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REVIEW

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Physiological and psychological determinants of long-term diet-induced type 2 diabetes (T2DM) remission: A narrative review

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Summary

Type 2 diabetes mellitus (T2DM) is a highly prevalent metabolic disease, causing a heavy burden on healthcare systems worldwide, with related complications and anti-diabetes drug prescriptions. Recently, it was demonstrated that T2DM can be put into remission via significant weight loss using low-carbohydrate diets (LCDs) and very low-energy diets (VLEDs) in individuals with overweight and obesity. Clinical trials demonstrated remission rates of 25–77%, and metabolic improvements such as improved blood lipid profile and blood pressure were observed. In contrast, clinical trials showed that remission rate declines with time, concurrent with weight gain, or diminished weight loss. This review aims to discuss existing literature regarding underlying determinants of long-term remission of T2DM including metabolic adaptations to weight loss (e.g., role of gastrointestinal hormones), type of dietary intervention (i.e., LCDs or VLEDs), maintaining beta (β)-cell function, early glycemic control, and psychosocial factors. This narrative review is significant because determining the factors that are associated with challenges in maintaining long-term remission may help in designing sustainable interventions for type 2 diabetes remission.

KEYWORDS
maintenance of remission, legacy effect, remission, type 2 diabetes

1 | INTRODUCTION

Type 2 diabetes (T2DM) is a highly prevalent metabolic disease, caused by environmental and genetic factors.[1] Primary modifiable risk factors for T2DM are excess adiposity, underpinned by unhealthy diets and/or sedentary lifestyles.[2,3] Microvascular and macrovascular complications of T2DM plus comorbidities contribute a high cost to healthcare systems worldwide.[4] Recent studies[5,6] using lifestyle interventions suggest that T2DM can be put into remission primarily by weight reduction. Indeed, "remission" has been identified as the top research priority by service users and experts.[7] There are varying diagnostic criteria of T2DM remission in the current literature[5,8,9]; however, recent criteria were determined by a consensus of international researchers, which is a hemoglobin a1c (HbA1c) < 6.5% (<48 mmol/mol), measured at 3 months post anti-diabetic medication cessation, without bariatric surgery.[10] This narrative review paper includes studies that consider diet-induced T2DM remission as having normalized HbA1c in the absence of any medication for a prolonged period. Due to varied accepted criteria within the literature, this was the best approach to use regarding inclusion of studies.

Weight-loss achieved T2DM remission can be facilitated by diet, primarily low and very low-energy (LED and VLED) and/or low-carbohydrate diets (LCD).[6] Landmark studies including the Diabetes REmission Clinical Trial (DiRECT) and Diabetes Intervention

Accentuating Diet and Enhancing Metabolism-I (DIADEM-I) showed that significant weight loss led to decreased HbA1c (<6.5%) and reduced need for medication. It resulted in T2DM remission of 46–60% in people at 1 year.[5,11] DiRECT, for example, showed a direct correlation between greater weight loss and higher remission rates, with participants who lost more than 10 kg having a greater chance of achieving remission compared to those who lost less weight.[12] Similarly, using a LCD yielded drug-free remission rates of 25–77% at year 1.[13,14] At a UK-based primary care practice, patients with T2DM also achieved remission via a median weight loss of 10 kg (IQR 84–109 to 76–99 kg) by following a lower carbohydrate diet in 33 months.[13]

Results from clinical and observational trials using these dietary approaches reported remission in the majority of participants and significant improvements in blood glucose, HbA1c, blood lipids, and increased quality of life. Indeed, it was found that the likelihood of achieving remission was greater in those who lost the most weight and had short-duration T2DM diagnosis.[12,13,15]

The benefits of inducing remission impact not only the lives of those with T2DM and overweight/obesity but also the healthcare system, significantly reducing treatment costs (such as cessation of antidiabetic medication and reductions in T2DM complications).[16–19] However, existing long-term data from remission studies show the number of people maintaining remission falls over time, concurrent with weight re-gain or with diminished weight loss.[5,20]

Addressing biochemical and psychological factors associated with the decline in remission rate will support long-term maintenance of remission through development of more effective interventions in diabetes care. This review aims to discuss existing literature regarding underlying determinants of long-term T2DM remission, with an emphasis on obesity and weight loss. These include physiological factors and psychosocial determinants for long-term remission.

2 | PHYSIOLOGICAL DETERMINANTS OF MAINTENANCE OF T2DM REMISSION

2.1 | Weight loss maintenance and remission

It is well established that T2DM remission is dependent on many physiological factors but primarily on the amount of ectopic fat (storage of triglycerides [TG] in tissues other than adipose tissue such as pancreas, liver, skeletal muscle, and heart[21]) lost and β-cell capacity.[22]

A decrease in ectopic and visceral fat through weight loss leads to a better lipid profile.[23–25] The metabolic improvements following weight loss include normalized blood glucose and HbA1c, too. Weight loss also leads to substantial improvements in insulin sensitivity due to reduced fatty acid mobilization and uptake.[26] The magnitude of weight loss is linked to better remission rates in clinical trials.[2,27] Furthermore, a loss of ≥10% of body weight in the early stages of diagnosis increased the chances of inducing remission at 5 years, independent of which diet had been used.[28]

Increased VLDL-TG production by the liver is often associated with dysregulated de novo lipogenesis (DNL), where it is often common in metabolic anomalies such as T2DM.[29] In a mechanistic study that was conducted within the DiRECT cohort, the researchers investigated hepatic lipoprotein export and first-phase insulin response and how it differed between maintainers and relapsers at 24 months. It was found that the relapse of T2DM is associated with increased liver-derived VLDL-1-TG and VLDL-palmitic acid (the main product of DNL).[30] Further, maintainers had sustained improved first-phase insulin response and weight loss, whereas the relapsers had not. These results highlight that excess hepatic and pancreatic fat content and DNL are closely associated with the risk of relapse, mainly by contributing to beta-cell dysfunction and impaired insulin response. The study suggests that maintaining fat content below personal thresholds is crucial for sustaining T2DM remission.[30]

2.2 | Metabolic adaptations to weight loss maintenance

Maintaining weight loss is crucial to remission, given that even a 5% reduction in body weight is significant in terms of metabolic health.[31] However, weight loss maintenance may be more challenging for many people with overweight and obesity.[32,33] Weight loss maintenance is partially dependent on physiological metabolic adaptations, and identifying these adaptations is key in therapeutic developments. Several underlying mechanistic adaptations that may challenge weight loss maintenance are of major interest. For example, adaptive thermogenesis, changes in appetite-related hormones and their regulation in the body in response to weight loss, and response of adipose tissue to weight loss could be among several explanations for inadequate long-term maintenance of weight loss.[33–35]

How gastrointestinal and adipose tissue hormones change in response to weight loss and regain is also of interest. For instance, leptin, ghrelin, adiponectin, and glucagon-like peptide-1 (GLP-1) all play a role in weight loss maintenance.[36] Additionally, understanding complex mechanisms in appetite signaling in the brain has led to significant pharmacotherapy developments such as GLP-1 receptor agonist (GLP-1 RA) drugs.[37] This drug mimics the action of endogenous GLP-1, which aids in weight management and glycemic control by stimulating insulin secretion and suppressing appetite.[37] GLP-1 RAs may also have cardioprotective effects in people with T2DM.[38]

Leptin is an anorexigenic hormone secreted predominantly from adipocytes and reflects adiposity in the body.[39] Leptin binds leptin receptor in hypothalamus and signals increasing satiety, hence ceasing food intake. Therefore, leptin plays role in energy homeostasis and weight maintenance in the long term.[40] Studies show that leptin deficient and leptin receptor deficient mice strains were found to be insulin resistant and displayed significant obesity due to an elevated drive to eat, culminating in an elevated fat mass.[41] Moreover, leptin deficiency has shown T2DM-like symptoms in mice.[41]

Despite having higher levels of leptin, people with a high body fat percentage display a decreased response to leptin (termed as "leptin

resistance").[42] This means that central leptin receptors are less sensitive, with smaller amounts of leptin passing through the blood brain barrier (BBB) and reaching the hypothalamus.[43] This resistance may result in disruptions in satiety control, energy balance, and cell metabolism.[44] Currently, there is no evidence regarding administration of exogenous leptin to either counter this resistance or improve its efficacy for inducing and maintaining weight loss in typical obesity.[45] However, there is a potential of developing new pharmacological approaches to reverse leptin resistance in the future, for instance, finding strategies to aid in passage of leptin into BBB, but these are yet to be fully explored.

Adiponectin has many features including acting as an insulin sensitizer, anti-inflammatory, and anti-atherogenic, and it plays a role in energy homeostasis.[46] It is known that people with obesity and T2DM have lower levels of adiponectin than people with a normal bodyweight.[47] Adiponectin levels increase with weight reduction, and this increase leads to better metabolic improvements and greater remission rates.[48,49] The adiponectin/leptin ratio is suggested as a good marker of metabolic conditions including insulin resistance, and this ratio is increased with weight loss and fat reduction.[50] However, adiponectin/leptin ratio does not seem to predict of diet-induced T2DM remission, indicating that there are likely other elements that influence this.[51]

The levels of two important anorexigenic gut hormones, which promote satiety (peptide YY [PYY] and cholecystokinin [CKK]), diminish over time with weight loss, thereby reducing satiety in response to food intake.[52] Furthermore, ghrelin is an orexigenic hormone that increases appetite and, therefore, promotes food intake.[53] It has been shown that levels of ghrelin rise after diet-induced weight loss as a response, and this regulates body weight in long term.[54] In the DiRECT cohort, ghrelin levels were found to be directly proportional to weight regained.[55] In fact, the increase in ghrelin at 12 months predicted weight regain at 24 months.[55] This association partly explains the weight gain after the intervention had ended.[56] There is more evidence supporting the ghrelin increase as response to weight loss therefore attenuating weight-reducing effects of calorie restriction.[52,57] Further, ghrelin action is suppressed by maintaining ketogenesis which could be induced by VLED or very low carbohydrate ketogenic diets (VLCKD). This might mean that in case of losing the effects of increased ketone levels, the hunger feeling is more pronounced, which may increase food intake.[58]

Obesity and T2DM present with elevated inflammatory markers (e.g., cytokines and chemokines) and reactive oxygen species (ROS) due to low-grade chronic inflammation in these conditions.[59] Loss of visceral fat is linked to lower inflammatory markers,[60] but there is a lack of evidence on the exact role of these inflammatory and oxidative factors in long-term weight loss maintenance. Alternatively, it has been suggested that shrinking adipocytes as a result of weight loss may cause inflammation and cellular stress that may inhibit lipolysis and therefore further weight loss.[35] More research is needed to assess the extent of changing hormone levels and inflammatory markers on long-term maintenance of diet-induced remission.

2.3 | Effects of different diets on maintenance of t2dm remission

2.3.1 | Low energy formula diets

The type of the dietary intervention used in studies yielded different remission rates in the short and long term. The DiRECT study used a low-energy formula diet, followed by a gradual food reintroduction. Using this approach, the researchers found diminished weight loss after transition onto normal diet (compared to the formula diet phase). In line with this, the remission rate fell from 46% at Year 1 to 36% at Year 2,[15] and to 8% at Year 5.[61] Those participants who maintained a significant weight loss of more than 15 kg had a higher level of remission maintenance, indicating maintaining weight loss is important for continuing remission.[5,15] This observation highlights a very real element that is not routinely captured in weight loss trials of 6 months or 1 year, that is, what happens in the long term. Similar studies have shown that weight regain is probable after an intensive short-term formula diet. For instance, at 3-year follow-up of a VLED formula diet trial, those who were assigned to total diet replacement in the beginning later experienced more weight regain than those in usual care.[62] It is thought that this is due to the extent of weight loss, rather than the rate of initial weight loss. Validating this hypothesis, a study compared low-calorie diets (1,250 kcal/day, over 12 weeks) with very low-energy meal replacement diets (500 kcal/day, for 5 weeks) to examine the rate of weight loss and weight regain between the two groups at 9-month follow-up. The weight loss rate did not have a significant impact on the extent of weight regain; however, fat-free mass percentage was lower in the VLED group, which was correlated with weight regain.[63] Together, these data indicate a very real challenge in the use of VLEDs to induce remission through weight loss and how this level of weight loss can be supported long term.

To best support those who opted for a VLED approach for T2DM remission, healthcare professionals should provide behavioral support, regular monitoring, and appropriate lifestyle and exercise advice to sustain the weight loss induced by VLED.

2.3.2 | Low-carbohydrate diets

Low/lower-carbohydrate diets (LCDs) have shown weight and HbA1c-lowering effects in many clinical trials[64,65] and standard care.[17] A service evaluation of a primary care practice in England that adopted a LCD approach showed that 46% of people with T2DM induced remission, accompanied with significant improvements in the lipid profile, blood pressure, and a decrease in bodyweight.[17] A highlight of this study was that people were not enrolled in a rigorously controlled clinical intervention, indicating that T2DM remission using LCD is possible in a real-world clinical setting. However, it is important to acknowledge limitations inherent to this non-controlled study design, which may impact robustness of these observed improvements. Additionally, those who did not achieve remission while

following an LCD or those did not adhere to their diet were possibly overlooked in this study.

There is substantial evidence showing LCDs are effective for weight loss in those with overweight/obesity for at least 6 months.[64,66] Furthermore, LCDs have remission-inducing effects even in the absence of weight loss. This situation is termed "diabetes mitigation."[6]

Virta health studies including digital intervention and ongoing support for achieving and maintaining nutritional ketosis, while reducing weight to manage T2DM, showed improved glycemia, metabolic parameters, and T2DM remission in 17.6% of participants.[65] However, 5-year follow-up data from the same trial indicated that only about one fifth of enrolled participants maintained remission without metformin.[67] This decline in remission rates is likely due to decreased adherence to VLCKD and, consequently, reduced nutritional ketosis. Ghrelin, as mentioned before, is suppressed by increased ketogenesis, and when ketosis is lost, ghrelin's function returns to normal. Although LCDs are effective for weight loss and T2DM remission, on return to usual diet, the improvements may be lost due to the beforementioned diabetes mitigation concept.[2,64] Nevertheless, residual improvements may still be found if glycemic control is restored in the early stages of diagnosis. More research is warranted to investigate if long-term adherence to LCDs and metabolic improvements are seen following LCDs and how these interplay with potentially maintaining T2DM remission.

In order for healthcare professionals to best support those who follow a LCD for T2DM remission, some considerations should be made regarding giving appropriate dietary education from suitably qualified health professionals such as registered dietitians; especially about sources of dietary fiber, as intakes could be inadequate.[68] Also providing regular monitoring of patients and finding strategies to make LCD diets more sustainable are crucial for long-term success.

2.4 | Maintaining β-cell capacity and early glycemic control

Maintaining and/or restoring β-cell function and mass are essential in long-term T2DM remission. Greater loss of β-cell mass and function occurs in people with T2DM, compared to healthy people.[69] There are several mechanisms of T2DM-linked β-cell failure including chronic hyperglycemia, glucotoxicity, inflammation, oxidative stress, metabolic stress, and hypoxia.[70–72] Duration of T2DM has been shown to inversely correlate with β-cell capacity and predicts the chance of achieving remission.[5,73]

An 8-week intensive VLED intervention showed fast restoration of first-phase insulin response with the presence of weight loss.[74] Similarly, responders (who achieved remission) had increased first-phase insulin response following weight loss, and this effect was maintained in the weight loss maintenance phase at 12 months. No such effect was seen in those who did not achieve remission.[20] The improvement in insulin response following rapid weight loss is most likely due to dedifferentiated β-cells regaining their function following a decrease in pancreatic fat content.[25,74] Although there is some evidence obtained from human and animal studies regarding dedifferentiation of β-cells,[75,76] results from population-based and clinical studies also support that dedifferentiation of β-cells is potentially reversible. Therefore, regaining function of β-cells following rapid weight loss and maintaining this weight loss is possible. This effect is more pronounced with the achievement of glycemic control at the early stages of T2DM diagnosis.[25,77] In order to monitor patients who achieved T2DM remission through various dietary and/or lifestyle interventions, some practical steps could be taken in primary care to improve chances of maintaining remission. In addition to HbA1c measurements at regular intervals, measurement of C-peptide is suggested to be a good indicator of β-cell capacity, as it gives an idea on endogenous insulin secretion.[78]

It is known that T2DM is associated with increased formation of advanced glycation end products (AGEs) and chronic inflammation markers, several epigenetic changes, glucotoxicity, increased TG, and other CVD risk markers.[79] Accumulation of these factors contributes to the risk of microvascular and macrovascular complications of T2DM and deterioration of metabolic health. Therefore, delayed treatment of T2DM following diagnosis and poor glycemic control might result in increased risks for complications in the long term. To be more specific, this situation may well be associated with "legacy effect." Several observational cohort studies with long follow-up demonstrated this "legacy effect," which refers to the intense early treatment for normalizing of blood glucose levels leads to diminished risk of microvascular and metabolic diseases in the long term.[77,80,81] This implies that even if people cannot maintain T2DM remission, initial dietary or surgical treatment to induce remission would still have beneficial effects in the long term.

3 | PSYCHOLOGICAL AND SOCIAL DETERMINANTS OF LONG-TERM REMISSION

T2DM and obesity are readily associated with many psychosocial challenges to patients that may lead to poor mental health.[82] Several factors contribute to this including stigma regarding both conditions, physical health burden, social limitations, and dependency on medication.[83,84] Furthermore, quality of life is usually decreased in the majority of people with T2DM.[85]

Lifestyle interventions to manage diabetes and maintain remission are more challenging when lower self-management behavior is observed.[86] As weight loss maintenance is central to T2DM remission, its determinants such as cognitive, behavioral, social, and psychological factors[87] apply to the maintenance of remission as well. For instance, emotional factors and ineffective coping mechanisms have substantial effects on weight maintenance phase.[88] Behavior change is found to be essential in successful long-term remission with essential elements of creating autonomy, a shift in people's perception of themselves, and social contagion and support received from their social environments.[89]

Socioeconomic status is a determinant factor in the incidence of T2DM and obesity,[90] so it may also be a determinant for long-term remission. Given the global increase in inflation and associated high costs of living, people's access and choice of healthy foods are likely to be impacted. This is highlighted in the Broken Plate 2022 report by the UK Food Foundation.[91] Healthy food is usually three times more expensive than less healthy food, which will have negative implications for people who are trying to adhere to their diet. Moreover, increases in energy prices may have led to difficulties in cooking food in a home environment, which may drive people to buy convenience foods from stores and/or fast-food chains. These issues bring into the discussion the concept of ultra-processed foods (UPFs), which are usually classified according to the NOVA classification based on their nature, and the extent and purpose of the industrial processing they undergo.[92] A 4-week randomized controlled trial of ad libitum food intake showed a significant association between a high intake of UPFs and greater energy consumption and short-term weight gain.[93] This is significant because the majority of the total energy comes from UPFs in adults and children in the United Kingdom.[94] However, it should be noted that some everyday foods such as a multi-seed sliced wholemeal loaf, dairy alternatives, unsaturated fat spreads, textured soya protein, and gluten-free bread are all considered as UPF; therefore, suggesting extreme care is needed when considering the role of UPFs in health, as not all are considered harmful to health.[95] The British Nutrition Foundation suggested in their position statement that consumers need to be supported to choose healthier versions of processed foods, and this can include some nutrient-dense, affordable UPFs.[96]

All these challenges may cause people who are in remission to deviate from their dietary intervention (whether it is an LCD or VLED) in the long-term and perhaps undo remission. Certainly, more research is needed to address both the potential physiological and psychosocial challenges of maintaining remission in the real-world. Furthermore, a more patient-centered approach should be adopted to deal with individual challenges and barriers.

4 | CONCLUSION

Lifestyle and dietary interventions can be effective in achieving T2DM remission. It is suggested that they should be the primary goal for newly diagnosed patients with T2DM in standard care. This ambitious goal of achieving remission will improve further as more clinicians become aware of T2DM remission being a feasible option for many people. However, maintenance of remission is challenging, and several physiological and psychological factors play a role in this. Maintenance of T2DM remission is especially challenging in a real-world setting in comparison to highly resourced interventional studies. Nonetheless, results indicate that remission is achievable and can be maintained with appropriate and adequate support. More real-world research studies with longer follow up periods are warranted to assess which factors exactly cause a decline or maintenance in remission rates over time. Lastly, a more personalized approach offering clinical and behavioral support to overcome psychosocial barriers may be needed for people struggling with remission; however, this will have cost and resource implications.

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CONFLICT OF INTEREST

Tom Butler is a research officer for the British Dietetic Association Public Health Nutrition Specialist Group and Scientific Officer for the British Association for Cardiovascular Prevention and Rehabilitation. Julie Abayomi is the Chair of the England board of the British Dietetic Association.

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