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# Dietary strategies for remission of type 2 diabetes: A narrative review

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Abstract

Type 2 diabetes (T2DM) is a growing health issue globally, which until recently has been considered to be one that is both chronic and progressive. Treatments, although having lifestyle and dietary change as core components, have been focused on optimising glycaemic control using pharmaceutical agents. With data from bariatric surgery and, more recently, total diet replacement (TDR) studies which have set out to achieve remission; remission of T2DM has emerged as treatment goal.

A group of specialist dietitians, medical practitioners was convened, supported by the British Dietetic Association and Diabetes UK, to discuss dietary approaches to T2DM, and undertook a review of the available clinical trial and practice audit data regarding dietary approaches to remission of T2DM.

Current available evidence suggests a range of dietary approaches, including low energy diets (mostly using TDR) and low carbohydrate diets, can be used to support the achievement of euglycaemia and potentially remission. The most significant predictor of remission is weight loss, and although euglycaemia may occur on a low carbohydrate diet without weight loss, which does not meet some definitions of remission, but may rather constitute a 'state of mitigation' of T2DM. This technical point may not be considered important for people living with T2DM, aside from that it may only last as long as the carbohydrate restriction is maintained.

The possibility of actively treating T2DM along with the possibility of achieving remission should be discussed by healthcare professionals with people living with T2DM, along with a range of different dietary approaches which can help to achieve it.

Practice Points

- Type 2 Diabetes (T2DM) remission should be considered as a treatment goal for people living with T2DM (especially for those within 6 years from being diagnosed). The ability to achieve this may be influenced by duration of diabetes, weight loss and gender. Therefore, it should be positively discussed with this in mind.

- Based on the evidence from clinical trials weight loss (typically 15kg or greater) is the main driver and predictor of remission. However, more data is needed so it is more reflective of an ethnically diverse population.

- Based on evidence from clinical trials, maintenance of weight loss appears to be the main driver of continued remission, and therefore needs to be a key focus of the planning and delivery of all services designed to achieve remission. If a diet low in carbohydrate is sustainable to the individual, normoglycaemia may be maintained in the absence of weight loss, although evidence is limited and loss of remission is likely to occur if carbohydrate restriction ceases.

- Total dietary replacements (TDR) and low carbohydrate diets have been demonstrated as being effective in facilitating weight loss and remission of T2DM. Evidence of effectiveness beyond twoyears is limited. The dietary approach should be one which the individual can maintain for the long term.

- TDR and low carbohydrate diets, if appropriately supported, are considered safe and should not be avoided in suitable individuals who find these approaches acceptable. Clinicians should therefore aim to support their use within clinical practice as part of person-centred diabetes care.

- Programmes supporting people toward achieving remission need to be structured and offer continued, regular support, including the involvement of dietitians (mandated by NHS England).

Practice Highlights

- Conversations with people with Type 2 diabetes should include discussing remission
- Weight loss is the primary driver of remission in type 2 diabetes
- The dietary approach to achieve remission is less important, total diet replacement and low carbohydrate diet can be effective as can Mediterranean diets.
- Normal glycaemia can be achieved without physiological changes, especially with low carbohydrate diets.

- Structured support is important for long-term success, ideally including a dietitian.

Graphicalabstract

Different dietary approaches as well as bariatric surgery have been shown to facilitiate remission of type 2 diabetes
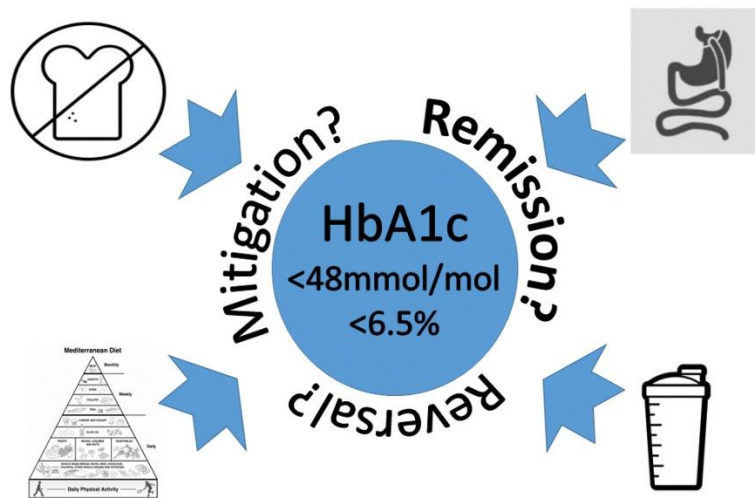


## Introduction

In recent years, the focus in supporting people with T2DM has shifted from an upward titration of medication to manage what has been considered to be a progressive life-long condition (1) to one which can be potentially (at least for a period of time) put into remission. The predominant view has been that T2DM care has focused upon risk reduction with respect to both macrovascular and microvascular complications (2), which has been seen to exist with deterioration of metabolic and primarily glycaemic control, thus justifying a need to escalate pharmaceutical management including eventually progressing to exogenous insulin therapy (IT) (3). The use of IT in the management of T2DM has changed in the last two decades with the introduction of incretin-based medications and sodium glucose transporter 2 inhibitors, which have potentially extended the time before IT is offered to individuals requiring improved glycaemic control (3). The focus on titrating and adding additional agents remains the core of glycaemic management in T2DM though (4), despite the emergence of remission as a possible treatment target (5, 6), especially related to sustained weight loss.

A group from the British Dietetic Association (BDA) Diabetes and Obesity Specialist Interest Groups, along with medical doctors with an interest in low carbohydrate dietary approaches and academic dietitians with research interests in diabetes and obesity management and Diabetes UK formed a focus group in June 2019. Part of the initial outcome from this group was to undertake a critical review of dietary approaches and interventions which support people with T2DM being able to achieve remission of their diabetes. This review will consider both the nutritional strategies and their mode of delivery, utilising data derived from both clinical trials and reported case series.

The focus in clinical practice on T2DM being a progressive disease (at least with respect to rate of progression and beta cell [β-cell] decline) has begun to decrease, with the publication of a number of studies showing the potential of educational, behavioural and lifestyle interventions suggesting T2DM is not necessarily progressive, but rather is potentially, transiently at least, metabolically reversible (7). However, this concept remains to be the focus in practice, with the majority of newly diagnosed people with T2DM being referred to structured education to help manage their blood glucose. Moreover, several systematic reviews and meta-analyses have demonstrated that self-management education is effective at reducing glycated haemoglobin (HbA1c) (8-10). The clinical impact of structured education varies, with some resulting in no difference in HbA1c at 1 year (11), whereas others maintain a reduction in HbA1c after a year in addition to a reduced requirement for prescribed medication compared to standard care (12). Despite the potential of education to help improve glycaemic control, the focus of much of the management of glycaemia in T2DM has focused on algorithms which facilitate the prescribing and dose escalation of pharmaceutical therapies, with a near sole focus of achieving optimal glycaemic control.

Despite most guidelines primarily focusing on the pharmaceutical management of hyperglycaemia in T2DM, weight loss has continued to be a core part of management guidelines (13). This focus on weight loss perhaps has been incongruent with the parallel recommendations of upward titration of either IT or sulphonylurea, which risk the side effect of inducing iatrogenic weight gain. Systematic reviews of bariatric surgery cohorts (14, 15) not only demonstrated acute improvements in glycaemic control, but also revealed that T2DM could be put into remission in between 58-95% of people (14, 16). The mechanism and latterly

the formalisation of definitions of remission have subsequently emerged over the past decade, however an international consensus definition is still awaited.

Perhaps the most widely accepted mechanism of remission is based upon Taylor's 'Twin Cycle' hypothesis (17). This hypothesis is based on the basic principle that excess intake of dietary energy, occurring in conjunction with insulin resistance, results in ectopic fat accumulation (both exogenous from the diet and *de novo* triglycerides synthesised in the liver) in hepatocytes and the islets of Langerhans of the pancreas. This results in increased hepatic insulin resistance and reduced first phase insulin secretion respectively. The long-term glycaemic benefits of bariatric surgery are multifaceted, although primarily associated with facilitating a significant reduction in body weight and adipose tissue (18). This mechanistically is thought to be associated with the reduction of the amount of lipids accumulated in the liver and pancreas and therefore has the dual effect of reducing insulin resistance and enhancing insulin secretion (17). More recently, the mechanisms around the rapid glycaemic benefit following bariatric surgery have been associated with significant reduction in acute energy (calorie) intake and hence intermediary metabolism substrate deficit following surgery (19). This would suggest that interventions that can mimic this energy deficit might help to drive similar acute changes in glycaemia, preventing the physiological rise in plasma glucose seen in the immediate postprandial state based on the meal composition.

## Approach to the Review

The review group, using their expertise from both clinical practice and research, undertook to critically review the literature. PubMed, Scopus and Medline were searched for original research articles using combinations of terms 'remission', 'reversal' 'type 2 diabetes', 'very low energy', 'low energy', 'very low calorie', 'low calorie', 'very low carbohydrate', 'low carbohydrate', 'ketogenic' until December 21st, 2020.

A pragmatic narrative approach was used, which considered how data from clinical trials can be interpreted alongside data from clinical practice and case series. A critical analysis of the available data was undertaken to update clinical recommendations and help inform clinical practice. Heterogeneity of studies was considered as a potential source of bias, in that some studies, such as the Diabetes Remission Clinical Trial (DiRECT) (5, 20), were designed to achieve T2DM

remission, whereas other studies did not have this as a primary aim, did not have a control arm, or were audits of clinical practice rather than controlled trials. Alongside the use of bariatric surgery (21) and low energy formula approaches (5), analysis of clinical practice (22, 23) and trials using very low carbohydrate, ketogenic diets (24) which havereported achieving T2DM remission as their outcome goal, were be considered as part of this review.

Additionally, data from other dietary approaches, including intermittent fasting, were also initially considered as these have been suggested as a potential approach by at least one healthcare provider (25). However, to date only limited data is available for intermittent fasting and currently only pilot study data is available that relates to reduction in medication use and not remission (26), therefore were not considered further as part of this review. Therefore, with the significant interest the potential of remission offers people living with T2DM, a practical, evidence informed review can support practitioners in providing individualised advice and care in a clinical setting.

## Defining Remission

The concept of remission in T2DM is relatively new, despite spontaneous remission being reported in the literature in the 1960s (27). A challenge in the interpretation of the literature is the heterogeneity in the definition of remission of T2DM, with variation in three main areas; discontinuation of glucose lowering medication, glycaemic thresholds, and duration (28). Additionally, the Association of British Clinical Endocrinologists and Primary Care Diabetes Society (ABCD/PCDS) definition includes a requirement of weight loss as one of its criteria (29).

Despite the variety in definitions of remission, the most common definitions used are those from the American Diabetes Association (ADA) (30), used in DiRECT(5) and Diabetes Intervention Accentuating Diet and Enhancing Metabolism (DIADEM-I) (31). This defined remission as an HbA1c <48 mmol/mol. Other definitions used in studies were that of Virta Health (24) which, along with the ABCD/PCDS definition (29), are summarised in Table 1.A proposed international consensus definitions from diabetes professional bodies is currently awaiting publication.

[TABLE 1 IDEALLY HERE]

The addition of weight loss as a defining feature of remission by the ABCD/ PCDS definition (29) could potentially mean it would exclude euglycaemia achieved following a low carbohydrate/ketogenic diet in the absence of weight loss, even when all diabetes medication is discontinued. The necessity of weight loss in the ABCD/ PCDS definition potentially leaves euglycaemia without weight loss on a low carbohydrate/ ketogenic diet without a classification, a point which is seemingly not concordant with the historic observations of O'Sullivan and Hurtwitz (27). Weight loss has been reported as a common feature associated with achieving remission of T2DM, with a target weight loss of 15kg being highly predictive of achieving success (5, 14, 16, 32). However, weight loss has not been universally reported in individuals achieving euglycaemia and therefore remission and as such, a potential alternative definition or status of below diagnostic levels of glycaemia maintained by a dietary approach such as a ketogenic or low carbohydrate diet. Therefore this group proposed the introduction of the term 'T2DM mitigation' for euglycaemia without weight loss, as this acknowledges its potential dependence on continued carbohydrate restriction and lack of the physiological changes associated with T2DM remission which, occur with weight loss (33-35).

Within this review, due to the heterogeneous nature of the data, it was necessary to use multiple definitions depending on the intervention used, for example for bariatric surgery the ADA definition of partial remission will be used (30) whereas for formula low energy diets (LED) also described as TDR the DiRECT definition will be applied (5). If alternative definitions are used, we have highlighted these along with the potential implications this could have for implementation of these approaches in routine clinical management of people with T2DM.

Bariatric surgery and remission of type 2 diabetes

The first indication that remission of T2DM was achievable came from patients' experiences following bariatric surgery. It was observed that people with T2DM were able to omit all diabetes medications including exogenous IT, with blood glucose concentrations returned to target range within 24-48 hours following surgery; well before any significant weight loss (36). This posed the question, what was driving this change? Remission rates particularly following a Roux-en-Y gastric bypass (RYGB) or biliopancreatic diversion (BPD) are far greater than those

achieved by traditional best medical care (14-16). These figures do however reduce in individuals with T2DM managed with insulin (37).

The exact mechanisms by which bariatric surgery elicits these improvements to glycaemia is not completely understood, though energy restriction (38), vagal tone (39), gut hormones

(40), bile acid metabolism (1) and reprogramming intestinal glucose metabolism have all been implicated (42). To date, the data on durability appears to favour bariatric surgery as this is the only approach to remission which has data showing its effect for up to 10 years (43).

## Remission with clinically significant weight loss from clinical trials

Studies have confirmed that marked energy restriction and weight loss can favourably alter key aspects of the pathophysiology of T2DM, resulting in normoglycaemia despite not specifically focussing on achieving remission (44-46). These studies showed that both a marked energy deficit (36, 47, 48) and an associated weight loss (47, 48) result in a return to normoglycaemia in people with T2DM. However, in all of these studies, the follow-up tests were carried out immediately following the energy restriction, and therefore it was unclear whether hyperglycaemia would return with resumption of usual dietary and lifestyle behaviours.

The landmark Counterpoint study (33) demonstrated that a formula very low energy diet (VLED) led to significant weight loss, which may have a durable effect on the key pathophysiology underlying T2DM and provided evidence for the 'Twin Cycle' hypothesis (17). In this study, 11 people with T2DM of less than four years duration consumed a formula VLED (600kcal/day) for eight weeks. Using this intervention subjects achieved normal glycaemia, liver insulin sensitivity was restored and the first-phase insulin response returned to levels of weight-matched controls without T2DM. After the VLED period, the subjects were followed up for 12 weeks, which found a mean weight gain of 3.1kg. The fasting and 2-hour glucose concentrations also increased marginally, with three subjects having reoccurrence of their T2DM. This study provided data suggesting that restoring the underlying pathophysiology could help manage glycaemia independently of calorie restriction alone. A further study by the same group examined the longer-term effects of a VLED and reported that remission of T2DM was sustained up to 6 months (34).

Importantly, remission in the studies described did not occur in all individuals (34). Those who responded had higher fasting plasma insulin, lower fasting plasma glucose, shorter duration of T2DM, were younger, and were on fewer medications. Importantly, they also had lower pancreatic, and total body fat, but there were no differences in hepatic triglyceride content (34). However, the primary factor distinguishing responders from non-responders was the return of the first-phase insulin response. The first-phase insulin response improved further in responders, whereas there was no change or little change in non-responders.

The larger DiRECT study confirmed these findings (5, 20), providing high-quality evidence that remission is possible within a primary care setting using a formula LED (~826- 850kcal/day). The restoration of β-cell function and the export of very low-density lipoprotein (VLDL-P) from the liver were key in achieving remission (35, 45). In this cluster randomised controlled trial involving 149 subjects per group, individuals with T2DM diagnosed in the last 6 years and a BMI of 27-45kg/m$^2$ were randomised to either an intensive weight management programme using a LED or standard care. The primary outcomes were two-fold, achieving 15kg or more weight loss and/or remission of T2DM (See Table 1). Although, a successful approach, caution needs to be taken due to the limited diversity of the population and the relatively high initial attrition in this study.

At 12 months, 46% of patients in the intervention group and 4% in the control group achieved remission. The proportion of patients achieving remission increased with greater weight loss, with those achieving a weight loss of 15kg or more having a remission rate of 86% at 12 months (odds ratio per kg weight loss = 1.32) (5). Mean weight loss achieved was 10.0 kg within the intervention group and 1.0kg within the control group, showing formula LED is an effective treatment in achieving T2DM remission and weight loss in this patient population. The 2-year data has shown that many of the benefits were sustained in relation to both weight loss and T2DM remission, although the percentage in remission fell from 46% to 36%. Mean weight loss was still significantly greater following the LED (7.6kg) compared with the control group (2.3kg), despite a mean 2.3kg weight regain; while 36% of the subjects sustained diabetes remission in the intervention group (compared to 3% in the control group), similar to the results at 12 months. Greater weight loss was again associated with a higher rate of remission (odds ratio per kg weight loss = 1.25) (5), showing that this is the key driver to remission.

More recently, data from Qatar (DIADEM-1) (31) has demonstrated that a TDR approach can be highly effective in achieving remission in a cohort of patients with Middle Eastern and North African origin. In this study, also delivered in primary care, 61% of participants achieved remission, while 33% achieved normoglycaemia (Hba1c<5.7% (<39 mmol/mol). The mean body weight loss was 11.98kg compared with 3.98kg in the control group, with 21% of participants achieving more than 15% weight loss at 12 months. The differences between DiRECT and DIADEM-1 may have been in part driven by the characteristics of the study population being predominantly male, younger, were diagnosed with T2DM with the last 24 months and mostly good glycaemic control, which has been shown to predict remission (32).

Therefore, high-quality data is available supporting the use of formula diets to support achieving remission of T2DM; with significant weight loss and a return of the first-phase insulin response. While reduction of ectopic fat and normalisation of hepatic insulin sensitivity are important in achieving remission, restoration of β-cell function appears to be essential for durable remission (35). Furthermore, there appears to be a point at which β-cell function declines to a degree from which it cannot recover (although lifestyle interventions aimed at inducing remission are still likely to result in significant clinical and quality of life benefits). Recently a post-hoc analysis of the DIRECT study looking at predictors of remission; confirmed weight loss to be the strongest predictor of remission at both 12- and 24-months. In addition, baseline predictors for both 12- and 24-months remission were fewer anti-diabetes medication, lower gamma-glutamyl transferase levels and better quality of life. While lower baseline HbA1c predicted 12-month remission and older age and being male predicted 24-month remission (32). Combining these data, this might suggest that a targeted use of these dietary interventions, are more likely to be effective within a clinical setting if they are implemented within 6 years of diagnosis of T2DM and ideally within 2 years, in those on less medication, better mental health, male and with better glycaemic control (32, 49).

Carbohydrate restriction as a means to achieving remission of T2DM and glycaemic mitigation

The role of carbohydrate restriction in the remission of T2DM has come to the forefront of dietary management with high-profile patient stories of 'remission'

achieved with a very low-carbohydrate diet and the publication of clinical audits resonating the same outcomes (22, 24). At present there remains a lack of consensus on the definition of a very-low or low-carbohydrate diet within the literature (50), though the definitions proposed by Feinman et al., 2015 have become commonly used in practice ( 51) (Table 2). A key issue in this area is that there is significant heterogeneity in the methods used between studies, hindering the drawing of firm conclusions and adding further confusion to both clinicians and patients, with respect to target levels of dietary carbohydrate. Furthermore, most studies have achieved substantial weight loss, and it is therefore not possible to determine the independent effect of adjusting any one macronutrient, including carbohydrate restriction on glycaemia and ability to achieve T2DM remission.

Several meta-analyses have reviewed the effect of carbohydrate restriction (usually compared with low-fat diets) on glucose homeostasis and weight loss, typically using fasting glucose or HbA1c as the primary outcome, although T2DM remission has not been the focus and has rarely been reported (52-55). In general, these studies have found that low carbohydrate diets and particularly very low carbohydrate diets are associated with greater improvement of HbA1c at least in the short term (up to 6 months) but no difference has been found over the long-term (12-months) (52-54). It is highly likely that at least some of the apparent lack of effect is due to a drop-off in ability to continue the level of carbohydrate restriction necessary over time to maintain these improvements. Supporting this, participants assigned to the low-carbohydrate arm of studies have shown increased carbohydrate intake over the course of the year (54-57), with a review of this phenomena suggesting the change in carbohydrate intake can vary from a 20% decrease to a six-fold increase at follow up (58). These reviews are also limited by a failure to consider the influence of changes in medication requirements. Within the trials included in meta-analyses it is common for the low-carbohydrate groups to reduce anti-hyperglycaemic medications to a greater degree than those in the control arms, and so a failure to consider this may result in the benefits of low carbohydrate diets being underestimated in some instances.

[TABLE 2 IDEALLY HERE]

While randomisation is considered to be important in trials to control and account for confounding factors, one of the key disadvantages in dietary trials is that

participants rarely adhere to the prescribed diet over a long period. Therefore, non-randomised trials, in which individuals are supported to choose the dietary approach they wish to adopt can be useful in providing an indication of what might be achievable within routine diabetes care. One example of this approach is a recent open-label, non-randomised trial by Virta Health (24, 59) which compared the effect of a well-formulated very low carbohydrate, ketogenic diet to usual diabetes care. A total of 349 patients with T2DM were enrolled, with 262 self-selecting the ketogenic diet. The care was delivered remotely, with one-to-one support using biomarkers (capillary β-hydroxybutyrate) to monitor ability to achieve and maintain nutritional ketosis. Participants had access to a web-based software application providing tele-medicine access to a care team, consisting of a health coach and a medical practitioner (physician or nurse), social support was provided by an online peer community. All participants maintained their existing primary healthcare provision. Each education session lasted 90 minutes, with 26 sessions being delivered over the 12 month period. At 12- months those on the continuous care usual care arm 0.20% [2.19mmol/mol]). The adjusted mean weight loss was 13.8kg at 12 months, with the usual care losing only 1.1kg. At 24-months weight loss was 11.7kg, usual care. As with DiRECT (5), this study focused on individuals who were clinically living with obesity, more research is needed with respect to individuals with T2DM who are not living with obesity.

Although the primary endpoints of this study did not focus on achieving remission, a post-hoc analysis was conducted to assess this outcome. Using the definition of T2DM remission used in DiRECT, 25% of participants achieved remission using an intention to treat analysis. The study protocol however intended for participants to remain on metformin (which would preclude them achieving remission based on the DiRECT criteria) due to the proposed benefits (3). A further 35% of participants met the criteria for remission at 12 months if the prescription of metformin was not considered, though given that the glucose-lowering effect of metformin can be in the order of 9-11mmol/mol (53) it can be hypothesised that a number of these individuals would not have remained in T2DM remission if metformin were removed. At 24 months, remission remained significantly better in the continuous care intervention arm, with 17.6% achieving remission compared with 2.4% in usual care. Similar to the results in DiRECT, there was a slight decline in remission rates over time despite substantial weight loss (59).

Although the direct comparison of DiRECT and Virta is challenging due to methodological differences, it should be noted that the mean duration of T2DM in this study was 8.4 years (24), compared to 3.0 years in DiRECT (5). In addition in Virta 57% were prescribed a diabetes medication other than metformin and 46% were prescribed insulin (24). This is in contrast to the DiRECT study (5) which excluded people taking IT and only included people with T2DM diagnosed within the previous six years. Given the tendency for β-cell function to decline with duration of T2DM, this might in part explain the differences in rates of remission at 12 and 24 months.

Despite impressive outcomes there are several limitations that have to be appreciated when interpreting the Virta Health data. The study used β-hydroxybutyrate as a marker for ability to follow the diet. The ketone data at both 12 and 24-months shows that patients struggled to maintain nutritional ketosis, with concentrations rarely exceeding the recommended 0.5mmol/L, with the mean being 0.3mmol/L (24, 59). This suggests that adherence to the diet deteriorated over time. Therefore, given the marked weight loss achieved it cannot be concluded that the ketogenic diet *per se* was the exclusive driver of improved glycaemia and T2DM remission. In addition, it is also worth mentioning that the level of contact was much higher than found within traditional clinical practice, and so replication of this model in primary care would be extremely challenging at present. Furthermore, the monthly cost of accessing the programme could impact on accessibility to only those with medical insurance or in the higher socio-economic classes. Therefore, questions remain about the generalisability to a public healthcare setting (such as the UK NHS), although the use of a digital platform may at least in part mitigate this as an issue.

Finally, there is growing interest in the use of carbohydrate restriction in primary care. Several clinical audits have been published which used carbohydrate restriction and weight loss to manage T2DM, in an attempt to achieve remission (22, 23, 60). This data can be challenging to interpret as often there are no published dietary protocols, and participants vary in terms of baseline characteristics, including duration of T2DM, initial HbA1c, and type and amounts of medications, while much of the data is self-reported. However, these clinical audits also show that, for some patients, glycaemia in the normal range can be achieved in conjunction with medication de-prescribing.

An example of this approach comes from Norwood Surgery (9,500 patients in Merseyside, UK), who have reported that 27% (n=128) of individuals with T2DM registered with the practice engaged with their carbohydrate restriction-based programme (61). This has been achieved using a mixture of 10-minute clinical visits, patient-friendly physiological explanations of how changing dietary carbohydrate choices can positively impact on blood glucose, diabetes and health, and group consultations. Utilising this approach this NHS practice has demonstrated an average a median improvement using routine clinical measurements of HbA1c of 17.5 mmol/mol and 46% remission rate at 23 months for those choosing the low carbohydrate approach. Surprisingly a sub-cohort (n=45) of participants who had T2DM longer than 6 years did better with an average improvement in HbA1c of 24mmol/mol, which did not appear to be associated with change in weight ($R^2$=0.0058, P=0.402) The practice spends £50,000 per year less than the local Clinical Commissioning Group average on drugs for diabetes, offering hope of novel revenue streams for better clinical care. Their approach goes beyond a single lifestyle intervention strategy and is grounded in the behavioural principle which centres on the concept of 'hope' (of what better health could be like) (62), along with peer support and social connectivity. The effectiveness of this approach is supported by observational data, which suggests that individuals who believe that they can achieve remission are more likely to achieve this goal. To date Norwood reports 87 individuals in T2DM remission at an average of 30 months (63). This model and approach has been successfully replicated in online platforms (64).

Carbohydrate restriction-based approaches have been shown in primary care to be a safe and acceptable way for individuals with T2DM to optimise their glycaemic control (61). The ability however of carbohydrate restriction specifically to produce T2DM remission is less clear, as weight loss is often also reported, making the attribution of causality difficult. This leads to the possibility that optimising T2DM control using carbohydrate restriction may be 'diabetes mitigation' rather than a physiological remission, as the underlying pathology may not be being altered if weight loss is not present, and a return to a normal dietary pattern may therefore lead to the return of dysglycaemia. Although this may be physiologically accurate, clinically it might not be significant, and maybe of little or no importance to an individual who can, is willing to maintain carbohydrate restriction, and who

benefits from reduced risks of complications due to optimal glycaemic control regardless of the underlying mechanism of effect.

Can current dietary advice for patients with T2DM result in diabetes remission?

Although there is increasing interest and evidence to support dietary approaches aimed at supporting T2DM remission, mainly from studies and use of TDR and carbohydrate restriction, practice is still largely focused on recommendations linked to the wider public health nutrition messages. Nutritional management of T2DM has historically focussed on improving blood glucose concentrations, and promoting weight loss, without specifically aiming to achieve remission (13, 65). While significant weight loss can help improve and even normalise glycaemia and aid T2DM remission, moderate weight loss (e.g., 5% body weight), more commonly seen in clinical practice, is usually not sufficient to achieve similar outcomes. Supporting this, a retrospective cohort study of people with T2DM receiving typical ADA care (including dietary advice) reported a 7-year cumulative incidence of partial remission of only 1.47%, and complete remission rate of just 0.14% (66). This shows that although remission was achievable following usual care, it was very rare.

Data from the Look AHEAD trial, which used a combination of meal replacements and an energy restricted, low-fat diet, showed in post-hoc analysis that remission occurred in 11.5% of people at 12 months in the intensive lifestyle group (ILI), despite an impressive weight loss of 8.6% (44). The prevalence of remission decreased during the follow-up period and reduced to 7.3% at year four, with about one-third in the ILI group returning to a clinical diagnosis of T2DM each year (44). The mean duration of T2DM in the cohort was only five years, similar to that seen within DiRECT. However, more than 80% of the Look AHEAD subjects were taking two or more hypoglycaemic medications; with 15% taking insulin, which, as with the Virta Health results, may have affected remission rates (24, 59). Indeed, multivariate analysis confirmed that shorter diabetes duration, lower HbA1c, not taking insulin and a greater weight loss at one year were associated with greater remission (44)..

The potential of the Mediterranean diet has also been explored, with a lower carbohydrate Mediterranean diet compared against a low-fat diet. Participants following a Mediterranean diet achieved greater remission rates across all years over a six year follow-up (67). At the end of the first year, any remission (partial or complete,

according to the ADA definition (30)) was 14.7% in the Mediterranean diet group compared to 4.1% in the low-fat group. These figures reduced year on year, with 5% of participants on the Mediterranean diet still being in remission at 6 years compared to 0% in the low-fat group (5, 67). This reduction in remission appears in part to be related to the weight regain observed over the study period. This data is difficult to directly compare with other remission studies as the initial aim was the introduction of anti-hyperglycaemia medications in people with newly diagnosed T2DM specifically and not remission. Furthermore, also the degree of carbohydrate restriction was modest at 40% of dietary energy from carbohydrate, compared to other studies which adopted a low carbohydrate approach (67).

More recently, several other studies have been conducted looking at intensive lifestyle interventions which have included supervised exercise programmes with low-fat, energy restricted diets (45, 46) and additional education sessions (68) to achieve T2DM remission. These have been conducted in a variety of different patient populations and show with intensive intervention T2DM remission is achievable, with figures ranging from 17.8-53.3% achieving partial or complete remission at 12 months (46, 68). However, as these studies utilised weight loss to facilitate remission, this provides evidence for intensive education supporting dietary energy restriction can be an effective strategy to improve glycaemia and induce T2DM remission.

Practical considerations when supporting people towards achieving remission

Although the use of formula TDR and low carbohydrate diets in T2DM and obesity are not novel concepts, the implementation and delivery of specific remission-focused services for T2DM is an emerging area and is therefore largely under-researched as part of routine diabetes care. The limited use of TDR, despite good evidence for their safety and efficacy (69), could be related to a lack of confidence from healthcare professionals in using these approaches, as well as a negative view of their palatability, safety and side effects (70). While the potential lack of use of low carbohydrate diet use might have been driven by the lack of recognition within international guideline, related to the concerns regarding the long-term safety and impact on cardiovascular risk, although this has now started to change, with a number of guidelines starting to recommend their use (3, 13).

At present there remains a dearth of guideline recommendations regarding mode of delivery of intervention components needed to help people achieve T2DM remission. In reviewing the studies that described interventions which led to remission there was significant heterogeneity in the intervention components meaning that firm conclusions are difficult to define (5, 18, 20, 55, 59, 60-64, 66-68, 71-74) However, there are several areas that should be discussed and considered when supporting people to achieve remission.

Currently, there is limited evidence, if any, that directly assess whether the intensity of the intervention (primarily based on contact time) has a positively impact on T2DM remission rates. When comparing total number of hours of dietary education within different interventions there appears to be no apparent difference in remission rates at one years (25% and 23%) between interventions delivering a total of 36 hours (73) compared with 46 hours (46) respectively. While remission rates of 46% have also been reported within in a real-world setting (22, 60) with a low intensity intervention of approximately five hours in total over a two-year period. These data might suggest that variables, other than contact time per se, may be influencing remission rates, however without direct comparison it is difficult to make a definitive conclusion.

Importantly, the amount of contact may vary between the different stages of T2DM remission, with requirements for initially achieving T2DM remission being different from those needed to maintain remission and weight loss. Although not directly looking at the correlation between intensity of intervention and remission, the number of contacts in the first year of the Look AHEAD trial predicted a greater likelihood of maintaining 10kg weight loss at 4 years (75). As weight loss appears to be the primary driver of T2DM remission (32), this may imply that contact time is in fact a key component to achieving remission.

With the advent of COVID-19, the mode of delivery is now of key importance, with digital delivery models being used effectively to support programmes remotely and able to increase the intensity of the intervention. Virta Health for example utilises continuous care through intensive digital support, including access to telemedicine, health coaching, behavioural education, biometric feedback and peer support via an online community (24), which has been reported to be key to the success of the programme. In addition, a small service evaluation of nine people of a remote digitally enabled T2DM remission programme (74), using a TDR

intervention shows promising outcomes. With patients achieving 16.6kg weight loss, a reduction in HbA1c of 24.3mmol/mol and 44% of patients were reported to have achieved remission. On further review, as they were continued on metformin (due to GP advice) they did not met remission criteria (Table 1) but instead met the Virta criteria for T2DM 'reversal'. However, similar to contact time, there is a lack of studies directly comparing delivery methods to suggest that one mode of delivery (i.e. group-based sessions, individual appointments or online/digital provision) is more effective than another. This lack of evidence of superiority might suggest that a more flexible approach should be offered instead.

The cost of the TDR product could present a barrier to wider use, with self-funding being highlighted as a barrier (76). These qualitative data revealed that some participant following the initial period where the TDR was free, reported that despite wanting to lose more weight with the TDR, cost was a barrier to continued access. Furthermore, more participants reporting that the need to purchase TDR along with a reduced sense of duty to follow the study protocol would impact their ability to continue following this approach. With this in mind, it is sensible pragmatic approach taken by NHS England pilot sites (77) in offering the TDR products to the participants free of charge, which should address these concerns. However, it remains to be seen what will happen following the TDR phase of the pilot and during the weight maintenance phase and whether continued formula product will be provided to enable further weight loss and support weight loss maintenance.

It is possible that using food-based approaches instead of, or in partial combination with formula products may be more affordable and acceptable to some, although currently there is a lack of evidence to support this approach. However recent evidence from The Dietary Approaches to the Management Of type 2 Diabetes (DIAMOND) trial demonstrated that it is feasible to implement a short term (12 week) intervention with a food-based, low-energy (800kcal per day), low carbohydrate diet with behavioural support delivered by practice nurses. Although this study demonstrated significant weight loss and improved glycaemic control, it did not investigate the efficacy of this approach in achieving remission (71). Wider implementation of a food-based low energy diet may be more time-consuming and require greater skilled dietary intervention to ensure nutritional adequacy, two clear

benefits of using a TDR, but could be a potential development for future clinical practice.

Self-efficacy may also play a role in an individual's likelihood to adhere to a new dietary regimen (78). Behaviour change counselling is an integral part of successful dietary interventions (79). The DiRECT study was based on behaviour change models delivered by trained dietitians and practice nurses with the aim of achieving long-term weight loss maintenance (80). An alternative to models based on high levels of healthcare professional input is to consider that the individualised support which can facilitate success can be achieved in a virtual platform if well designed (81) as discussed above. It is likely that providers of services undertaking the NHS England low calorie pilot would need to train their team to deliver this support, but this one-off cost is less than one year of T2DM medications for an individual (80) and thus represents a worthwhile investment.

Most remission interventions have been developed and delivered by a multidisciplinary team who were either already experienced in the delivery of the dietary approach being assessed or were trained to do so. The professional background of educators reported in the literature were either general practitioners, physicians, dietitians, nurses, health coaches, psychologists or lay educators. Although to date there is a lack of evidence to advocate for the essential professional disciplines involved in delivering programmes aimed at achieve T2DM remission, the majority of trials to date have reported the inclusion of a dietitian as a core team member, and this principle has been retained in emerging clinical guidelines (13).

A history of eating disorders is an exclusion criterion for many TRD programmes. Where available, clinical psychologists have been used to facilitate this screening. However, many services may not have access to psychological support. Use of screening questionnaires such as the Eating Disorder Examination Questionnaire (EDE-Q) (82) should be used as part of the screening process, not only prior using formula TDR programmes, but for any planned dietary intervention which has the potential to reduce body weight or alter patients' relationship with food. If carefully supported by a healthcare team, ideally including a dietitian and clinical psychologist, a systematic review of the data suggests that these approaches can be beneficial and does not appear to trigger binge eating behaviour (82).

Additionally, TDRs can be considered in those who have been treated for and effectively manage their binge eating tendencies (83).

A key consideration when looking to achieve remission, especially when looking to follow either a low carbohydrate diet or a TDR, is that medication will need to be adjusted. In the case of DiRECT, oral hypoglycaemic agents, antihypertensive agents and diuretics were withdrawn on commencing the TDR (84). If the approach, is one involving a low carbohydrate diet; insulins, sulfonylureas and meglitinides will usually need to be reduced or stopped to avoid hypoglycaemia (85). SGLT-2is may carry a risk of causing ketoacidosis and should usually be stopped. Other diabetes medications do not require immediate adjustment, however, once a low carbohydrate diet has been commenced, they may become unnecessary. Additionally, a low carbohydrate diet can lead to an improvement in blood pressure, so antihypertensive medication may also need to be lowered or stopped (85).

Another implication to consider is that of the cultural beliefs and practices of individuals and, whilst ethnicity and culture are not synonymous, there is limited published data in diverse populations, with evidence on remission using TDR mainly being in White populations (20). Further trials would therefore need to engage a wider ethnic background to assess whether a TDR would be acceptable and achievable to individuals still wishing to engage in the eating, drinking and social activities associated with their belief, religion and/or culture (86). Recent data from Qatar demonstrated that a TDR approach can be effective in achieving remission (61%) and normoglycaemia (Hba1c<5.7% (<39 mmol/mol); 33%) in a cohort of Middle Eastern and North African origin. This population was predominantly male, was younger (than in DiRECT), and had recent diagnosis of T2DM and mostly good glycaemic control, which may not be representative of a general UK multi-ethnic population that would be seen in a routine healthcare setting (31).

The cost effectiveness of any programme is key to its implementation within clinical practice. Currently, only three interventions have analysed and reported cost effectiveness (87, 88) or cost savings (67, 89). Although independent economic evaluations have previously shown T2DM self-management group education to be cost effective, these did not have remission as a primary goal (90). However, as all the interventions reported remission rates, savings from de-prescribing would be evident. Also, as the remission of T2DM has the potential to reduce the risk of longer-term complications, achieving remission is likely to prove cost-effective

long-term, regardless of the method used to achieve it; particularly if it is feasible to implement it as part of current care pathways. Based on the cost analysis from DiRECT (87, 88) the cost per intervention (largely consisting (95%) of TDR formula costs and clinic visits) was £1223 (87), with each case of T2DM remission costing on average £2564. Costs in the control group were substantially lower (£846), however with remission rate only being 4% at 1 year this is not a clinically effective option. This compares favourably with data from Look AHEAD, where lifestyle interventions cost 2865 USD per intensive lifestyle intervention, resulting in a 11.5% (partial or complete) remission rate (75, 90), and bariatric surgery, where the estimated cost per remission is 14,389 USD (91). At 2 years, the healthcare costs in DiRECT were reported to increase to £3036 and £2420 for the intervention and control group, respectively, per remission. To date, studies have not shown overall healthcare cost savings, but modelling suggests this could be achieved at 6 years, assuming remission can be maintained(88).

DiRECT report that a high proportion of the participants were from socially deprived circumstances, despite being ethnically homogeneous (5). Yau (92) emphasises that low socio-economic status has a strong, positive correlation with non-adherence to dietary advice. Cost has also been cited as a possible reason for the low uptake in using TDR. As the meal replacement products were provided free of charge for DiRECT participants this may partly explain the enhanced adherence to the intervention compared to other studies. However, despite this, almost one third of participants in the intervention arm still withdrew by 24 months (30). It is therefore important that measures to increase retention are explored. The advance in digital technology and digital programmes with in-built support functionalities, which have already been demonstrated to enable cost effective scaling of self-management education in an open label single arm convenience sampled cohort of people with T2DM (63), may help on this front, although more data from better controlled implementation studies are required.

Limitations of evidence for dietary approaches to remission.

The literature suggests that both the availability (both current and future) of TDR product and perceived duty to follow the study protocol may influence an individual's willingness and ability to follow a LED aimed at achieving remission. This represents a potential challenge when translating findings from clinical trials

into routine practice, which is in part overcome by providing TDR product free of charge. This, to a point, is contrasted by the evidence from primary care practitioners who have used low carbohydrate approaches with good success (22, 61). This apparent difference should be treated with caution as it is not possible to quantify the sense of duty and attachment to the practitioner with respect to a potential 'practitioner effect' in those using a low carbohydrate approach. It cannot therefore be ruled out that how remission is approached, and by whom, will have an impact on the effectiveness of an intervention beyond that of the dietary approach applied.

As previously highlighted within this review, caution needs to be taken when considering how interventions have been delivered and with regards to which aspects are integral to their overall success. The variable definitions used to define remission are an additional challenge when interpreting the data, especially if reported outcomes use definitions which permit continued prescribing of metformin. This may impact on the reported remission rates due to differences in de-prescribing protocols rather than due to differences in the effectiveness of the intervention. For example, in one study, metformin was only discontinued due to contraindication, intolerance or patient request (24).

Further limitations that are likely to impact on reported remission rates are that some clinical trials have made use of run-in periods to assess adherence, with only participants who have confirmed compliance to the diet being included (44, 68). The effect of variability in reporting is also seen in analyses of routine clinical practice data, where some groups report the remission rate only in those who have adopted a low carbohydrate diet (22) whereas others reported the remission rate for the entire list of diabetes patients in their practice cohort (61). The overall impact of these could potentially overestimate remission rates in some interventions and cohorts.

Conclusion

From the available evidence it appears that a wide range of options have the potential to bring about T2DM remission. The published clinical trials and real-life examples for both LED and low carbohydrate vary with respect to robustness, numbers of participants, education strategies, intensity of intervention and lengths of follow up. With no direct comparison of these two dietary methods to date, it is

challenging to determine which dietary intervention is the most successful in relation to T2DM remission.

Like many healthcare interventions, one size does not fit all, and individualisation needs to be considered. This may mean that a mixture of different levels of follow up intensity, and mode of delivery (virtual compared to face to face) are likely to be necessary to maximise remission rates, with a more blended approach being taken. There is also a need for longer term evidence for all of these approaches, with data from high quality controlled trials limited to outcomes at, at most, two to four years; though there is some data from five years plus for uncontrolled and observational evidence. Based on this, patients who would like to achieve T2DM remission should be offered a 'menu' of options with respect to educational and dietary approaches if they wish to attempt to achieve remission. This may be key to driving forward remission in a primary care setting.

Lifestyle, including dietary interventions, have not historically been viewed as a form of treatment in the same way as pharmaceuticals. The emerging data with respect to T2DM remission challenges this viewpoint and could lead to the idea that individuals ought to be supported to balance the choice between using diet as an active treatment with one that is compatible with an enjoyable way of living. Therefore, the dietary approach that brings about T2DM remission should be seen as an active treatment, and unless the individual finds this approach sustainable in the long term it might be considered only a partial remission of their condition.

Several of the points about the physiological effect of low carbohydrate or TDR diets on remission could be considered to be academic, and the importance, or lack thereof of these factors to people with T2DM should be respected. However, the potential for diet, either LED, with or without TDR, or low carbohydrate, to dramatically improve glycaemic control and bring about remission needs to be fully embraced within dietetics and wider diabetes care. This should then be used to support people with T2DM to achieve their goals and initiate the conversation about the potential of T2DM remission, wherever it is appropriate.

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Table 1: Summary table highlighting the definitions of remission from type 2 diabetes.

| Guideline for Remission | Partial or complete? | Glucose lowering agents | Glycaemic parameters | Duration | Notes |
|---|---|---|---|---|---|
| American Diabetes Association (30) | Partial | No diabetes medication | HbA1c <48mmol/mol (<6.5%) | >1 year | |
| | Complete | No diabetes medication | Fasting glucose <5.6 mmol/l | >1 year | |
| DiRECT (5)/ DIADEM-1 (31) | Remission | No diabetes medication for >2-3 months in previous 12 months | HbA1c <48mmol/mol (<6.5%) | >1 year | |
| Virta Health(24, 59) | Reversal | No medication or metformin alone | HbA1c <48mmol/mol (<6.5%) | >1 year | |
| | Remission | No medication | HbA1c <48mmol/mol (<6.5%) | >1 year | |
| ABCD/PCDS(29) | Remission | Cessation of all diabetes medication | Fasting glucose <7.0 mmol/l HbA1c < 48 mmol/mol | >6months | Occurs along with weight loss |

Table 2. Suggested consensus for carbohydrate restriction (50, 51)

| Definition | Carbohydrate (g/day) | Carbohydrate (% of energy)* |
|---|---|---|
| Very low carbohydrate or ketogenic diet | 20-50g | 6-10% |
| Low carbohydrate | <130g | <26% |
| Moderate carbohydrate | 130-225g | 26-45% |
| High carbohydrate | >225g | >45% |

Note: *based on 2000 kcal/day diet