epidemiology, pathophysiology, and management of T5DM, compare its clinical and metabolic characteristics with those of T1DM and T2DM, and evaluate its broader clinical and public health implications.

METHOD

This study employed a narrative literature review design. A systematic search was conducted in PubMed, Scopus, EMBASE, and Google Scholar up to from January 2020 to March 2026 using keywords including *"Type 5 diabetes," "malnutrition-related diabetes,"* and *"lean diabetes."*

Eligibility Criteria

Studies were included based on the PICOS framework:
Population: Patients with T5DM
Outcomes: Epidemiology, clinical features, pathophysiology, and treatment
Study Design: Observational studies, clinical trials, reviews, and guidelines
Articles published before 2020, case reports, and non-relevant studies were excluded.

Data Extraction

A total of 120 articles were identified, followed by screening and assessment based on predefined inclusion and exclusion criteria. Data were extracted independently by two reviewers, including study characteristics, epidemiology, clinical findings, and treatment outcomes. Of these, 6 studies

met the eligibility criteria and were included in the final analysis. All extracted data were synthesized descriptively.

RESULT

Study Selection

A total of relevant articles were identified through database searching, followed by screening based on predefined inclusion and exclusion criteria. Studies published between 2020 and 2025 that met the eligibility criteria were included for qualitative synthesis. Although this review did not perform a quantitative meta-analysis, the selection process followed a structured approach to ensure methodological rigor. The included studies comprised observational studies, reviews, and consensus statements focusing on epidemiology, pathophysiology, clinical characteristics, and therapeutic outcomes of T5DM.

Epidemiological Findings

T5DM, historically referred to as malnutrition-related diabetes mellitus (MRDM), has been reported predominantly in low- and middle-income countries (LMICs), particularly in South Asia and Sub-Saharan Africa. The estimated prevalence ranges from 5% to 21.4% of all diabetes cases in these regions (Garg, 2025; Bavuma et al., 2019).

The disease typically presents in young individuals, with a mean age at diagnosis of approximately 23.6 ± 4.4 years, representing an intermediate onset between T1DM and T2DM. Patients are characteristically underweight, with body mass index (BMI) commonly below 18.5 kg/m², and often exhibit clinical features of chronic malnutrition, including reduced muscle mass, parotid enlargement, and dermatologic changes. Epidemiological studies also indicate a higher prevalence among males, with a reported male-to-female ratio of approximately 2.5:1, and a strong association with low socioeconomic status.

Pathophysiological Mechanisms

Impaired Pancreatic Development and β-Cell Dysfunction

The primary mechanism underlying T5DM is impaired pancreatic development due to chronic undernutrition during fetal and early childhood periods. Adaptive metabolic responses to nutrient deprivation prioritize vital organs such as the brain, often at the expense of pancreatic development. This results in reduced β-cell mass and impaired insulin secretion, while peripheral insulin sensitivity remains relatively preserved.

Epigenetic and Molecular Alterations

Early-life malnutrition induces long-lasting epigenetic modifications, including DNA methylation and histone alterations affecting key metabolic genes such as *PDX1* and *HNF4A*. These changes disrupt insulin signaling pathways and glucose metabolism. Additionally, alterations in hypothalamic regulation impair appetite control and glucose homeostasis, contributing to long-term metabolic dysregulation.

Insulin Signaling and Secretion Defects

Although insulin receptor activation may remain intact, downstream signaling pathways—particularly the PI3K–Akt pathway are impaired, limiting glucose uptake. Furthermore, β-cell dysfunction leads to reduced glucose-stimulated insulin secretion due to mitochondrial dysfunction and impaired ATP production, resulting in defective calcium-mediated insulin release.

C-Peptide Profile

Patients with T5DM typically exhibit detectable but reduced C-peptide levels, reflecting residual β-cell function. This profile distinguishes T5DM from T1DM (markedly low or absent C-peptide) and T2DM (normal or elevated levels due to insulin resistance).

Pancreatic Structural Abnormalities
In some cases, particularly those associated with fibrocalculous pancreatic diabetes (FCPD), imaging studies reveal pancreatic calcifications, ductal dilation, and fibrosis. These findings highlight the overlap between T5DM and pancreatogenic diabetes (type 3c diabetes), although their etiologies differ.

Clinical Characteristics
T5DM presents with a distinct clinical phenotype. Patients are typically young, underweight, and exhibit features of chronic malnutrition. Despite severe hyperglycemia, ketosis and diabetic ketoacidosis are uncommon, distinguishing T5DM from T1DM. From a biochemical perspective, patients lack pancreatic autoantibodies and demonstrate preserved insulin sensitivity. C-peptide levels are reduced but detectable, indicating partial β-cell function. These characteristics often lead to misdiagnosis as T1DM or atypical T2DM.

Therapeutic Outcomes
Patients with T5DM generally require lower insulin doses compared with T1DM, typically ranging from 0.3 to 0.5 units/kg/day. This reflects preserved insulin sensitivity and reduced glycogen stores, necessitating cautious titration to avoid hypoglycemia. A significant proportion of patients retain sufficient β-cell function to respond to oral antidiabetic drugs (OADs). Sulfonylureas are commonly used due to their insulin secretagogue effect, with approximately 40–50% of patients achieving glycemic control. Metformin may provide modest benefit, although its role is limited due to the absence of significant insulin resistance. Evidence for newer agents such as SGLT2 inhibitors and GLP-1 receptor agonists remains limited.

DISCUSSION
This review highlights that T5DM represents a distinct form of diabetes characterized primarily by insulin deficiency resulting from impaired pancreatic development associated with chronic undernutrition, rather than autoimmune destruction or insulin resistance. This unique pathophysiological profile challenges the traditional binary classification of diabetes and underscores the need for a more nuanced and inclusive framework. Misclassification of T5DM as either type 1 or type 2 diabetes has significant clinical consequences, as overestimation of insulin requirements may increase the risk of hypoglycemia, while under-recognition of residual β-cell function may limit the appropriate use of oral antidiabetic therapies. Therefore, accurate identification is essential to ensure individualized and effective management strategies.

From a global health perspective, T5DM predominantly affects populations in low- and middle-income countries (LMICs), where chronic undernutrition remains prevalent, reflecting a dual burden of communicable and non-communicable diseases. This intersection highlights the importance of integrated public health approaches that address both nutritional deficiencies and metabolic disorders. Therapeutically, management of T5DM should prioritize nutritional rehabilitation, cautious insulin titration, and selective use of oral agents based on residual β-cell function.

However, current evidence remains limited, and future research should focus on establishing standardized diagnostic criteria, identifying reliable biomarkers, and conducting well-designed clinical trials to determine optimal treatment strategies. Additionally, increasing awareness among clinicians is crucial to improve early recognition and appropriate management. While this review provides a comprehensive synthesis of current evidence, it is limited by its narrative design and the scarcity of high-quality studies, reflecting the ongoing underrecognition and underreporting of T5DM in the global literature.

CONCLUSION

Type 5 diabetes mellitus (T5DM) represents a distinct and underrecognized subtype of diabetes characterized by insulin deficiency secondary to chronic undernutrition and impaired pancreatic development, rather than autoimmune destruction or insulin resistance. Its clinical presentation typically involving young, lean individuals with preserved insulin sensitivity and detectable C-peptide levels differs substantially from both type 1 and type 2 diabetes, yet it is frequently misclassified due to the absence of standardized diagnostic criteria.

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