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Nutritional Approach to Alleviate Fatigue in T2DM, a Narrative Review

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Abstract

Type 2 Diabetes Mellitus (T2DM) is a persistent metabolic disease characterized by peripheral insulin resistance and dysregulated glucose homeostasis resulting from impaired insulin signaling and pancreatic β-cells dysfunction, affecting millions globally. Beyond its well-known complications, T2DM is increasingly associated with fatigue and sleep disturbances, which significantly impair quality of life and are often underrecognized in clinical care. This review explores the multifactorial origins of fatigue in T2DM, including neuromuscular dysfunction, mitochondrial impairment, oxidative stress, and glycemic variability. It also highlights the systemic impact of poorly managed T2DM on cognitive function, muscle performance, and sleep quality. Special attention is given to nutritional strategies aimed at alleviating fatigue and improving metabolic outcomes. Key dietary components-such as low-glycemic index carbohydrates, dietary fiber, high-quality proteins, healthy fats, and inositol-are examined for their roles in glycemic control, muscle preservation, and energy regulation. The review also discusses the emerging role of diabetes-specific nutrition formulas (DSNFs) and bioactive compounds, particularly polyphenols, in managing fatigue and enhancing sleep quality. These compounds, found in plant-based foods, show antioxidant, anti-inflammatory, and insulin-sensitizing properties that may complement conventional therapies. Micronutrients such as vitamin D, magnesium, and iron are also explored for their influence on sleep and fatigue. By integrating current evidence, this paper highlights the importance of a holistic, nutrition-centered approach to T2DM management that addresses both metabolic and quality-of-life outcomes. The findings support the potential of targeted nutritional interventions as adjunctive strategies for reducing fatigue and improving overall well-being in individuals with T2DM.

Keywords: *Type 2 Diabetes Mellitus; Fatigue; Nutritional Interventions; Glycemic Control; Diabetes Specific Nutritional Formulas*

Abbreviations

DM: Diabetes Mellitus; T2DM: Type 2 Diabetes Mellitus; T1DM: Type 1 Diabetes Mellitus; MCI: Mild Cognitive Impairment; IR: Insulin Resistance; ATP: Adenosine Triphosphate; FACIT-F: Functional Assessment Chronic Illness Therapy-Fatigue; FSS: Fatigue Severity Scale; FSA: Fatigue Assessment Scale; VAFS: Visual Analog Fatigue Scale; MFI-20: Multidimensional Fatigue Inventory-20; MD: Mitochondrial

Dysfunction; UKPDS: The United Kingdom Prospective Diabetes Study; DNA: Deoxyribonucleic Acid; SCFs: Short-Chain Fatty Acids; BMI: Body Mass Index; DSNFs: Diabetes-Specific Nutritional Formulas

Introduction

Type 2 Diabetes Mellitus (T2DM), recognized as a global epidemic and one of the major public health challenges in Latin America, is characterized as a group of metabolic disorders, such as insulin resistance and relative deficiency, that result in elevated glucose levels in the blood, named hyperglycemia [1-4].

According to Cho, Shaw [2], it is not possible to accurately estimate the prevalence of Type 1 (T1DM) and Type 2 Diabetes Mellitus separately on a global scale. According to the International Diabetes Federation [5], estimates that approximately 589 million adults aged 20 to 79 years currently live with diabetes mellitus (DM) worldwide. This scenario represents about 11.1% of the global adult population, with projections indicating a significant increase to 853 million individuals by 2050, or roughly 1 in 8 adults. The projected 46% increase in prevalence accentuates the intensifying global diabetes burden and emphasizes the critical necessity for public health strategies aimed at prevention, early diagnosis, and integrated disease management.

Recently, sleep disorders associated with diabetes mellitus (DM) have been studied as an emerging physical health issue that can affect the body, leading not only to fatigue but also to mental, social, and emotional difficulties during the daytime [6]. This disorder can be explained by a lack of or difficulty with sleep, which, according to Shannag, Al-Jabari [7], affects about 35% of people with T2DM. Furthermore, Shannag, Al-Jabari [7] highlighted the economic and quality of life impacts of insomnia symptoms in individuals with a prolonged duration of DM. Economically, these symptoms are associated with work absenteeism, reduced productivity, and increased treatment costs. In terms of quality of life, fatigue is directly related, encompassing not only loss of concentration but also a decline in decision-making abilities.

Fatigue, one of the main disorders caused by insomnia, can be defined as a multifaceted biopsychological condition that encompasses both mental fatigue, which is subjectively experienced, and physical fatigue, which is objectively measured. It typically results from extended periods of cognitive or physical exertion and can significantly impair productivity and overall quality of life. This issue is particularly critical for individuals in high-demand roles such as athletes, astronauts, soldiers, and those engaged in intensive mental tasks [8].

Some lifestyle behaviors might be associated with DM complications, such as poor diet, smoking, and low physical activity [6]. Then, treatments for T2DM involves lifestyle modifications-particularly dietary changes, increasing nutrients that helps alleviate the fatigue-pharmacotherapy, and regular monitoring of blood glucose levels to minimize the risk of complications [4].

Given the central role of lifestyle in managing T2DM, there is increasing interest in not only broad dietary patterns but also in the specific nutrients and compounds that may offer therapeutic benefits [8,9]. Among these, certain bioactive compounds have shown promise in addressing both the metabolic dysfunctions and the fatigue commonly associated with diabetes [8]. These naturally occurring substances, found in a variety of plant-based foods, it may potentiate the efficacy of standard therapeutic approaches by modulating oxidative stress and inflammatory pathways, both of which are central to the pathogenesis of diabetic complications [10]. This growing body of evidence has led researchers to explore the potential of polyphenols, a diverse group of compounds known for their antioxidant properties, in the context of diabetes management and fatigue reduction [11-14].

Polyphenols, a diverse group of naturally occurring compounds characterized by their strong antioxidant activity, have garnered significant scientific interest for their potential role in mitigating fatigue and in the reduce the incidence and progression of chronic diseases such as diabetes, obesity, and cancer, owing to their widespread availability and accessibility [12,13].

Despite increasing recognition of fatigue as a significant complication in T2DM, current literature remains fragmented, with limited comprehensive reviews that integrate both the physiological mechanisms of fatigue and the therapeutic potential of natural bioactive compounds. In particular, the role of polyphenols in alleviating diabetes-related fatigue has not been thoroughly explored, especially in the context of their accessibility and potential as adjunctive, non-pharmacological interventions.

Aim of the Study

This paper aims to review the impact of fatigue syndrome in individuals with T2DM, explore the underlying mechanisms contributing to this condition, and examine the potential of some nutrients, as alternative strategies for alleviating fatigue in people with DM.

Materials and Methods

Diabetes mellitus: Classification and systemic impact

Diabetes mellitus, a chronic and multifaceted metabolic disorder, exists in four primary forms-type 1, type 2, gestational diabetes and other less prevalent forms (e.g. MODY)-each distinguished by unique etiologies and clinical manifestations [15]. Diabetes progressively affects nearly every organ system, contributing to a substantial long-term health burden [16]. As a global public health crisis with pandemic-level implications, diabetes demands urgent and sustained attention. Among its forms, T2DM is particularly concerning in older adults, as it is associated with neurodegenerative changes and an increased risk of mild cognitive impairment (MCI) and dementia [16,17]. Notably, the general population, individuals with mild cognitive impairment (MCI) exhibit an annual conversion rate to dementia ranging between 0.2% and 3.9. In contrast, this rate increases significantly to between 6% and 25% among patients with T2DM, indicating a markedly higher risk of cognitive decline in this population [17]. Beyond cognitive complications, T2DM also exerts widespread systemic effects that contribute to physical symptoms such as fatigue, which are often overlooked in clinical care. Due to that, early identification of cognitive decline in T2DM patients is therefore essential for mitigating deterioration and enhancing quality of life. Furthermore, accurate and timely prediction of blood glucose fluctuations is critical for optimizing diabetes management and preventing complications [18]. However, even with optimal glycemic control, many individuals with T2DM continue to experience persistent fatigue, suggesting the involvement of additional physiological mechanisms.

Type 2 diabetes mellitus

T2DM constitutes for over 90% of all diabetes cases and is predominantly defined by defective insulin secretion from pancreatic β-cells in conjunction with peripheral insulin resistance (IR) in peripheral tissues, and an insufficient compensatory insulin response. In addition, as the disease progresses, the pancreas becomes increasingly unable to maintain glucose homeostasis, leading to chronic hyperglycemia [19-22].

The development of T2DM involves a dynamic interaction between genetic predisposition, metabolic imbalances, and environmental influences. Galicia-Garcia, Benito-Vicente [22] emphasize that although factors like ethnicity and family history cannot be changed, lifestyle-related elements-such as diet, physical activity, and weight management-are modifiable and contribute significantly to the prevention of pathological conditions.

Epidemiological research indicates that a significant ratio of T2DM cases can be prevented through effective weight management, regular physical activity, and the adoption of healthier dietary patterns [19]. In addition to improving metabolic parameters, exercise plays a crucial role in mitigating systemic inflammation and oxidative stress-two key factors involved in the pathogenesis of T2DM [23].

Physical activity offers several protective benefits against T2DM. Firstly, muscle contractions during exercise increase blood flow and enhance glucose uptake by skeletal muscles [22,23]. Secondly, regular physical activity reduces visceral fat, a key contributor to insulin resistance [22,24]. Lastly, moderate-intensity exercise has been shown to enhance glucose uptake by up to 40% [22,25].

Genetic predisposition remains a significant determinant of T2DM risk, with individuals who have a familial history of the disease exhibiting a significantly elevated likelihood of developing the condition [22].

Acknowledging the diverse and interrelated contributors to the development of T2DM, effectively addressing its rising prevalence necessitates a comprehensive and coordinated public health strategy. This strategy should emphasize the encouragement of consistent physical activity, the implementation of balanced and nutrient-rich dietary patterns, enhanced accessibility to high-quality healthcare services, and the expansion of comprehensive health education programs. Collectively, these interventions are vital for alleviating the burden of T2DM and fostering better health outcomes at the population level [19].

Fatigue and systemic effects of poorly managed T2DM

One of the most concerning consequences of untreated or poorly managed T2DM is its impact on multiple organ systems, particularly the cardiovascular, renal, and neuromuscular systems. Chronic hyperglycemia induces oxidative stress in neurons and alters the intrinsic properties of skeletal muscles, especially those involved in strength production [26]. This leads to a cascade of neuromuscular impairments, including reduced muscle strength, power, mass, and endurance. These effects are most pronounced in the lower limbs, where changes in muscle fiber composition and motor unit recruitment patterns contribute to premature fatigue and diminished work capacity [26].

These neuromuscular impairments are further compounded by behavioral and psychological factors, such as sleep disturbances, which are highly prevalent in individuals with T2DM.

In addition to metabolic and neuromuscular symptoms, T2DM is closely associated with sleep disturbances, particularly insomnia. Insomnia not only worsens fatigue but also contributes to poor glycemic control and reduced quality of life. A recent study in Jordan highlighted the high prevalence of both insomnia and fatigue among patients with T2DM, emphasizing the need for greater clinical attention to these symptoms in diabetes care, especially in developing countries [7].

In addition to sleep-related fatigue, fluctuations in blood glucose levels themselves can directly disrupt energy metabolism and contribute to both physical and mental exhaustion. Despite their significant impact, these symptoms are often underdiagnosed and undertreated, underscoring a critical gap in comprehensive diabetes management.

Fatigue is a prevalent and debilitating symptom among individuals with T2DM, even in the absence of severe comorbidities [27]. While glucose variability is more pronounced in individuals with T1DM due to their heightened sensitivity to insulin and altered hormonal responses, patients with T2DM are not immune to these fluctuations. Over time, the stress of managing these swings can lead to feelings of failure, burnout, and disengagement from self-care routines, further exacerbating glycemic instability and increasing the risk of complications [27]. This highlights the need for comprehensive treatment strategies that go beyond glycemic control to address the broader symptom burden of T2DM.

Effective treatment typically involves a combination of dietary monitoring, oral hypoglycemic agents, and insulin therapy [27]. The intricate nature of disease progression and the difficulty in achieving a definitive cure underscore the need for ongoing, personalized care approaches [28].

Untreated or inadequately managed T2DM poses serious risks that extend beyond glycemic control. The interplay between hyperglycemia, neuromuscular dysfunction, fatigue, and sleep disturbances creates a vicious cycle that can severely impair daily functioning and long-term health outcomes [27]. Addressing these interconnected symptoms through multidisciplinary care-including medical, nutritional, psychological, and lifestyle interventions-is essential for improving patient outcomes and quality of life. Given the

multifactorial origins and systemic consequences of fatigue in T2DM, identifying effective, non-pharmacological interventions-such as nutritional strategies-has become increasingly important.

Fatigue assessment and monitoring tools in T2DM

Fatigue in individuals with T2DM is a multifaceted condition that encompasses both physical and mental dimensions, which must be clearly distinguished for effective assessment [29]. Traditionally, fatigue has been evaluated through self-reporting methods, where individuals are asked to describe their experiences of tiredness, sleepiness, or exhaustion, often in relation to their sleep and work patterns [29]. Mental fatigue, in particular, has been identified as a significant contributor to reduced productivity and impaired cognitive functioning, affecting attention, information processing, and response inhibition [30]. In clinical practice, mental fatigue and stress are commonly assessed using self-reported questionnaires [30], although these two states differ in their underlying mechanisms and triggers. Stress arises from perceived threats and activates a physiological fight-or-flight response without necessarily inducing tiredness, whereas mental fatigue leads to a subjective sense of exhaustion [30-33]. To enhance fatigue prediction, bio-mathematical models have been developed that incorporate sleep-wake cycles, work-rest schedules, and circadian rhythms [30,34]. While several self-administered tools exist for assessing fatigue in diabetic populations such as the Functional Assessment Chronic Illness Therapy-Fatigue (FACIT-F), Fatigue Severity Scale (FSS), Fatigue Assessment Scale (FSA), and Visual Analog Fatigue Scale (VAFS). These instruments are typically unidimensional and may not capture the full complexity of fatigue. In contrast, Romadlon, Huang [35] emphasized that the Multidimensional Fatigue Inventory-20 (MFI-20) provides a more comprehensive assessment by evaluating five distinct domains: general fatigue, physical fatigue, reduced activity, reduced motivation, and mental fatigue. This multidimensional approach offers a more reliable and nuanced understanding of fatigue, particularly in patients with T2DM.

Pathophysiological insights into type 2 diabetes

Mitochondrial dysfunction, oxidative stress, and metabolic disorder

Mitochondria are essential organelles responsible for cellular energy production through the oxidation of glucose and lipids, leading to adenosine triphosphate (ATP) synthesis [36,37]. Beyond their role in energy metabolism, they are also central to glucose processing, insulin biosynthesis and secretion, and the regulation of fuel metabolism in insulin-responsive tissues [37,38].

A key byproduct of mitochondrial activity is the production of reactive oxygen species (ROS), which, under normal physiological conditions, exist at low levels and help activate protective cellular mechanisms such as antioxidant production and autophagy. These processes help maintain cellular integrity and function [38]. However, when ROS levels become excessive, they overwhelm the cell's antioxidant defenses, leading to oxidative stress. This imbalance results in the accumulation of damaged mitochondria, which compromises cellular viability and function [38,39].

In the context of T2DM, oxidative stress plays a pivotal role in disease onset and progression. Chronic hyperglycemia and mitochondrial dysfunction contribute to elevated ROS production, which exacerbates oxidative damage. This stress impairs pancreatic β-cell function and promotes IR, both of which are central to the pathophysiology of T2DM [39].

T2DM, which constitutes approximately 90% of all diabetes cases, is primarily defined by peripheral insulin resistance. In the early stages, compensatory hyperinsulinemia occurs as the body attempts to regulate elevated blood glucose levels. However, due to impaired insulin responsiveness, glucose uptake remains suboptimal, resulting in chronic hyperglycemia and subsequent cellular energy deficits [37].

Mitochondrial dysfunction (MD) is growing recognition as critical factor not only to the development of T2DM but also to its complications. MD often arises from an imbalance in nutrient signaling, energy production, and oxidative respiration, disrupting normal mitochondrial processes and contributing to metabolic disorders linked to mitochondrial impairment [40,41]. Since this dysfunction affects multiple tissues, targeting mitochondria therapeutically could offer a comprehensive approach to managing both the primary and secondary effects of the disease [37].

One of the key metabolic disturbances in T2DM is increased hepatic glucose production, which contributes to hyperglycemia. Under normal physiological conditions, insulin inhibits hepatic glucose production while promoting glucose uptake in skeletal muscle tissue. In insulin-resistant states, these regulatory mechanisms are impaired, further aggravating hyperglycemia [37].

Oxidative stress refers to a disruption in the equilibrium between the generation of reactive oxygen species (ROS) and the capacity of antioxidant systems to neutralize them, leads to widespread cellular damage. ROS can harm proteins, lipids, and DNA, triggering inflammation and disrupting normal physiological processes. This damage is particularly detrimental in diabetes, where it contributes to β-cell apoptosis and worsens insulin resistance [39].

As individuals age, mitochondrial efficiency declines-ATP production decreases while ROS generation increases. This age-related shift, combined with weakened antioxidant systems, further amplifies oxidative stress [39].

There is also a strong link between oxidative stress and inflammation. In diabetes, chronic inflammation perpetuates ROS production through immune activation, creating a vicious cycle. This chronic inflammatory state, commonly observed in T2DM, sustains elevated ROS levels, thereby perpetuating cellular damage and metabolic dysfunction [39]. In summary, mitochondrial dysfunction and oxidative stress form a critical axis in the pathogenesis of T2DM, offering potential targets for therapeutic intervention.

Challenges in glycemic control and its clinical implications

Glycated hemoglobin (HbA1c) is widely regarded as a benchmark indicator for evaluating long-term glycemic control, and predicting chronic complications, particularly microvascular ones, in individuals with diabetes [42-44]. Indeed, HbA1c is preferred because it reflects average blood glucose over several weeks and is less influenced by short-term fluctuations [44]. Epidemiological studies have shown that HbA1c levels exceeding 7% (53 mmol/mol) are significantly connected with increased risks of both microvascular and macrovascular complications, regardless of treatment modality [44].

Despite the well-established importance of managing glycemic and cardiovascular risk factors in T2DM, a substantial proportion of patients fail to achieve recommended targets. Up to 60% of individuals with T2DM do not meet HbA1c goals, and over one-third have uncontrolled blood pressure, contributing to heightened rates of morbidity and mortality, diminished quality of life, and imposes a substantial economic burden on patients, their families, and healthcare systems [44,45].

Poor glycemic control is commonly defined by elevated HbA1c levels, with thresholds ranging from above 7.5% (59 mmol/mol) to over 9.0% (75 mmol/mol) in the literature [45]. The UK Prospective Diabetes Study (UKPDS) confirmed that maintaining tight glycemic control reduces the risk of diabetes-related complications, yet achieving and sustaining these targets remains a major clinical challenge [46].

Factors influencing glycemic control are multifaceted. For instance, Hartz, Kent [47] found that improved control was not significantly linked to demographic or baseline clinical characteristics but was positively associated with diabetes knowledge, adherence to dietary recommendations, and regular glucose monitoring. Conversely, increased medication use was inversely related to achieving control, and life changes played a role in some cases. In many instances, the decision not to intensify treatment was clinically justified. Building upon this framework, the American Diabetes Association advocates for a comprehensive, patient-centered model that integrates lifestyle

interventions-particularly nutritional modifications and regular physical activity-alongside pharmacologic treatment to optimize clinical outcomes [48]. This underscores the importance of exploring targeted nutritional strategies, especially in addressing common challenges such as fatigue in individuals with type T2DM [48,49].

Nutritional strategies to alleviate fatigue in T2DM

Key nutrients, dietary sources, and energy regulation

Carbohydrates and glycemic control

Maintaining a structured diet can be challenging, especially for individuals with limited nutritional knowledge or cooking skills [48]. However, the quality of carbohydrates consumed plays a critical role in managing blood glucose levels. Low glycemic index (GI) and slow-digesting carbohydrates are particularly effective in minimizing postprandial glucose spikes and promoting more stable blood sugar levels throughout the day [50]. The glycemic index and glycemic load (GL) remain valuable tools for classifying carbohydrate-rich foods based on their impact on glycemia, helping predict post-meal glucose responses and guide dietary choices in T2DM management [11,51]. Some carbohydrates cause a rapid rise and fall in blood glucose, while others lead to a more gradual and sustained increase, which is preferable for glycemic control [11,52]. Research has shown that incorporating low-GI carbohydrates into a comprehensive nutrition plan can be just as effective in improving glycemic control as diets that include a broader range of carbohydrate types, making them a practical and beneficial component of diabetes nutrition therapy [51,53,54].

Dietary fiber

Fiber intake is essential for regulating blood glucose levels and promoting metabolic health. It slows digestion, reduces glucose absorption, and promotes satiety, making it a key component in diabetes-specific nutrition formulas (DSNFs) that support improved metabolic outcomes [55,56]. For years, fiber has been recognized for its broad health benefits [10,57], prompting the food and health sectors to incorporate it into various products [57]. In a study by Tan, Chia [57], replacing 50% of carbohydrates in food with soluble corn fiber (SCF) significantly lowered both glucose and insulin responses, as measured by incremental area under the glucose and insulin curves (iAUGC and iAUIC). These observations indicate that soluble dietary fiber (SCF) may contribute to delaying the transition from prediabetes to overt diabetes. Additionally, epidemiological evidence associates higher fiber consumption with a decreased risk of developing type 2 diabetes and cardiovascular disease [58]. In another study, Hall, Parry-Strong [58] provided psyllium fiber supplements to participants with elevated HbA1c levels over 12 weeks. While improvements were observed in body mass index (BMI) and lipid profiles, HbA1c levels did not significantly change. Importantly, the gut microbiota plays a central role in mediating fiber's metabolic effects. Hall, Parry-Strong [58] pointed out that the fermentation of fibers such as psyllium by gut microbiota leads to the production of short-chain fatty acids (SCFAs), which play a role in enhancing immune responses and mitigating inflammation-both critical factors in the management of T2DM.

Proteins and muscle mass preservation

Protein intake plays a crucial role in preserving lean body mass, which is particularly important for individuals with T2DM, as skeletal muscle is a primary site for glucose uptake and insulin activity-key processes in glycemic control. Diabetes-specific nutritional formulas (DSNFs) are designed to provide high-quality protein to support muscle maintenance and overall metabolic health [55].

Traditionally, dietary strategies for diabetes management have focused on reducing carbohydrate intake [59]. In a 12-week study involving 44 T2DM patients, Luger, Holstein [59] demonstrated that a high-protein diet significantly reduced insulin requirements, fasting plasma glucose, body mass index, fat mass, and increased serum folate levels compared to a standard diet, suggesting its feasibility and effectiveness for diabetes management. Conventional medical nutrition therapy (MNT) often recommends a Mediterranean diet, which emphasizes high carbohydrate (50–60% of energy), low fat (≤30%), and increased fiber intake, with a emphasis on plant-based foods and healthy fats like olive oil [60].

However, emerging evidence supports the efficacy of increasing dietary protein intake to approximately 30% of total caloric consumption, which has been shown to enhance both fasting and postprandial glycemic control, particularly in individuals exhibiting insulin resistance [61]. Nuttall and Gannon [62] found that replacing carbohydrates with protein (increasing protein from 15% to 30% and reducing carbohydrates from 55% to 40%) led to reductions in glycohemoglobin and postprandial glucose, along with a modest rise in insulin levels. Similarly, [63] observed that a 5-week high-protein, low-carbohydrate diet in untreated T2DM patients improved 24-hour blood glucose profiles and significantly lowered glycated hemoglobin levels.

Fats and GLP-1 secretion

Monounsaturated (MUFA) and polyunsaturated fatty acids (PUFA) are recognized for their positive effects on cardiometabolic health. MUFAs, in particular, have been shown to promote the secretion of glucagon-like peptide-1 (GLP-1), an incretin hormone that facilitates insulin release and contributes to improved glycemic regulation [55]. Incretins like GLP-1 play a vital role in postprandial insulin secretion and help regulate blood glucose levels [64]. While saturated fats are more commonly consumed in Western diets, the Mediterranean region favors MUFAs, especially from olive oil, which has been linked to enhanced cholesterol levels, improved blood sugar regulation, and lower blood pressure in people with T2DM [65].

Clinical studies comparing the metabolic effects of saturated versus monounsaturated fats found that butter increased insulin and fatty acid levels more than olive oil, which had a more neutral effect on these markers [65]. Thomsen, Storm [66] further demonstrated that meals enriched with olive oil led to lower triacylglycerol levels and higher HDL cholesterol compared to butter, without significantly affecting glucose or insulin levels. Additionally, GLP-1 receptor agonists-pharmaceutical analogues of the natural hormone-have emerged as effective treatments for type 2 diabetes. These agents boost insulin secretion in response to glucose, reduce excessive glucagon production, delay stomach emptying, support long-term weight reduction, and help protect pancreatic β-cells [67].

Inositol and insulin sensitivity

It is widely recognized that fiber-rich diets help prevent and manage chronic conditions, especially those related to impaired glucose and insulin regulation. [68]. This benefit is partly attributed to the high inositol content found in fiber, as inositol and its derivatives have been shown to suppress colon carcinogenesis and improve glucose metabolism [68-70].

Inositol, chemically known as hexa-hydroxy-cyclohexane, comprises a family of nine stereoisomers [68]. Inositol, a naturally occurring substance, has demonstrated potential in enhancing insulin sensitivity and improving metabolic health. Incorporating it into dietary strategies may provide added advantages for those with insulin resistance or T2DM. Among its various forms, both myo-inositol and D-chiro-inositol have been shown to mimic insulin activity in conditions characterized by insulin resistance [71-73].

A study by Pintaudi, Di Vieste [73]. evaluated the safety and effectiveness of supplementing these two forms of inositol in 20 patients with T2DM, five of whom were male, and half of whom had diabetes-related complications. For the first time, research has shown that supplementing with both myo-inositol and D-chiro-inositol directly improves blood sugar control, leading to notable decreases in blood glucose and HbA1c levels.

Diabetes-specific nutrition formulas (DSNFs)

Diabetes-specific nutritional formulas (DSNFs) are tailored dietary products designed to support the management of abnormal blood sugar levels, malnutrition, and cardiometabolic risks. They usually contain low-glycemic index (GI) carbohydrates, fiber, healthy fats, protein, and essential vitamins and minerals, all within controlled calorie portions [55,56]. Depending on clinical needs, DSNFs can be used as meal replacements, nutritional supplements, or as part of enteral nutrition. Research has shown that DSNFs lead to reduced postprandial glucose and insulin spikes compared to standard nutritional formulas or common foods, and they offer long-term benefits

in glycemic control and cardiometabolic health [9,48,55,56]. Their effectiveness is largely attributed to their unique composition, which influences outcomes such as weight management, glucose regulation, and overall metabolic health [48].

These nutritional formulas are designed for flexible use across different clinical scenarios: they can serve as meal or snack replacements with controlled or reduced calories, high-calorie supplements for individuals with malnutrition, components of very-low-calorie diets, or as part of enteral feeding plans. Their specific use is determined by the patient's needs and the healthcare provider's clinical judgment [55].

In a study, the effects of skipping breakfast, consuming a whole-food healthful breakfast, and using a glycemia-targeted specialized nutrition (GTSN) product were compared in individuals with T2DM. The findings demonstrated that GTSN significantly improved postprandial glycemic control and increased glucagon-like peptide-1 (GLP-1) secretion compared to both oatmeal and breakfast skipping. Importantly, these benefits were achieved without negatively affecting appetite or total energy intake. The results suggest that GTSNs, which contain slowly digested carbohydrates and monounsaturated fatty acids (MUFAs), offer distinct metabolic advantages when used as meal replacements and may be effectively integrated into diabetes management strategies [9].

In a recent 12-week randomized controlled trial, Tey, Chee [48] evaluate the impact of using a diabetes-specific formula (DSF) as a full or partial meal replacement alongside standard of care (SOC), compared to SOC alone, in overweight or obese adults T2DM. This study involved 235 participants, who were grouped based on their initial HbA1c and BMI and randomly assigned to either the DSF + SOC group (n = 117) or the SOC-only group (n = 118). The DSF group exhibited significantly better improvements in glycemic control, with HbA1c reductions noticeable by day 45 (−0.44% vs. −0.26%, $p = 0.015$) and even greater by day 90 (−0.50% vs. −0.21%, $p = 0.002$). Fasting glucose levels also dropped in the DSF group but rose in the control group ($p = 0.036$). Beyond glycemic improvements, the DSF group experienced nearly double the weight loss and more favorable changes in body composition, including greater decreases in body fat percentage, visceral fat (−6.52% vs. −0.95%, $p < 0.001$), and waist and hip measurements. Additionally, they saw an increase in fat-free mass and a drop in diastolic blood pressure. These results highlight the potential of DSFs to provide meaningful metabolic and physical health benefits when incorporated into daily nutrition. According to Tey, Chee [48] the was the first research to highlight the role of DSFs in enhancing medical nutrition therapy for T2D, particularly within Asian populations, by supporting improved glycemic control and cardiometabolic health.

The role of bioactive compounds and micronutrients in managing fatigue and sleep disorders

A wide range of strategies has been utilized to combat fatigue, including energy drinks, pharmaceutical sprays, medications, and sleep therapy [8]. Recently, attention has shifted toward bioactive compounds-such as polysaccharides, peptides, polyphenols, and saponins-extracted from natural sources, which offer a safe and accessible alternative for fatigue relief [8]. Natural products, defined as chemical substances synthesized by living organisms, are widely regarded for their safety and therapeutic versatility. These compounds are commonly applied in medical treatments, cosmetic formulations, and natural dyes, and have been extensively researched for their antibacterial, blood sugar-lowering, lipid-regulating, antihypertensive, and anticancer properties [8,74,75]. In parallel, emerging research underscores the importance of micronutrients-including folic acid, iron, calcium, magnesium, and vitamin D-in influencing sleep quality [76]. Vitamin D deficiency, in particular, has been associated with increased risks of sleep disturbances, such as reduced sleep duration and frequent nighttime awakenings across age groups [77]. A cross-sectional study conducted by Kazeminejad, Esfahani [76] involving 260 individuals with T2DM revealed that higher scores on the dietary micronutrient adequacy index (DMAI) correlated with better sleep quality and longer sleep duration, although no significant link was found with chronic fatigue. Among bioactive compounds, polyphenols have garnered significant interest due to their reactive chemical nature and their potential to modulate cellular metabolism and molecular responses. These compounds have been studied for their protective effects against cancer, cardiovascular diseases, neurodegenerative disorders, and metabolic conditions [78]. Found in foods such as vegetables, berries, pears, and various beverages, polyphenols exhibit

a range of beneficial properties including anti-aging, anti-inflammatory, antioxidant, and antiproliferative effects [79]. Their ability to counteract oxidative stress and inflammation is believed to reduce the risk of metabolic syndrome and complications associated with T2DM [79]. Additionally, polyphenols may safeguard pancreatic β-cells from glucotoxic damage and enhance insulin secretion, thereby contributing to improved glycemic control in T2DM. Given the chronic low-grade inflammation linked to obesity-related T2DM, their anti-inflammatory properties may offer further therapeutic advantages [80].

Conclusion

Fatigue in Type 2 Diabetes Mellitus (T2DM) is a complex and multifactorial condition that extends beyond glycemic control, involving neuromuscular, metabolic, and psychological dimensions. Despite its prevalence and impact, fatigue remains underdiagnosed and undertreated in diabetes care. This review highlights the critical role of nutritional strategies in addressing fatigue and related symptoms in T2DM. Evidence supports the use of low-glycemic index carbohydrates, dietary fiber, high-quality protein, healthy fats, and inositol to improve glycemic control, preserve muscle mass, and support energy metabolism. Additionally, diabetes-specific nutrition formulas and bioactive compounds-particularly polyphenols-offer promising adjunctive benefits through their antioxidant and anti-inflammatory effects. Micronutrients such as vitamin D, magnesium, and iron also play a role in modulating sleep and fatigue.

Although the American Diabetes Association (ADA) has not formally validated specific fatigue assessment tools for T2DM, numerous studies have demonstrated the reliability and validity of instruments such as the MFI-20, Fatigue Severity Scale (FSS), Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F). These tools are widely accepted in clinical research and provide valuable insights into the multidimensional nature of fatigue in this population.

Together, these findings advocate for a comprehensive, nutrition-focused approach to T2DM management that not only targets metabolic parameters but also enhances patient quality of life. Future research should continue to explore the synergistic effects of dietary components and natural compounds in mitigating fatigue and improving long-term outcomes in individuals with T2DM.

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Conflict of Interest

Patrica Ruffo and Jessica Lorenzo works at Abbott Nutrition for Latin America. All other authors declare no competing interests.

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