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Opportunities and mechanisms for achieving type 2 diabetes remission through nutritional interventions

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ABSTRACT

Background: The number of people with type 2 diabetes continues to grow, as this complex metabolic disease has many layers to its development. While there are numerous pharmacological and nutritional interventions, it remains difficult to develop consistent clinical recommendations for dietary interventions due to the large number of dietary models. *Objective:* This paper aims to analyze selected nutritional models used in the management of type 2 diabetes and evaluate their impact on pathophysiological mechanisms and their potential to achieve disease remission. *Methods:* This is a narrative review that includes the current published literature and the major clinical trials assessing the efficacy of three main types of dietary interventions. *Results:* The reviewed dietary interventions show considerable promise for achieving remission of type 2 diabetes through different mechanisms. Very-low-calorie diets achieve high remission rates that are closely associated with the amount of weight loss. The Mediterranean diet has also been demonstrated to provide prolonged remission of diabetes by decreasing systemic inflammation. The ketogenic diet has produced near-immediate improvements in glucose levels and marked reductions in the need for diabetes medications. *Conclusions*: An essential aspect of a holistic treatment approach is nutritional interventions, which can help regulate the onset of type 2 diabetes. Individualized patient treatment will provide the greatest clinical benefit and ensure optimal long-term effectiveness. Clinicians should provide nutritional interventions based on patient preference and the length of time since diagnosis.

Keywords: type 2 diabetes; type 2 diabetes remission; very-low-calorie diet; Mediterranean diet; ketogenic diet.

1. INTRODUCTION

Type 2 diabetes is a metabolic disorder with a very complex, multi-level cause of disease, such as insulin resistance. Therefore, the recent increase in the discovery and prevalence of these patients has made it even more important to develop effective and sustainable solutions. At this time, diabetes treatment includes various approaches, both pharmacological and non-pharmacological. Many of these

treatments include a nutritional component and are designed specifically to influence factors such as glycaemic control and other metabolic parameters in patients. This type of intervention is a major component of a holistic treatment strategy for type 2 diabetes (Młynarska et al., 2025).

According to the American Diabetes Association guidelines, there is no single, universal nutritional model that applies to all individuals with diabetes. The ADA has the following approach to delivering nutritional recommendations on a personalized basis with long-term evaluation of whether the recommendations are maintained. There is a belief that different dietary patterns can be useful when matched to patient-specific characteristics (ADA, 2025; Westman et al., 2021).

The literature covers a broad spectrum of nutritional interventions. Such interventions differ in definitions, composition, and research methodologies. Because of the varying definitions, composition, and methodologies of the respective nutritional intervention(s), it is difficult to make direct comparisons and form unequivocal recommendations, as recently reported by many systematic reviews (Marume et al., 2025). This paper analyzes selected nutritional models used in type 2 diabetes and evaluates their impact on the pathophysiological mechanisms described below.

2. REVIEW METHODS

Our review has a narrative and thematic quality. In our review process, we searched for articles on nutrition-based therapies and remission from type 2 diabetes via searching keywords in three large databases (PubMed, Scopus, and Web of Science), between the years January 2009 and March 2026. We excluded case studies, review articles without novel information, research conducted among children, and any other papers not reporting metabolic effects. We also sought key articles in various databases via their reference sections.

The process of selecting articles consisted of two steps. First, we evaluated the title and abstract for compliance with the inclusion criteria. Second, we reviewed full-text articles that met the inclusion criteria. We divided the literature into thematic groups (e.g., very-low-calorie, Mediterranean, or ketogenic diets) and analyzed it using a qualitative thematic synthesis. We did not conduct a quantitative meta-analysis. The themes generated from the qualitative synthesis of the data include observational evidence, results from experimental studies, proposed biological explanations, and any limitations/gaps in the existing research that require further investigation. The article screening process followed the PRISMA guidelines (Figure 1).

3. RESULTS AND DISCUSSION

Pathophysiology

Multiple levels contribute to the pathogenesis of type 2 diabetes. A variety of peripheral metabolic disorders, prolonged elevated insulin levels, and a gradual decline in the pancreas's beta cell function are among the factors involved in diabetes. We will consider each successive stage to which these factors lead in the sections below (Westman et al., 2021; Młynarska et al., 2025).

Insulin Resistance

The diminished ability of peripheral tissues (muscles, fat, and liver) to respond to insulin indicates insulin resistance. Insulin resistance results in diminished glucose uptake by the muscle. Likewise, insulin resistance results in abnormal suppression of hepatic gluconeogenesis. In response to the initial phase of insulin resistance, the body compensates by increasing insulin secretion to maintain relative normoglycemia. Unfortunately, chronic overload will further impair insulin signaling and worsen metabolic disease (Westman et al., 2021; Młynarska et al., 2025).

Excessive fat deposition in the liver and muscle, insulin signal transduction interruption due to abnormal post-translational changes to specific proteins (such as phosphorylation), and chronic, low-grade inflammation associated with unhealthy levels of adipokine releases from fat tissue are all contributing factors that interact and reinforce each other in mechanisms leading to the development of insulin resistance, at the cellular level (Młynarska et al., 2025; Vilas-Boas et al., 2021).

Pancreatic beta-cell Dysfunction

In response to increased insulin resistance, beta cells increase insulin secretion. Over time, their capacity for compensation diminishes. The number of active beta-cells then decreases. Their secretory mechanisms become impaired, which leads to a permanent decline in insulin secretion and worsening hyperglycemia (Młynarska et al., 2025).

Chronic glucotoxicity, lipotoxicity, oxidative stress, endoplasmic reticulum stress, and any combination of these may lead to beta-cell dysfunction. These stresses either harm beta cells, leading to their dysfunction and, eventually, their loss (Vilas-Boas et al., 2021; Młynarska et al., 2025).

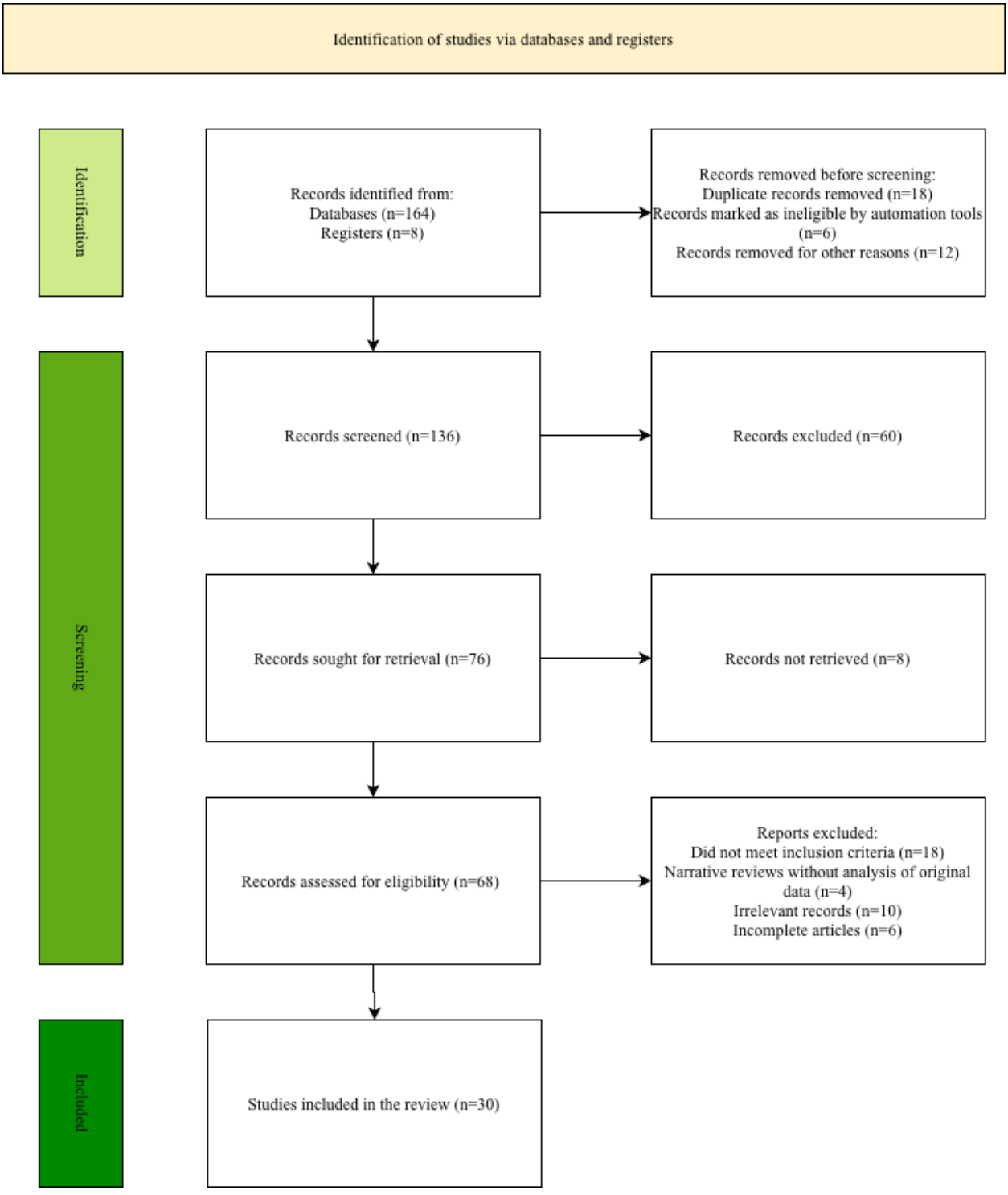

Figure 1. PRISMA flow diagram.

Risk Modifying Factors and Rate of Progression

Chronic excessive energy consumption and low levels of exercise, as well as obesity, particularly visceral obesity, significantly raise a person's chance of developing insulin resistance. Additionally, these factors lead to beta cells becoming unable to function properly

and/or produce enough insulin for the body. There is also a genetic component to this susceptibility that accounts for the great variability in the clinical presentation of patients with type 2 diabetes (Młynarska et al, 2025).

Recent studies and literature reviews have shown that the understanding of early metabolic signals and the use of detection technologies, such as wearable devices that monitor metabolic disturbances, can provide new insights into the early stages of disease progression. Multiple studies show that combining wearable device technology can help identify individuals who have experienced an initial phase (e.g., a preexisting condition) of disease progression. The studies also prove that gut microbiota plays a role in regulating inflammation and metabolism. There is evidence that the composition and function of gut microbiota can affect energy production and the way the body responds to inflammation; however, further research needs to occur before we can establish whether these processes are appropriate targets for treatment (Hartshorn, 2026; Marume et al., 2025).

Very-low-calorie diets

Very-low-calorie diets (VLCDs) are among the best-researched nutrition interventions for inducing remission of type 2 diabetes. It is an intensive medical intervention that restricts daily energy intake to approximately 600-800 kcal/day, usually by using exclusively liquid meal-replacement formulas, such as Total Diet Replacement (TDR). The diet includes providing all necessary nutrients and certain amounts of non-starchy vegetables to ensure micronutrient adequacy and minimize the effects of the diet. The TDR phase is typically short (8-16 weeks) and is followed by a refeeding phase in which regular food is slowly reintroduced into the diet (Lim et al., 2011).

The Diabetes Remission Clinical Trial (DiRECT) firmly established the clinical efficacy of TDR in a routine primary care setting. It used a formula diet of 825–853 kcal/day for 3 to 5 months, followed by a stepped food reintroduction phase and long-term weight-loss maintenance support (Lean et al., 2018). The trial defined remission as achieving HbA1c below 6,5%. The cohort consisted of 306 participants, aged 20-65, with type 2 diabetes diagnosed up to 6 years ago.

In the intervention group, 46% of participants achieved remission of type 2 diabetes at 12 months. The trial showed that the likelihood of remission was closely associated with the amount of weight loss. Out of participants who lost 15 kg or more, 86% achieved remission at 12 months. In comparison, only 7% of participants who lost 0-5 kg achieved remission. Durability analyses demonstrated that at 24 months, 36% of the intervention group remained in remission. The number was higher among participants who maintained a weight loss of at least 10 kg, 64% of them sustained normoglycemia (Lean et al., 2019). The 5-year extension study indicated that 13% of intervention participants who continued the extension phase remained in remission. That shows that sustained weight reduction remains the dominant clinical driver of long-term diabetes remission (Lean et al., 2024).

Numerous global studies indicate that VLCD effectively induces remission of diabetes across diverse populations, including different ethnicities. The DiRECT-Aus trial has shown that VLCD is effective in achieving long-term weight loss and remission of type 2 diabetes. The subjects (20 to 65 years) had been diagnosed with T2DM for 6 years or less and had been on an 800kcal/day VLCD for 13 weeks, followed by a reintroduction phase. The 12-month remission rate in the treatment group was 56%, rising to 87% among participants who lost >15% of their starting body weight (Hocking et al., 2024).

The DIADEM-I trial evaluated a Middle Eastern and North African demographic aged 18–50 years with early-onset type 2 diabetes, diagnosed no longer than 3 years earlier (Taheri et al., 2020). The VLCD intervention consisted of 12 weeks of 800-820 kcal/day TDR intervention, followed by 12 weeks of reintroduction phase. The trial defined remission as achieving HbA1c below 6,5% without the use of hypoglycaemic medication. At 12 months, 61% of participants achieved it.

The New Zealand-based PROGRESS NZ longitudinal study was conducted over five years with a multi-ethnic participant group of both males and females between 18 and 65 years of age who were either pre-diabetic or were newly diagnosed with diabetes. The participant sample included individuals from European, Maori, Pacific Islands, and South Asian ethnicities. Among individuals who achieved at least a 10% weight loss, 56% reverted to a normoglycemia (Whitfield et al., 2024).

The baseline characteristics of patients and how macronutrients are met in the VLCD diet are key components in achieving remission of type 2 diabetes. In Germany, a randomized controlled trial evaluated patients based on the duration of their diabetes. Patients who had been living with diabetes for less than four years had an 82% remission rate after following the VLCD protocol, and patients who had had diabetes for over eight years only had a 50% rate of remission after being placed on the VLCD protocol, even though both groups lost comparable amounts of weight. Moreover, the VLCD group, which ate a diet rich in fiber and protein and low in carbs and fat, was statistically significantly more likely to attain remission than the control group (91% versus 56%) (Schuppelius et al., 2026).

The Mediterranean diet

The Mediterranean diet is a nutritional model traditionally observed as the main dietary pattern in the Mediterranean basin before the mid-1960s (Trichopoulou et al., 2014). It is a plant-based diet composed mostly of unprocessed foods, such as vegetables, fruits, whole grains, legumes, and nuts. It uses extra virgin olive oil as the primary lipid source. It allows a moderate intake of fish, poultry, and red wine, while maintaining a characteristically low intake of red meat, dairy products, and animal-derived saturated fats. Because of such composition, it provides a high level of monounsaturated fatty acids, while maintaining a low level of saturated fatty acids, substantial dietary fiber intake, and high concentration of antioxidants and phytosterols (Radd-Vagenas et al., 2017; Davis et al., 2015; Saura-Calixto and Goñi, 2008).

A review of randomized controlled trials found that consuming a Mediterranean diet benefits patients with diabetes. In addition, fasting plasma glucose and BMI decreased in patients with Type 2 diabetes following a Mediterranean diet (Wu et al., 2025). Results from clinical studies show that nutritional interventions through the Mediterranean diet can lead to remission of type 2 diabetes. A randomized trial compared a low-carbohydrate Mediterranean diet to a low-fat diet in patients with short-term type 2 diabetes. It showed that participants following the Mediterranean diet were significantly more likely to achieve remission, reaching 14,7% after 1 year, compared with the low-fat diet group (3,6%). The numbers decreased over time. However, the Mediterranean diet group had a higher likelihood of sustained remission, with a remission rate of 5% at year six (Esposito et al., 2014).

The Mediterranean diet significantly affects inflammation, oxidizes and accumulates potential toxins through metabolism, predominantly over an extended period, which greatly influences type 2 diabetes remission. Long-term adherence to the Mediterranean dietary pattern is associated with a decrease in serum concentrations of advanced glycation end products (AGE) (particularly methylglyoxal (MG)). According to current literature, the level of serum MG also indicates the risk of developing type 2 diabetes. Furthermore, variations in specific amino acids and immune cell patterns modulate the likelihood of achieving remission from type 2 diabetes. Lower postprandial plasma levels of branched-chain amino acids (BCAAs) - specifically isoleucine, leucine, and valine - after consuming a Mediterranean diet are strongly associated with disease remission. Improved beta-cell function and insulin sensitivity in those who respond to the treatment are associated with significantly decreased absolute neutrophil counts and corresponding neutrophil ratios. Lower baseline neutrophil counts are over four times more likely than individuals with higher baseline neutrophil counts to enter remission from their type 2 diabetes (Gutierrez-Mariscal et al., 2021; Cardelo et al., 2022; Boughanem et al., 2025).

Ketogenic diet

Ketogenic diets are defined as restricting carbohydrate intake to less than 50 g per day or as regimens that lead to ketonemia. Numerous research projects have evaluated the impact of different forms of this nutrition intervention. These studies include both short-term experimental clinical trials and long-term programs with significant patient support. The results showed consistent short-term improvements in blood sugar levels and weight loss. The methodology and design of the studies evaluating the nutrition intervention's effect depended on the amount and maintenance of change (Hallberg et al., 2018; Athinarayanan et al., 2019; Goldenberg et al., 2021; Parry-Strong et al., 2022; Dening et al., 2023).

The Virta program documented significant parameter changes, in which average HbA1c dropped from ~7.6% to ~6.3% after 12 months of the diet, and the average weight loss was ~13.8 kg. Regarding pharmacotherapy, 94% of participants using insulin reduced their doses or discontinued treatment entirely. In addition, there was approximately a 62% reduction in insulin use over the 2-year study period among subjects who received the intervention. This data indicates that combining carbohydrate restriction with an appropriate intensive care approach produces the best clinical results. These results, therefore, do not necessarily stem solely from the diet. When reviewing the findings, it is important to consider that the results in this document are from observational studies conducted within a continuous care model, as well as any potential design issues and biases (Hallberg et al., 2018; Athinarayanan et al., 2019).

In shorter, randomized interventions with lower support intensity, more moderate but still significant benefits are obtained. In the T2Diet study, individuals on a low-carbohydrate diet recorded an average HbA1c reduction of 0.65 pp. and a weight loss of 3.26 kg after 16 weeks. Furthermore, around 25% of participants achieved a greater than 20% reduction in total medication dosage, indicating practical clinical benefit (even within the first few weeks of using low-dose medications as support) and consistent with the literature from systematic reviews and meta-analyses of randomized controlled trials. On the other hand, these sources indicate a diminishing of beneficial effects over longer observation periods and significant study heterogeneity (different diet definitions, different support

protocols) (Goldenberg et al., 2021; Parry-Strong et al., 2022; Silverii et al., 2020; Tay et al., 2015). Summarized results of the review are shown in Table 1.

Table 1. Summary of the review

Feature/Metric	VLCD	Mediterranean diet	Ketogenic diet
Typical intervention duration	8-16 weeks, followed by the reintroduction phase.	Long-term dietary pattern over extended periods.	Variable; from short-term interventions to long-term continuous programs.
Remission rates at 12 months	DiRECT: 46% remission rate. DiRECT-Aus: 56% remission rate. DIADEM-1: 61% remission rate. PROGRESS NZ: 56% in patients who lost >10% body weight. Schuppelius et al., 2016: 82% remission rate in patients diagnosed ≤4 years prior vs. 50% remission rate in patients diagnosed ≥8 years prior.	Esposito et al., 2014: 14,7% remission rate.	Virta Program: Average HbA1c dropped from ~7.6% to ~6.3% at 12 months. T2Diet study: Average HbA1c reduction of 0.65 percentage points at 16 weeks.
Long-term remission rates	DiRECT: 36% at 24 months, 13% at 5 years.	Esposito et al., 2014: 5% remission rate at 6 years.	Short-term blood sugar and weight benefits are consistent, but studies show a diminishing of beneficial effects over longer observation periods.
Primary clinical drivers and biological mechanisms	Sustained weight reduction is the dominant driver. Effectiveness is highest when diagnosed early (<4 years).	Reduces inflammation and advanced glycation end products (AGE); lowers postprandial branched-chain amino acids (BCAAs); low baseline neutrophil counts favor remission.	Combination of strict carbohydrate restriction and intensive continuous care/patient support protocols favor remission.

Strengths and Weaknesses of the Available Studies

The data on effectiveness include multiple lines of evidence of efficacy from large trials such as DiRECT, as well as from smaller studies (DIADEM-I & PROGRESS NZ) across diverse ethnic groups and people of all ages. The growing body of evidence regarding the relationship between specific immune cells (e.g., neutrophils) and successful remissions is also noteworthy (Lean et al., 2018; Taheri et al., 2020; Whitfield et al., 2024; Gutierrez-Mariscal et al., 2021).

In terms of weaknesses, inconsistent definitions of dietary composition and of dietary assessment make it challenging to compare studies. Also, since the data used to obtain these results came from observational studies based on continuous care models, there is a

potential for bias due to observations made within the health care system. Finally, longer follow-up observations often diminish beneficial findings related to the diet (Lean et al., 2024; Goldenberg et al., 2021).

Main Knowledge Gaps

The link between losing weight and achieving remission from disease is well known; however, it is still unclear how gut bacteria affect our bodies' metabolisms and manage inflammation through their influence on our immune systems. Additionally, dietary recommendations will differ from person to person because of how an individual's genetics and their body's response to certain foods interact (Młynarska et al., 2025; Marume et al., 2025).

Directions for Future Research

Future studies are needed to: (1) research the use of wearable devices to track physical activity levels and help identify those at risk for early metabolic dysfunction and diagnose individuals who are at risk for developing chronic disease based on their movement patterns and activity levels; (2) develop clear clinical recommendations by establishing a single definition and composition of nutrition interventions; and (3) further understand the role of changes in the composition of the gut microbiome on chronic inflammation and metabolism over time.

4. CONCLUSION

Nutritional interventions, such as very-low-calorie diets, Mediterranean diets, and ketogenic diets, can be used as holistic and effective strategies for achieving remission from type 2 diabetes. Very-low-calorie diets achieve high rates of remission primarily because of the amount of weight lost; the Mediterranean diet achieves glycemic control over time through its anti-inflammatory benefits. Both the ketogenic diet and the Mediterranean diet will result in rapid improvements in blood sugar levels and reduction of other medications to help control type 2 diabetes; however, most patients on a ketogenic diet require considerable amounts of continuous clinical support to maintain long-term success.

Success in therapy commonly depends on the individualization of nutrition recommendations under appropriate medical supervision and on consideration of the individual patient's characteristics (e.g., how long they have had a particular disability and their likes and dislikes). Future research will need to provide consensual definitions of nutrition to allow proper monitoring and evaluation of metabolic imbalances and to improve long-term outcomes.

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Informed consent

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Ethical approval

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Data and materials availability

All data associated with this study will be available based on the reasonable request to corresponding author.

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