RGe ISSN: 2177-3246

TYPE 5 DIABETES MELLITUS: PATHOPHYSIOLOGY, B-CELL RECOVERY AND LOW GLYCAEMIC INDEX DIETARY MANAGEMENT

DIABETES MELLITUS TIPO 5: FISIOPATOLOGIA, RECUPERAÇÃO DAS CÉLULAS B E MANEJO DIETÉTICO COM BAIXO ÍNDICE GLICÊMICO

DIABETES MELLITUS TIPO 5: FISIOPATOLOGÍA, RECUPERACIÓN DE LAS CÉLULAS B Y MANEJO DIETÉTICO CON BAJO ÍNDICE GLUCÉMICO

10.56238/revgeov17n5-056

Kevin Oliver Dino[1], Pedro Henrique Lopes dos Santos[2], Thiago Vieira Klann[3], Camila Brito Felix[4], Giorge Fellipe Araújo Lopes[5]

ABSTRACT

Background: Type 5 diabetes mellitus (T5DM), officially recognized in 2025 by the International Diabetes Federation, represents a distinct diabetes phenotype associated with chronic undernutrition and low body mass index (BMI <18.5 kg/m²). T5DM affects approximately 15–25 million individuals globally, predominantly in South Asia, Sub-Saharan Africa, and resource-limited settings.

Objectives: To synthesize current evidence on (1) physiological changes during recovery from chronic undernutrition, (2) the capacity for pancreatic β-cell recovery after nutritional rehabilitation, and (3) dietary management strategies emphasizing low glycaemic index (GI) feeding patterns.

Methods: Narrative synthesis of clinical studies, experimental models, and systematic reviews (2016–2025, with selective inclusion of seminal earlier works) addressing malnutrition-related diabetes, pancreatic plasticity, and low-GI dietary interventions. Literature was searched in PubMed/MEDLINE, Scopus, and Web of Science. Search terms combined: (“type 5 diabetes” OR “malnutrition-related diabetes”) AND (“beta-cell recovery” OR “pancreatic plasticity”) AND (“low glycemic index” OR “nutritional rehabilitation”).

Results: Three main findings emerged: (1) Chronic malnutrition induces persistent metabolic adaptations (elevated NEFA, reduced BCAA, hormonal dysregulation) that persist beyond weight restoration; (2) Pancreatic β-cells demonstrate remarkable plasticity through four mechanisms: neogenesis from progenitor cells, proliferation, transdifferentiation of α-cells, and redifferentiation of dedifferentiated cells. A critical temporal window (3–6 months in

[1] Undergraduted student. Universidad Central del Paraguay. Orcid: 0000-0001-6119-2390
[2] Undergraduted student. Graduated in Nutrition. Universidad Central del Paraguay. Orcid: 0009-0007-9966-7671
[3] Undergraduted student. Universidad Central del Paraguay. Orcid: 0009-0005-2047-3512
[4] Undergraduted student. Graduated in Physical Education. Universidad Central del Paraguay. Orcid: 0009-0005-2714-9483
[5] Undergraduted student. Universidad Central del Paraguay. Orcid: 0009-0006-3963-5988

children, narrower in adults) exists for maximal recovery; (3) Low-GI dietary patterns reduce HbA1c by 0.3–0.5% and postprandial glycaemia by 20–30% in diabetes populations. Micronutrient repletion enhances β-cell recovery.

Conclusions: T5DM represents a potentially reversible diabetes phenotype when early, adequate nutritional rehabilitation is implemented. Gradual caloric reintroduction combined with micronutrient repletion and low-GI dietary patterns may optimize β-cell recovery.

Keywords: Type 5 Diabetes Mellitus. Malnutrition-Related Diabetes. B-Cell Recovery. Pancreatic Plasticity. Low Glycaemic Index. Nutritional Rehabilitation.

RESUMO

Introdução: O diabetes mellitus tipo 5 (DM5), oficialmente reconhecido em 2025 pela International Diabetes Federation, representa um fenótipo distinto de diabetes associado à desnutrição crônica e ao baixo índice de massa corporal (IMC <18,5 kg/m²). O DM5 afeta aproximadamente 15–25 milhões de indivíduos globalmente, predominantemente no Sul da Ásia, África Subsaariana e contextos com recursos limitados.

Objetivos: Sintetizar as evidências atuais sobre (1) alterações fisiológicas durante a recuperação da desnutrição crônica, (2) a capacidade de recuperação das células β pancreáticas após reabilitação nutricional e (3) estratégias de manejo dietético com ênfase em padrões alimentares de baixo índice glicêmico (IG).

Métodos: Síntese narrativa de estudos clínicos, modelos experimentais e revisões sistemáticas (2016–2025, com inclusão seletiva de trabalhos clássicos anteriores) abordando diabetes relacionado à desnutrição, plasticidade pancreática e intervenções dietéticas de baixo IG. A literatura foi pesquisada nas bases PubMed/MEDLINE, Scopus e Web of Science. Os termos de busca combinaram: (“type 5 diabetes” OR “malnutrition-related diabetes”) AND (“beta-cell recovery” OR “pancreatic plasticity”) AND (“low glycemic index” OR “nutritional rehabilitation”).

Resultados: Três principais achados emergiram: (1) A desnutrição crônica induz adaptações metabólicas persistentes (elevação de AGNE, redução de BCAA e desregulação hormonal) que permanecem além da restauração ponderal; (2) As células β pancreáticas demonstram notável plasticidade por meio de quatro mecanismos: neogênese a partir de células progenitoras, proliferação, transdiferenciação de células α e rediferenciação de células desdiferenciadas. Existe uma janela temporal crítica (3–6 meses em crianças, mais estreita em adultos) para recuperação máxima; (3) Padrões alimentares de baixo IG reduzem a HbA1c em 0,3–0,5% e a glicemia pós-prandial em 20–30% em populações diabéticas. A reposição de micronutrientes potencializa a recuperação das células β.

Conclusões: O DM5 representa um fenótipo de diabetes potencialmente reversível quando a reabilitação nutricional precoce e adequada é implementada. A reintrodução gradual de calorias combinada à reposição de micronutrientes e a padrões alimentares de baixo IG pode otimizar a recuperação das células β.

Palavras-chave: Diabetes Mellitus Tipo 5. Diabetes Relacionado à Desnutrição. Recuperação das Células β. Plasticidade Pancreática. Baixo Índice Glicêmico. Reabilitação Nutricional.

RESUMEN

Introducción: La diabetes mellitus tipo 5 (DM5), oficialmente reconocida en 2025 por la International Diabetes Federation, representa un fenotipo distinto de diabetes asociado con

desnutrición crónica y bajo índice de masa corporal (IMC <18,5 kg/m²). La DM5 afecta aproximadamente a 15–25 millones de personas en todo el mundo, predominantemente en el sur de Asia, África subsahariana y contextos con recursos limitados.

Objetivos: Sintetizar la evidencia actual sobre (1) los cambios fisiológicos durante la recuperación de la desnutrición crónica, (2) la capacidad de recuperación de las células β pancreáticas tras la rehabilitación nutricional y (3) las estrategias de manejo dietético con énfasis en patrones alimentarios de bajo índice glucémico (IG).

Métodos: Síntesis narrativa de estudios clínicos, modelos experimentales y revisiones sistemáticas (2016–2025, con inclusión selectiva de trabajos clásicos previos) relacionados con diabetes asociada a la desnutrición, plasticidad pancreática e intervenciones dietéticas de bajo IG. La literatura fue consultada en PubMed/MEDLINE, Scopus y Web of Science. Los términos de búsqueda combinaron: ("type 5 diabetes" OR "malnutrition-related diabetes") AND ("beta-cell recovery" OR "pancreatic plasticity") AND ("low glycemic index" OR "nutritional rehabilitation").

Resultados: Surgieron tres hallazgos principales: (1) La desnutrición crónica induce adaptaciones metabólicas persistentes (elevación de AGNE, reducción de BCAA y desregulación hormonal) que persisten más allá de la restauración del peso corporal; (2) Las células β pancreáticas demuestran una notable plasticidad mediante cuatro mecanismos: neogénesis a partir de células progenitoras, proliferación, transdiferenciación de células α y rediferenciación de células desdiferenciadas. Existe una ventana temporal crítica (3–6 meses en niños, más estrecha en adultos) para la recuperación máxima; (3) Los patrones alimentarios de bajo IG reducen la HbA1c en 0,3–0,5% y la glucemia posprandial en 20–30% en poblaciones diabéticas. La reposición de micronutrientes potencia la recuperación de las células β.

Conclusiones: La DM5 representa un fenotipo de diabetes potencialmente reversible cuando se implementa una rehabilitación nutricional temprana y adecuada. La reintroducción gradual de calorías combinada con la reposición de micronutrientes y patrones alimentarios de bajo IG puede optimizar la recuperación de las células β.

Palabras clave: Diabetes Mellitus Tipo 5. Diabetes Relacionada con la Desnutrición. Recuperación de las Células β. Plasticidad Pancreática. Bajo Índice Glucémico. Rehabilitación Nutricional.

1 INTRODUCTION

In 2025, malnutrition-related diabetes was officially recognized as type 5 diabetes mellitus (T5DM), consolidating the understanding that hyperglycaemia associated with chronic undernutrition represents a distinct metabolic phenotype, rather than merely a variation of type 2 diabetes or a transient condition secondary to weight loss (1,2). Recent technical documents from the International Diabetes Federation (IDF) established specific diagnostic criteria for this condition, separating it from other diabetic etiologies.

Prolonged undernutrition imposes significant metabolic stress on the endocrine pancreas (3). Experimental and clinical evidence demonstrates that energy and protein restriction impair insulin synthesis and secretion, alter the incretin response, and promote oxidative and inflammatory stress, contributing to β-cell dysfunction (3–5). For decades, this pancreatic damage was assumed to be predominantly irreversible.

However, recent studies challenge this paradigm by demonstrating that refeeding constitutes a distinct physiological phase characterized by hormonal and metabolic adaptations that may result in progressive improvement in glucose tolerance and insulin secretion, particularly when intervention occurs in earlier stages of the disease (3,6). Experimental models indicate that the pancreas retains a relevant degree of functional plasticity, allowing partial recovery when exposed to favorable nutritional conditions (6–8).

Micronutrient deficiency emerges as a central factor both in the pathophysiology of T5DM and in the response to nutritional rehabilitation. Minerals such as zinc, magnesium, and chromium, as well as antioxidant vitamins, play fundamental roles in maintaining β-cell structural integrity, insulin biosynthesis, and signaling. Correction of these deficiencies may attenuate oxidative stress and favor functional pancreatic recovery (9–12).

In this context, dietary strategies based on low glycaemic index (GI) foods assume particular relevance. Low-GI diets reduce postprandial glycaemic spikes, decrease secretory overload on vulnerable β-cells, and contribute to greater metabolic stability during the refeeding phase. When combined with adequate micronutrient repletion, these strategies may create a more favorable metabolic environment for pancreatic recovery and glycaemic control in T5DM (13–15).

This article aims to synthesize recent evidence on physiological alterations in malnutrition, the recovery capacity of pancreatic β-cells, and the rationale for using low-GI diets in the management of T5DM.

2 METHODS

This narrative review was conducted in accordance with methodological rigor principles commonly applied in integrative reviews, with the objective of synthesizing recent evidence related to: (1) physiological mechanisms involved in recovery from malnutrition and their impact on glucose homeostasis; (2) regenerative potential and functional recovery of pancreatic β-cells; and (3) the effectiveness of low glycaemic index (GI) dietary patterns in the management of type 5 diabetes mellitus (T5DM).

2.1 DATA SOURCES AND SEARCH STRATEGY

The literature was searched in PubMed/MEDLINE, Scopus, Web of Science, ScienceDirect, and Google Scholar. The search strategy combined controlled and free-text terms, such as: “type 5 diabetes” AND “beta-cell recovery”; “malnutrition-related diabetes” AND “refeeding syndrome”; “low glycemic index” AND “insulin secretion.” Studies published between 2016 and 2025 were prioritized.

2.2 INCLUSION CRITERIA

Clinical, experimental, and translational studies evaluating the physiology of malnutrition, β-cell regeneration, and low-GI diets were included. Official IDF documents and relevant systematic reviews were also considered.

2.3 EXCLUSION CRITERIA

Articles without full-text access, studies focused exclusively on type 1 or type 2 diabetes without relation to malnutrition, and studies that did not report relevant glycaemic outcomes were excluded.

2.4 SELECTION PROCESS

Screening was conducted in two stages: (1) title and abstract screening to assess adherence to scope; and (2) full-text review to confirm eligibility. Discrepancies were resolved by consensus between two independent reviewers. For each included study, the following data were extracted: study type, population, objectives, methods, main findings, and limitations.

2.5 DATA SYNTHESIS

Due to heterogeneity in study designs (animal models, cellular studies, reviews, and clinical trials), a structured narrative synthesis was adopted. Results were organized into

three thematic axes: physiological alterations in malnutrition and recovery; pancreatic β-cell recovery and regeneration; and effects of low-GI diets on glycaemic control. The analysis sought to integrate biological and physiological foundations with clinical evidence and implications for managing patients with T5DM.

3 RESULTS

3.1 PHYSIOLOGICAL ALTERATIONS INDUCED BY CHRONIC MALNUTRITION

Chronic malnutrition and severe acute malnutrition (SAM) trigger profound physiological adaptations involving endocrine, metabolic, and cellular alterations that directly impact glucose homeostasis and pancreatic function. These adaptations persist even after weight restoration and constitute one of the pillars of the pathophysiology of T5DM (1,3).

3.1.1 Metabolic alterations and metabolic profile

Metabolic analyses in individuals with SAM reveal profound alterations characterized by significant elevations in non-esterified fatty acids (NEFA), ketone bodies, and acylcarnitines, concomitant with marked reductions in branched-chain amino acids (BCAA), insulin, leptin, and IGF-1 (16,17). These alterations reflect a pronounced catabolic state, with intense lipolysis and preferential fatty acid oxidation, while compensatory mechanisms preserve euglycaemia in many cases (3,16). During nutritional rehabilitation, partial normalization of these parameters is observed, although recovery kinetics vary among metabolites (16,18).

The role of essential amino acids, particularly leucine, isoleucine, and valine, in activating the mTORC1 (mechanistic target of rapamycin complex 1) pathway has been recognized as central in the pathogenesis of growth retardation and persistent metabolic alterations observed in children with a history of severe malnutrition (17). Chronic BCAA depletion compromises not only muscle protein synthesis but also pancreatic anabolic signaling, contributing to long-term β-cell dysfunction (17,18).

Long-term evidence in SAM survivors indicates that early-life exposure to malnutrition is associated with altered metabolic profiles in adulthood, including increased presence of metabolites related to glycolysis, the urea cycle, and branched-chain amino acids, suggesting higher risk of glucose intolerance and other late metabolic complications (4,19). These data support the notion that severe malnutrition exerts lasting effects on energy metabolism, increasing vulnerability to glycaemic dysfunction even after weight recovery (4,19,20).

3.1.2 Hormonal dysfunction and endocrine axes

Hormonal changes in SAM include sustained reductions in insulin and adipokines such as leptin and adiponectin, while counter-regulatory hormones such as growth hormone (GH) and cortisol remain elevated, contributing to insulin resistance and metabolic redistribution of energy substrates (16,21,22). These adaptations demonstrate that glycaemic dysfunction in malnutrition does not arise solely from glucose scarcity, but rather from a multifactorial metabolic repositioning involving lipolysis, proteolysis, and compensatory hormonal alterations (16,21).

Alteration of the GH–IGF-1 axis is particularly relevant. While GH levels are elevated, IGF-1 levels are characteristically reduced, configuring a state of GH resistance that reflects adaptation to energy deprivation (16,22). This dissociation contributes to persistent protein catabolism and compromises anabolic processes essential for pancreatic recovery (22).

Studies in anorexia nervosa models, which share pathophysiological aspects with severe malnutrition, demonstrate profound alterations in bone metabolism and in the reproductive and thyroid axes, mediated by chronic hypoleptinemia and hypercortisolism (22). These multisystem endocrine alterations highlight that malnutrition induces not merely local energy deprivation, but a comprehensive neuroendocrine reorganization with long-lasting metabolic consequences.

3.1.3 Pancreatic impact: endocrine and exocrine dysfunction

From a pancreatic perspective, prolonged energy and protein restriction reduces insulin secretion through mechanisms including mitochondrial dysfunction, oxidative stress, and epigenetic alterations in genes critical for β-cell function, such as PDX1, MAFA, and NKX6.1 (3–5,23). As malnutrition progresses, the pancreas exhibits not only reduced basal secretory capacity but also a blunted secretory response to glycaemic stimulation — a pathophysiological pattern distinct from that observeEpigenetic modifications induced by early malnutrition, particularly alterations in DNA methylation patterns in genes regulating pancreatic development, constitute molecular mechanisms through which nutritional deprivation during gestation and early childhood programs permanent metabolic dysfunction (5,23). Experimental studies demonstrate that maternal protein restriction induces hypomethylation of promoters of insulin-suppressing genes and hypermethylation of genes involved in β-cell differentiation, alterations that persist into adulthood and increase susceptibility to diabetes (5,23).

Prolonged malnutrition also severely compromises exocrine pancreatic function, with reduced secretion of digestive enzymes (lipase, amylase, trypsin) and consequent nutrient

malabsorption, which may persist even after nutritional restoration, worsening malabsorption and perpetuating essential metabolic deficits (19,24). This combination of endocrine and exocrine pancreatic dysfunction partially explains the complexity and persistence of metabolic abnormalities observed in T5DM (19,24).

Studies reveal that children with SAM exhibit elevated fecal elastase-1 and reduced chymotrypsin, markers of exocrine pancreatic insufficiency, which correlate inversely with weight gain during rehabilitation (17,20). Exocrine dysfunction compromises absorption of fat-soluble micronutrients and proteins, creating a vicious cycle that hinders nutritional and pancreatic recovery (17,20,24).

3.1.4 Long-term metabolic consequences

Another central pathophysiological aspect is long-term metabolic programming induced by early malnutrition. Exposure to nutritional restriction during critical developmental periods establishes a new "set point" for glucose regulation that may persist for decades (4,5,20,23). Animal models demonstrate that maternal protein restriction results in offspring with impaired glucose tolerance, insulin resistance, and reduced β-cell mass in adulthood, even when postnatal nutrition is adequate (20).

In humans, cohort evidence from SAM survivors shows that, decades after weight recovery, these individuals maintain higher risk of glucose intolerance, early-onset type 2 diabetes, and metabolic syndrome, even when adult BMI is normal (4,19). These observations reinforce the concept that T5DM does not merely represent a mechanical consequence of low body mass, but rather the result of long-lasting metabolic and epigenetic alterations induced by prior malnutrition (1,4,5,23).

Increased intestinal permeability, characteristic of severe malnutrition (especially in kwashiorkor), contributes to bacterial translocation, chronic endotoxemia, and low-grade systemic inflammation, which may perpetuate insulin resistance and β-cell dysfunction even after nutritional recovery (21). This metabolic endotoxemia represents yet another mechanism by which malnutrition programs persistent metabolic dysfunction (21).

Collectively, the metabolic and endocrine adaptations observed in chronic malnutrition constitute a state of profound physiological reorganization, in which glucose homeostasis is maintained at minimal levels through alternative energy production and utilization mechanisms. This multifactorial state of metabolic and endocrinological dysfunction provides a solid basis for characterizing T5DM not merely as hyperglycaemia associated with weight loss, but as a distinct pathophysiological phenotype marked by prolonged adaptive responses and enduring endocrine reorganization (1,3–5,16–24).

3.2 PHYSIOLOGICAL ALTERATIONS DURING REFEEDING AND NUTRITIONAL REHABILITATION

The refeeding phase following severe malnutrition represents a unique and metabolically complex physiological period, characterized by a rapid transition from a catabolic state to an intensely anabolic environment. Although essential for recovery, this transition imposes significant metabolic challenges and clinical risks that require careful management, particularly regarding glycaemic homeostasis and pancreatic function (25–28).

3.2.1 Refeeding Syndrome: Metabolic Risks and Management

Refeeding syndrome constitutes the most feared complication during nutritional rehabilitation, characterized by severe electrolyte disturbances (hypophosphatemia, hypokalemia, hypomagnesemia), cardiovascular overload, rebound hyperglycaemia, and multiple organ dysfunction (26–28). Its incidence ranges from 25% to 80% among patients with severe malnutrition undergoing refeeding, depending on the severity of baseline malnutrition and the rate of caloric reintroduction (27).

The pathophysiology of refeeding syndrome involves an abrupt transition from oxidative fat metabolism to anaerobic carbohydrate metabolism, leading to a sudden increase in insulin secretion (26,28). This insulin surge promotes rapid cellular uptake of glucose, phosphate, potassium, and magnesium, resulting in serum depletion of these electrolytes, with potentially fatal consequences: rhabdomyolysis, cardiac arrhythmias, respiratory failure, and encephalopathy (26–28).

Prospective studies demonstrate that hypophosphatemia (serum phosphate <0.6 mmol/L) occurs in 34% of patients within the first 72 hours of refeeding and is associated with a threefold increase in mortality (27). Hypophosphatemia compromises ATP synthesis, which is essential for all cellular processes, including insulin secretion by pancreatic β-cells (27,28).

Current guidelines recommend a conservative initiation of 10–20 kcal/kg/day, with gradual progression over 5–7 days, combined with prophylactic supplementation of thiamine (100–300 mg/day), phosphate, potassium, and magnesium, alongside rigorous laboratory monitoring during the first two weeks (25,26,28). In patients with BMI <14 kg/m² or prolonged fasting (>10 days), caloric progression should be even more cautious, starting at 5–10 kcal/kg/day (25,28).

3.2.2 Anabolic Hormonal Response During Refeeding

Refeeding triggers a dramatic shift in the hormonal profile, characterized by rapid increases in insulin, IGF-1, and leptin, accompanied by reductions in counter-regulatory

hormones (cortisol, GH, glucagon) (16,25). Although essential for anabolism, this hormonal reversal may be excessively abrupt and generate significant metabolic instability (16,25).

Studies in children with SAM demonstrate that insulin levels increase three- to fivefold within the first 48–72 hours of refeeding, whereas IGF-1 and leptin normalize progressively over 2–4 weeks (16). This hormonal restoration is not uniform: while insulin rises early, insulin sensitivity frequently remains impaired during the first weeks, creating a transient state of hyperinsulinaemia with relative insulin resistance (16,25).

Leptin, virtually undetectable in severe malnutrition, increases proportionally with recovery of adipose mass and plays a critical regulatory role in normalizing the hypothalamic–pituitary–gonadal axis and modulating insulin sensitivity (22). The kinetics of leptin recovery correlate with improved glucose tolerance and predict successful nutritional rehabilitation (16,22).

IGF-1, profoundly suppressed during malnutrition, increases progressively during refeeding and serves as a sensitive marker of nutritional adequacy and protein anabolism (16,22). Normalization of the GH–IGF-1 axis is essential not only for linear growth in children but also for proliferation and differentiation of pancreatic β-cells (22,29).

3.2.3 Restoration of Mitochondrial Function and Energy Metabolism

Severe malnutrition profoundly impairs mitochondrial function, with reduced mitochondrial density, altered fission–fusion dynamics, and decreased oxidative phosphorylation capacity (3,18). Adequate refeeding promotes progressive restoration of mitochondrial biogenesis, mediated by activation of PGC-1α (peroxisome proliferator-activated receptor-gamma coactivator 1-alpha), AMPK (AMP-activated protein kinase), and nutrient-dependent signaling pathways (18).

In pancreatic β-cells, recovery of mitochondrial function is particularly critical, since mitochondrial glucose metabolism constitutes the primary signal for insulin secretion (3,29,30). Experimental studies demonstrate that refeeding with nutritionally complete diets restores mitochondrial membrane potential, increases ATP production, and normalizes the ATP/ADP ratio in β-cells, thereby improving glucose-stimulated insulin secretion (3,30).

Supplementation with mitochondrial cofactors (thiamine, riboflavin, niacin, coenzyme Q10) during refeeding may accelerate restoration of mitochondrial function and improve cellular energetic efficiency, although specific clinical evidence in T5DM remains limited (9,18).

3.2.4 Critical Temporal Window for Intervention

Growing evidence suggests the existence of a "window of opportunity" during refeeding, in which specific nutritional interventions may maximize functional pancreatic recovery and minimize long-term metabolic sequelae (6,7,24,25). This window appears broader in children and adolescents, whose pancreatic plasticity is greater compared to adults with prolonged chronic malnutrition (6,24,31,32).

Experimental studies demonstrate that cyclic fasting-mimicking diets, characterized by intermittent caloric restriction followed by refeeding, promote activation of Ngn3+ pancreatic progenitor cells and regeneration of functional β-cells, reversing diabetes in murine models (7). Although direct applicability of these findings to human T5DM remains uncertain, such studies reinforce the concept that properly conducted refeeding may positively modulate pancreatic recovery (7,31,32).

Clinical cohort data in children with SAM indicate that those subjected to gradual refeeding protocols, with controlled caloric progression and adequate mineral supplementation, demonstrate better recovery of pancreatic function (assessed by C-peptide and insulin secretion indices) compared to those refed rapidly or irregularly (24,25). These findings emphasize that not only the quantity, but also the quality and rate of nutrient introduction influence metabolic recovery (24–28).

3.2.5 Nutritional Modulation of Glycaemic Recovery

The macronutrient composition of the refeeding diet significantly impacts glycaemic stability and pancreatic recovery. Diets high in refined carbohydrates and with a high glycaemic index, although rapidly providing energy, impose excessive secretory burden on fragile β-cells and may perpetuate pancreatic dysfunction (13–15).

In contrast, refeeding strategies based on low-glycaemic-index complex carbohydrates, high-quality proteins, and unsaturated lipids promote a more stable glycaemic response, reduce postprandial insulin peaks, and create a metabolic environment more conducive to β-cell recovery (13–15). Meta-analyses in diabetic populations demonstrate that low-GI diets reduce HbA1c by 0.3–0.5% and decrease postprandial glycaemic excursions by 20–30%, effects that may be particularly beneficial in the context of T5DM (14,15,33).

Supplementation with micronutrients essential to pancreatic function (zinc, magnesium, chromium, B vitamins, antioxidant vitamins) should be initiated early and maintained throughout the rehabilitation phase, aiming to correct chronic deficiencies and optimize the recovery capacity of β-cells (9–12).

In summary, refeeding after severe malnutrition constitutes a critical physiological period that presents both significant metabolic risks and unique opportunities for positive modulation of pancreatic recovery. Proper management of this phase — including controlled caloric progression, prevention of refeeding syndrome, optimization of nutritional composition, and micronutrient supplementation — represents a fundamental strategy to maximize functional β-cell recovery and improve long-term glycaemic outcomes in patients with T5DM (6,7,24–28,31,32).

3.3 STRUCTURAL AND FUNCTIONAL RECOVERY OF PANCREATIC B-CELLS

The capacity for recovery of pancreatic β-cells after severe malnutrition represents one of the most promising and least understood aspects of T5DM pathophysiology. Evidence accumulated over recent decades challenges the historical dogma of irreversibility of malnutrition-induced pancreatic dysfunction, demonstrating remarkable cellular plasticity and multiple mechanisms of regeneration and functional recovery (8,31,32,34).

3.3.1 Mechanisms of β-Cell Regeneration: Neogenesis, Proliferation, and Transdifferentiation

The adult pancreas retains residual regenerative capacity through three main mechanisms: (1) neogenesis from ductal progenitor cells; (2) proliferation (replication) of pre-existing β-cells; and (3) transdifferentiation of non-β islet cells (α, δ, and PP cells) into functional β-cells (8,31,32,34).

Pancreatic neogenesis: Studies demonstrate that Ngn3+ (neurogenin-3 positive) progenitor cells residing in pancreatic ducts can be activated in response to injury or metabolic deprivation, differentiating into new insulin-producing β-cells (7,31). This process, highly active during embryonic development, remains latent in adulthood but may be reactivated under specific conditions, including prolonged fasting followed by refeeding (7,31). Experiments using fasting-mimicking diets have shown that cycles of severe caloric restriction (3–5 days) followed by refeeding activate Ngn3 expression, promote differentiation of ductal progenitor cells, and increase β-cell mass by up to 40% in murine models of type 1 and type 2 diabetes (7)

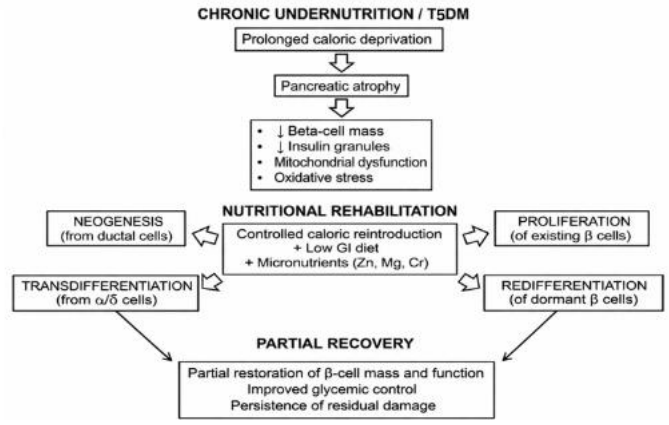
β-cell proliferation: Replication of pre-existing β-cells constitutes the predominant mechanism of β-cell mass expansion in the adult pancreas (32,34). The basal proliferation rate of human β-cells is extremely low (<1% per year in adults), but may increase significantly in response to metabolic demands such as pregnancy, obesity, and potentially refeeding after malnutrition (32,34). Proliferative signals include glucose, amino acids, incretins (GLP-1,

GIP), growth factors (IGF-1, HGF), and specific cytokines (29,32,34). During refeeding, elevation of these signals may stimulate compensatory proliferation, although the magnitude and duration of this effect in humans with T5DM remain insufficiently characterized (16,32,34)

Cellular transdifferentiation: Recent findings demonstrate that pancreatic α-cells (glucagon-producing cells) can transdifferentiate into functional β-cells in response to severe β-cell injury or experimental ablation (31,34). This process involves epigenetic reprogramming and reactivation of β-cell transcription factors (PDX1, MAFA, NKX6.1) previously silenced (31,34). Experimental studies in β-cell ablation models show that up to 30% of α-cells may convert into β-cells over weeks to months, contributing to significant functional restoration (34). Although the relevance of this mechanism in human malnutrition remains speculative, the observation of intense cellular plasticity within pancreatic islets opens promising therapeutic perspectives (31,34).

Figure 1

Summarizes the pathophysiology of T5DM and the four cellular mechanisms of partial β-cell recovery during adequate nutritional rehabilitation



3.3.2 Dedifferentiation and redifferentiation: dysfunction versus cell loss

Recent paradigms suggest that β-cell dysfunction in diabetes does not result exclusively from cell death (apoptosis), but frequently from dedifferentiation — a process by which mature β-cells lose markers of cellular identity and secretory function without actual cell death (30,34). This concept is particularly relevant to T5DM, as it implies that dysfunctional β-cells may potentially be "rescued" through redifferentiation (30,34).

Studies in type 2 diabetes models demonstrate that β-cells chronically exposed to hyperglycaemia and lipotoxicity undergo dedifferentiation, with reduced expression of essential genes (INS, PDX1, MAFA, NKX6.1, GLUT2) and reversion to a progenitor-like

phenotype (30,34). Crucially, these dedifferentiated cells are not dead, but rather "dormant," and may be redifferentiated upon restoration of a favorable metabolic environment (30,34).

In severe malnutrition, similar mechanisms may operate: β-cells chronically exposed to energy deficiency, hypoinsulinemia, and deprivation of trophic signals (IGF-1, amino acids) may dedifferentiate as an adaptive survival mechanism (3,30,34). During refeeding, anabolic signals (glucose, amino acids, insulin, IGF-1) may promote redifferentiation of these cells, restoring β-cell gene expression and secretory function (16,30,34).

This hypothesis is supported by clinical observations in patients with T5DM who demonstrate substantial improvement in insulin secretion (assessed by C-peptide) after months of adequate nutritional rehabilitation, without evidence of significant expansion of total β-cell mass (suggesting functional recovery of pre-existing cells rather than neogenesis) (24).

3.3.3 Role of the islet microenvironment and trophic factors

The pancreatic islet microenvironment exerts a critical influence on β-cell survival, function, and proliferation (29). Key components include endothelial cells (vascularization), resident macrophages, extracellular matrix, supporting cells (α, δ, PP), and autonomic innervation (29).

Severe malnutrition compromises pancreatic vascularization, reduces capillary density within islets, and induces extracellular matrix atrophy, creating a hostile environment for β-cell function (3,29). Refeeding promotes progressive revascularization, mediated by VEGF (vascular endothelial growth factor) and other angiogenic factors, restoring adequate oxygen and nutrient supply to β-cells (29).

Specific trophic factors that modulate β-cell recovery include:

IGF-1: promotes β-cell proliferation, survival, and secretory function (16,22,29). Its normalization during refeeding is critical for pancreatic recovery.

GLP-1 (glucagon-like peptide-1): an incretin hormone that stimulates glucose-dependent insulin secretion, inhibits β-cell apoptosis, and may promote neogenesis and proliferation (29,32). Patients with severe malnutrition exhibit an attenuated incretin response, which progressively improves during rehabilitation (19).

Amino acids (particularly leucine): activate mTORC1, promoting protein synthesis, cellular proliferation, and mitochondrial function in β-cells (17,29). Supplementation with branched-chain amino acids during refeeding may potentiate pancreatic recovery (17).

Zinc: essential for insulin synthesis, storage, and secretion. Zinc deficiency is closely associated with β-cell dysfunction, and its repletion improves secretory function (9–11).

3.3.4 Temporal window and reversibility: clinical and experimental evidence

The capacity for β-cell recovery is not unlimited and appears to depend critically on two factors: (1) duration and severity of malnutrition; and (2) timing and adequacy of nutritional intervention (4,6,24,31,32).

Experimental studies in rodents demonstrate that protein restriction during gestation and lactation results in offspring with reduced β-cell mass, impaired secretory function, and predisposition to diabetes in adulthood (20). However, if adequate nutritional intervention is instituted during the early post-weaning period, significant recovery of β-cell mass and function occurs, with normalization of glucose tolerance (6,20). In contrast, if malnutrition persists into adulthood, recovery capacity is drastically reduced, suggesting the existence of "critical periods" of pancreatic plasticity (20,31).

In humans, evidence from pediatric cohorts suggests that children with severe acute malnutrition (SAM) treated adequately before 24 months of age exhibit better pancreatic function recovery (assessed by C-peptide curves during OGTT) compared to those treated later (24). Long-term follow-up studies (10–20 years) show that although most survivors of childhood SAM maintain suboptimal β-cell function, approximately 30–40% fully normalize glucose tolerance in adulthood, indicating substantial recovery capacity in a significant subgroup (19,24).

Data in adults are more limited but suggest that even in adults with chronic malnutrition, nutritional rehabilitation may promote partial functional improvement of β cells, although complete normalization is rare (3,24). The magnitude of recovery correlates inversely with duration of malnutrition and presence of comorbidities (HIV, tuberculosis, liver disease) (24).

3.3.5 Clinical evidence and therapeutic perspectives

The demonstration of β-cell plasticity in experimental models has motivated investigation into therapeutic strategies applicable to humans with T5DM. Although specific clinical trials remain limited, preliminary evidence suggests that nutritional and pharmacological interventions may positively modulate pancreatic recovery during nutritional rehabilitation (6,24,25).

Observational studies in cohorts of children with SAM show that refeeding protocols incorporating gradual caloric progression, low–glycemic index complex carbohydrates, and adequate mineral supplementation are associated with better recovery of insulin secretion (assessed by fasting and post-OGTT C-peptide) compared to conventional protocols (24,25). Although these data are observational and do not allow definitive causal inferences, they

suggest that the qualitative composition of the refeeding diet may influence pancreatic outcomes (24,25).

Experimental pharmacological interventions include GLP-1 receptor agonists (exenatide, liraglutide) and DPP-4 inhibitors (sitagliptin, vildagliptin), which in type 2 diabetes contexts demonstrate protective effects on β-cells, including reduction of apoptosis, stimulation of proliferation, and possible promotion of neogenesis (29,32). However, the use of these agents in T5DM has not been systematically investigated, and their applicability remains speculative, particularly considering the distinct pathophysiological profile (primary β-cell dysfunction without significant insulin resistance) and issues of cost and access in regions where T5DM is prevalent (1,3,29,32).

Antioxidants (N-acetylcysteine, alpha-lipoic acid, vitamins C and E) have been proposed as adjuvants to reduce oxidative stress and provide mitochondrial protection during refeeding (9). Although the biological rationale is sound, clinical evidence of benefit in T5DM is insufficient, and priority should be given to optimization of essential micronutrients through diet and conventional oral supplementation (9–12).

In summary, recovery of pancreatic β-cells after severe malnutrition is biologically plausible and partially documented in experimental and observational studies. The magnitude of recovery depends critically on early intervention, adequacy of nutritional rehabilitation, and optimization of nutritional trophic factors. Specific therapeutic strategies to potentiate β-cell recovery in T5DM remain investigational and represent a priority for future research (6–12,24,31,32,34).

3.4 NUTRITIONAL MANAGEMENT OF T5DM: LOW–GLYCEMIC INDEX DIETS AND MICRONUTRIENT SUPPLEMENTATION

Nutritional management of T5DM presents unique challenges requiring an integrated approach that combines adequate energy intake for weight recovery with strategies that minimize metabolic overload on fragile β-cells. In this context, diets based on low-glycaemic-index (GI) foods, combined with repletion of micronutrients essential for pancreatic function, emerge as a rational strategy grounded in solid pathophysiological principles (3,9,13–15).

3.4.1 Physiological foundations: glycemic index and β-cell function

The glycaemic index quantifies the rate and magnitude of blood glucose elevation following ingestion of a carbohydrate-containing food (14,15). Low-GI foods (GI <55) promote slower intestinal glucose absorption due to higher soluble fiber content, resistant starch structure, and more complex food matrix, resulting in a more stable postprandial glycaemic

response, with a 30–50% lower glycaemic peak and a 20–30% reduction in glycaemic area under the curve compared to high-GI foods (14,15,35,36).

This glycaemic stability reduces secretory demand on β-cells, decreases exposure to glucotoxicity, and attenuates glycaemic oscillations that may perpetuate pancreatic dysfunction (14,15). Beyond acute effects, chronically low-GI diets promote sustained improvement in insulin sensitivity, reduction in systemic inflammation, and attenuation of oxidative stress — all factors that favor preservation and recovery of β-cell function (14,15,35,36). Mechanistic studies demonstrate that low-GI diets favorably modulate incretin secretion (GLP-1 and GIP), hormones that potentiate glucose-dependent insulin secretion and exert trophic effects on β-cells (14,29).

Meta-analyses in type 2 diabetes show that low-GI diets reduce HbA1c by 0.3–0.5% and decrease postprandial glycaemic excursions by 20–30% (14,15,33,35,36). Although direct extrapolation to T5DM should be cautious due to pathophysiological differences, β-cell protective mechanisms are biologically relevant in both contexts (1,3,14,15).

3.4.2 Specific challenges and practical considerations in T5DM

Implementation of low-GI dietary strategies in patients with T5DM faces multidimensional challenges (1,24,25):

Nutritional challenges: Patients with severe malnutrition require substantially increased caloric intake (30–50% above standard recommendations) for weight recovery (25,26). Many low-GI foods have relatively low energy density, requiring careful selection of low-GI foods with adequate caloric density and caloric enrichment strategies (addition of vegetable oils, nuts, avocado, full-fat dairy) (13,14). Additionally, patients with SAM frequently present with intestinal mucosal atrophy, exocrine pancreatic insufficiency, and gastrointestinal dysmotility, resulting in malabsorption and initial intolerance to high-fiber foods, requiring gradual introduction and appropriate food processing (19,21,24).

Socioeconomic challenges: T5DM is prevalent predominantly in low-income regions where availability of low-GI foods may be limited and economically inaccessible (1,24). Food preferences are strongly influenced by cultural context, and staple foods in many such regions are predominantly refined high-GI carbohydrates (white rice, refined maize, white flours), requiring culturally sensitive nutrition education strategies (1,24). Effective implementation requires specialized knowledge often unavailable in low-resource settings, necessitating community-based nutrition programs and use of community health workers (24).

Clinical heterogeneity: T5DM is not a homogeneous entity. Patients vary in age, duration and severity of prior malnutrition, presence of comorbidities, degree of pancreatic dysfunction, and socioeconomic context, requiring individualized nutritional approaches (1,3,24). The acute rehabilitation phase (first 8–12 weeks) has priorities distinct from long-term maintenance, and nutritional strategies must evolve across these phases (24,25).

3.4.3 Conceptual proposal for a phased nutritional approach

Based on extrapolation from evidence derived from studies on severe acute malnutrition, refeeding syndrome, and type 2 diabetes, and considering the pathophysiological plausibility of nutritional interventions in the context of T5DM, a conceptual phased nutritional management approach is proposed, combining principles of low glycaemic index, micronutrient supplementation, and controlled caloric progression (9–15,24–28,33,35,36). Importantly, this proposal has not been specifically validated in patients with T5DM through randomized clinical trials and represents a synthesis of therapeutic principles grounded in pathophysiologically related conditions, as presented in Table 1.

Table 1

Conceptual proposal for a phased nutritional approach to type 5 diabetes mellitus: elements based on indirect evidence and pathophysiological principles (requires prospective clinical validation)

Phase / Period	Therapeutic Objectives	Energy Adequacy and Macronutrients	Carbohydrate Quality (GI and Fiber)	Micronutrients	Suggested Monitoring
Phase 1: Initial stabilization (Weeks 1–2)	• Prevent refeeding sydrome • Gradual and safe caloric reintroduction • Metabolic and electrolyte stabilization[25,26,28]	**Energy intake:** • Conservative initiation (10-15 kcal/kg/day) • If severe malnutrition (BMI <14 kg/m²): more cautious start (5-10	**Glycaemic index:** • Preferences for moderate GI (55-69) • Examples: Sweet potato, parboiled rice, oats • Combine with proteins/lipids to attenuate	**Prophylaxis (reefeding syndrome):** • Thiamine: 100-300 mg/day • Phosphate, potassium, magnesium:	• Body weight • Serum electrolytes (specially during first 5-7 days) • Blood

Phase / Period	Therapeutic Objectives	Energy Adequacy and Macronutrients	Carbohydrate Quality (GI and Fiber)	Micronutrients	Suggested Monitoring
		kcal/kg/dia) • Individualized gradual progression • Fractionation into 6-8 smalls meals[25,26,28] **Distribution:** • CHO: 45-50% of total energy intake • PTN: 15-20% of total energy intake • LIP: 30-35% of total energy intake [25,26,28]	glycemic response[14,25] **Dietary fiber:** • Gradual and cautious reintroduction • Considering gastrointestinal tolerance and exocrine pancreatic function • Prioritize solube, well-tolerated forms (oats, ripe banana) • *No specific quantitative evidence available for T5DM: absence*[37,38]	replace according to identified deficits[26,28] **Pancreatic support:** • Zinc, magnesium, multivitamin • Individualized dosing based on nutritional assessment[9-11]	glucose (when avaiable) • Clinical signs of intolerance[26,27]
Phase 2: Intensification (weeks 3-8)	• Full energy adequacy • Promotion of consistent weight gain • Progressive transition to a low-GI pattern • Optimization of the metabolic environment for β-cell recovery[25]	**Energy intake:** • Individualized adequacy (typically 35-50 kcal/kg/day) • Fractionation into 5-6 meals[7,15,25] **Distribution:** • CHO: 50-55% of total energy intake • PTN: 15-20% of total energy	**Glycemic index:** • **Progressive transition to low GI (<55)** • Suggested foods: whole legumes, minimally processed whole grains, sweet potato, whole fruits, low-fat dairy[13–15] **Practical strategies:** • Food substitutions (white rice →	**Sustained repletion:** • Zinc, magnesium, chromium • Antioxidants (vitamins C and E, selenium) • Omega-3 • Multivitamin • Doses and	• Weight (weekly) • Electrolytes (first 4 weeks) • Blood glucose • HbA1c, C-peptide (after 8–12 weeks, if available)[24]

Phase / Period	Therapeutic Objectives	Energy Adequacy and Macronutrients	Carbohydrate Quality (GI and Fiber)	Micronutrients	Suggested Monitoring
		intake (1,5-2,0 g/kg/day), prioritizing high biological value • LIP: 30-35% of total energy intake (emphasis on unsaturated fats)[7,15,25]	parboiled; white bread → whole grain) • Culinary techniques (soaking legumes; cooling cooked grains to increase resistant starch) • Addition of organic acids (vinegar, lemon) • Inclusion of non-starchy vegetables[14] **Dietary fiber:** • Gradual increase according to tolerance • Combination of soluble and insoluble sources • Guidance based on general diabetes guidelines (ADA: ≥14 g/1000 kcal; IDF: ≥35 g/day), not specific for T5DM	duration individualized (typically 3–6 months)[9-12]	
Phase 3: Consolidation and maintenance (>8 weeks)	• Consolidation of weight recovery (BMI ≥18.5 kg/m²)	**Energy intake:** • Adjusted for weight maintenance (typically	**Glycemic index:** • **Consolidated low-GI pattern** (≥70% of	**Long-term maintenance:**	• Weight (monthly)

Phase / Period	Therapeutic Objectives	Energy Adequacy and Macronutrients	Carbohydrate Quality (GI and Fiber)	Micronutrients	Suggested Monitoring
	• Preservation of β-cell function • Prevention of chronic hyperglycemia • Establishment of a sustainable dietary pattern[13–15,24]	25–35 kcal/kg/day) • 4-5 daily meals[13-15] **Distribuição:** • CHO: 50-55% of total energy intake • PTN: 15-20% of total energy intake • LIP: 30-35% of total energy intake[13-15]	meals) • Based on: legumes, whole grains, lean proteins, abundant vegetables, whole fruits, unsaturated fats[13-15] **Dietary fiber:** • Maintenance of adequate intake according to general guidelines (IDF: ≥35 g/day; ADA: ≥14 g/1000 kcal) • **Note:** These recommendations derive from studies in type 2 diabetes, not specific for T5DM • Emphasis on natural food sources • Individualized adjustment according to tolerance and metabolic response	• Zinc, magnesium, chromium in reduced doses • Multivitamin • Omega-3 • Duration: individualized, potentially indefinite[9-12]	• HbA1c (quarterly during the first year, then semiannually)) • C-peptide (annually, if available) • Nutritional assessment (quarterly) • Lipid profile (semiannually) [24]

Abbreviations: BMI, body mass index; CHO, carbohydrates; GI, glycaemic index; HbA1c, glycated haemoglobin; LIP, lipids; OGTT, oral glucose tolerance test; PRO, protein; SAM, severe acute malnutrition; T5DM, type 5 diabetes mellitus.

Note: This phased framework integrates principles derived from the management of severe acute malnutrition, the prevention of refeeding syndrome, and evidence on low-GI dietary patterns in type 2 diabetes. It has not been prospectively validated in randomized controlled trials specific to T5DM and should be regarded as a hypothesis-generating reference framework rather than a definitive clinical guideline.

4 DISCUSSION

This review synthesized contemporary evidence on pathophysiological mechanisms, potential pancreatic recovery, and nutritional management strategies in type 5 diabetes mellitus (T5DM), a recently recognized entity representing a clinical and public health challenge in regions with high prevalence of malnutrition (1,2).

Clinically, the findings reinforce that the refeeding phase must be treated as a high-risk stage and simultaneously as a window of metabolic modulation opportunity. The occurrence of refeeding syndrome in 25–80% of cases and hypophosphatemia (serum phosphate <0.6 mmol/L) in 34% within the first 72 hours—associated with threefold higher mortality—underscores the need for controlled caloric progression and close monitoring during early nutritional rehabilitation (27).

Discussion of dietary management also benefits from a more precise interpretation of available evidence. Although trials specific to T5DM are scarce, metabolic effects of low-GI diets described in other diabetic populations demonstrate HbA1c reductions of 0.3–0.5% and 20–30% reductions in postprandial glycaemic excursions. These findings are consistent with the need to reduce secretory overload on vulnerable β-cells, particularly during nutritional rehabilitation (14,15,33,35,36).

Translating these recommendations into real-world contexts remains challenging. In settings where T5DM is most prevalent, availability of low-GI foods and micronutrients may be limited, requiring operational simplification without compromising safety (1,24). Thus, strategies based on local foods, community education, and rehabilitation protocols with minimal reliance on sophisticated laboratory tests are essential to reduce disparities and enhance applicability (24).

This review has inherent limitations related to its narrative design. Methodological heterogeneity among included studies limits quantitative synthesis and causal inference strength. Direct evidence specific to T5DM remains scarce; a substantial portion of the argument relies on extrapolation from other forms of diabetes or experimental models. Most critically, randomized controlled trials specifically evaluating low-GI diets in T5DM are lacking. The proposed recommendations are based on biological plausibility and indirect evidence rather than direct demonstration of efficacy (24).

The formal recognition of T5DM as a distinct nosological entity in 2025 opens opportunities for scientific advancement. Three research priorities emerge: randomized clinical trials evaluating low-GI–based refeeding protocols versus conventional protocols (24,33,35,36); mechanistic studies on biomarkers of β-cell function, incretin response, inflammation, and oxidative stress (3,18,29,32); and implementation studies assessing

feasibility, acceptability, and cost-effectiveness in low-resource settings, where T5DM prevalence is highest (24).

In conclusion, evidence supports a paradigm shift in understanding and managing T5DM: from an irreversible condition to a potentially modifiable phenotype through qualified nutritional intervention. Translating this knowledge into improved clinical outcomes for millions of affected individuals worldwide constitutes a scientific, clinical, and ethical imperative.

5 CONCLUSIONS

Type 5 diabetes mellitus should be understood as a malnutrition-related phenotype in which β-cell dysfunction is not necessarily permanent. The nutritional rehabilitation phase is critical: when conducted safely, it may promote functional pancreatic recovery; when conducted inadequately, it increases the risk of refeeding syndrome and glycemic instability.

Low-glycemic-index dietary strategies, combined with controlled caloric progression and systematic correction of micronutrient deficiencies, represent pathophysiologically coherent approaches to reducing secretory burden on fragile β-cells during recovery. Nevertheless, direct evidence in T5DM remains limited, and specific clinical trials are required to establish feasible, safe, and context-appropriate protocols for low-resource settings.

DECLARATIONS

Conflicts of Interest

The authors declare no conflicts of interest related to the content of this manuscript. No author has commercial, financial, or consulting relationships with companies or organizations whose products or services are discussed in this review.

Funding

This study received no specific funding from public, commercial, or not-for-profit funding agencies.

REFERENCES

1. Selim, S. (2025). Type 5 diabetes mellitus: Global recognition of a previously overlooked subtype. Bangladesh Journal of Endocrinology and Metabolism, 4, 59–60.

2. International Diabetes Federation. (2025). IDF Diabetes Atlas (11th ed.). International Diabetes Federation.

3. Misra, A. (2024). Malnutrition-related diabetes mellitus: Current evidence and evolving

concepts. Diabetes Research and Clinical Practice, 205, 110857.

4. Vial-Dahmer, D., Rosa-Santos, C. A., Silva, L. R., Arantes, V. C., Reis, M. A. B., Milanski, M., et al. (2021). Protein malnutrition early in life increases apoptosis but does not alter β-cell mass during gestation. British Journal of Nutrition, 125(10), 1111–1124.

5. Cheng, C. W., Villani, V., Buono, R., Wei, M., Kumar, S., Yilmaz, O. H., et al. (2017). Fasting-mimicking diet promotes Ngn3-driven β-cell regeneration to reverse diabetes. Cell, 168(5), 775–788.

6. Chernysheva, M. B., Ruchko, E. S., Karimova, M. V., Vorotelyak, E. A., & Vasiliev, A. V. (2024). Development, regeneration, and physiological expansion of functional β-cells: Cellular sources and regulators. Frontiers in Cell and Developmental Biology, 12, 1424278. https://doi.org/10.3389/fcell.2024.1424278

7. Hosseini, A., Shafiee-Nick, R., & Ghorbani, A. (2015). Pancreatic beta cell protection/regeneration with phytotherapy. Brazilian Journal of Pharmaceutical Sciences, 51(1), 1–13. https://doi.org/10.1590/S1984-82502015000100001

8. Rosyid, F. N. (2022). Micronutrient deficiency in type 1 and 2 diabetes mellitus: Diagnosis and therapy. International Journal of Research in Medical Sciences, 10(4), 973–979. https://doi.org/10.18203/2320-6012.ijrms20221035

9. Kiprotich, D., Yegon, N. C., & Walekhwa, M. N. (2021). Level of micronutrients affects pathophysiology of diabetes mellitus: A scoping review. European Journal of Medical and Health Sciences, 3(5), 98–116.

10. Mostafaei, Z., Paknahad, Z., Feizi, A., & Hovsepian, S. (2025). Dietary antioxidant minerals (Cr, Mg, Cu, Se, Zn) in diabetic children and their relationship with fasting and postprandial blood glucose. International Journal of Preventive Medicine, 16, 24. https://doi.org/10.4103/ijpvm.ijpvm_181_24

11. Sun, L., Goh, H. J., Govindharajulu, P., Leow, M. K., & Henry, C. J. (2022). Low-glycemic index diets as an intervention in metabolic diseases: A systematic review and meta-analysis. Nutrients, 14(2), 307. https://doi.org/10.3390/nu14020307

12. Jenkins, D. J., Willett, W. C., Yusuf, S., Hu, F. B., Glenn, A. J., Liu, S., et al. (2024). Association of glycaemic index and glycaemic load with type 2 diabetes, cardiovascular disease, cancer, and all-cause mortality: A meta-analysis of megacohorts of more than 100 000 participants. Lancet Diabetes & Endocrinology, 12(2), 107–118.

13. Livesey, G., Taylor, R., Livesey, H. F., Buyken, A. E., Jenkins, D. J. A., Augustin, L. S. A., Sievenpiper, J. L., Barclay, A. W., Vinoy, S., Loughman, G., Tosh, S. M., Wolever, T. M. S., Stevenson, L., Trichopoulou, A., Meek, J., Dahal, A., Middleton, D., Brouns, F. J., & Brand-Miller, J. C. (2019). Dietary glycemic index and load and the risk of type 2 diabetes: Assessment of causal relations. Nutrients, 11(6), 1280. https://doi.org/10.3390/nu11061280

14. Page, L., McCain, E., & Freemark, M. (2025). Adaptive responses in severe acute malnutrition: Endocrinology, metabolomics, mortality, and growth. Nutrients, 17(17), 2864. https://doi.org/10.3390/nu17172864

15. Semba, R. D., Trehan, I., Gonzalez-Freire, M., Kraemer, K., Moaddel, R., Ordiz, M. I., et

al. (2016). Perspective: The potential role of essential amino acids and the mechanistic target of rapamycin complex 1 (mTORC1) pathway in the pathogenesis of child stunting. Advances in Nutrition, 7(5), 853–865.

16. Thompson, D. S., Hoang, T. T., Arredondo, B. P., Brickman, C. M., Mwakamui, S., Vos, M. B., Dedhia, M., Soleimani, B., Ladesic, O., Spratlen, M. J., Freemark, M., Manary, M. J., Ilkayeva, O., Sharma, R., Wyce, A., Bain, J. R., Williams, S. M., Stein, A. D., Martorell, R., & Stein, C. R. (2020). Childhood severe acute malnutrition is associated with metabolomic changes in adulthood. JCI Insight, 5(24), e141316. https://doi.org/10.1172/jci.insight.141316

17. Ferdous, F., Filteau, S., Schwartz, N. B., Gumede-Moyo, S., & Cox, S. E. (2023). Association of postnatal severe acute malnutrition with pancreatic exocrine and endocrine function in children and adults: A systematic review. British Journal of Nutrition, 129(4), 576–609. https://doi.org/10.1017/S0007114522001416

18. Portha, B., Chavey, A., & Movassat, J. (2011). Early-life origins of type 2 diabetes: Fetal programming of the beta-cell mass. Experimental Diabetes Research, 2011, 105076. https://doi.org/10.1155/2011/105076

19. Fernandez-Twinn, D. S., Hjort, L., Novakovic, B., Ozanne, S. E., & Saffery, R. (2019). Intrauterine programming of obesity and type 2 diabetes. Diabetologia, 62(10), 1789–1801. https://doi.org/10.1007/s00125-019-4951-9

20. Gehrig, J. L., Venkatesh, S., Chang, H. W., Hibberd, M. C., Kung, V. L., Cheng, J., Chen, R. Y., Subramanian, S., Cowardin, C. A., Meier, M. F., O'Donnell, D., Talcott, M., Spears, L. D., Semenkovich, C. F., Henrissat, B., Giannone, R. J., Hettich, R. L., Ilkayeva, O., Muehlbauer, M., Newgard, C. B., Sawyer, C., Head, R. D., Rodionov, D. A., Arzamasov, A. A., Leyn, S. A., Osterman, A. L., & Gordon, J. I. (2019). Effects of microbiota-directed foods in gnotobiotic animals and undernourished children. Science, 365(6449), eaau4732. https://doi.org/10.1126/science.aau4732

21. Fazeli, P. K., & Klibanski, A. (2018). Effects of anorexia nervosa on bone metabolism. Endocrine Reviews, 39(6), 895–910. https://doi.org/10.1210/er.2018-00063

22. Zheng, J., Xiao, X., Zhang, Q., Yu, M., Xu, J., & Wang, Z. (2014). DNA methylation: The pivotal interaction between early-life nutrition and glucose metabolism in later life. British Journal of Nutrition, 112(11), 1850–1857. https://doi.org/10.1017/S0007114514002827

23. Sandovici, I., Hammerle, C. M., Ozanne, S. E., & Constância, M. (2013). Developmental and environmental epigenetic programming of the endocrine pancreas: Consequences for type 2 diabetes. Cellular and Molecular Life Sciences, 70(9), 1575–1595. https://doi.org/10.1007/s00018-012-1190-8