



INVITED REVIEW

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

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Funding information

None.

Abstract

Type 2 diabetes (T2DM) is a growing health issue globally, which, until recently, was considered to be both chronic and progressive. Although having lifestyle and dietary changes as core components, treatments have focused on optimising glycaemic control using pharmaceutical agents. With data from bariatric surgery and, more recently, total diet replacement (TDR) studies that have set out to achieve remission, remission of T2DM has emerged as a treatment goal. A group of specialist dietitians and medical practitioners was convened, supported by the British Dietetic Association and Diabetes UK, to discuss dietary approaches to T2DM and consequently undertook a review of the available clinical trial and practice audit data regarding dietary approaches to remission of T2DM. Current available evidence suggests that 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, it may rather constitute a 'state of mitigation' of T2DM. This technical point may not be considered as 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 that can help to achieve this.

KEYWORDS

cellular and physiological function, diabetes, dietary intervention, disease, endocrinology, food intake, therapeutic areas

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 15 kg or greater) is the main driver and predictor of remission. However, more data are needed so that 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 this 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 2 years 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 the National Health Service England).

INTRODUCTION

In recent years, the focus on supporting people with type 2 diabetes (T2DM) has shifted from an upward titration of medication to manage what has been considered to be a progressive life-long condition¹ to one that 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 the 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,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's Diabetes and Obesity Specialist Interest Groups, in addition to medical doctors with an interest in low carbohydrate dietary approaches and academic dietitians with research interests in diabetes and obesity management, along with a representative from 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 that support people with T2DM being able to achieve remission of their diabetes. This review considers 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 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 that 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 1 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 that 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 for between 58% and 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 Mechanistically, this is considered 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 a significant reduction in acute energy (calorie) intake and hence an 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' and 'ketogenic' until 21 December 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 surgery²¹ and low energy formula approaches,⁵ analysis of clinical practice^{22,23} and trials using very low carbohydrate, ketogenic diets,²⁴ which have reported 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 because these have been suggested as a potential approach by at least one healthcare provider.²⁵ However, to date, only limited data are available for intermittent fasting and currently only pilot study data are available that relates to

reduction in medication use and not remission²⁶; therefore, these 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 DiRECT⁵ and Diabetes Intervention Accentuating Diet and Enhancing Metabolism (DIADEM-I).³¹ This defined remission as an HbA1c < 48 mmol mol⁻¹. Other definitions used in studies were that of Virta Health²⁴ 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.

The addition of weight loss as a defining feature of remission by the ABCD/PCDS definition²⁹ could potentially mean that 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 15 kg 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 have been excluded by this definition. Therefore, this group proposed the introduction of the term 'T2DM mitigation' for euglycaemia without weight loss because this acknowledges its potential dependence on continued carbohydrate restriction and lack of the physiological changes associated with T2DM remission that occur with weight loss.^{33–35}

Within this review, as a result of the heterogeneous nature of the data, it was necessary to use multiple definitions depending on the intervention used; for example, for

TABLE 1 Summary of 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 < 48 mmol mol ⁻¹ (<6.5%)	>1 year	
	Complete	No diabetes medication	Fasting glucose < 5.6 mmol L ⁻¹	>1 year	
DiRECT (5)/DIADEM-1 ³¹	Remission	No diabetes medication for > 2–3 months in previous 12 months	HbA1c < 48 mmol mol ⁻¹ (<6.5%)	>1 year	
Virva Health ^{2,4,59}	Reversal	No medication or metformin alone	HbA1c < 48 mmol mol ⁻¹ (<6.5%)	>1 year	
	Remission	No medication	HbA1c < 48 mmol mol ⁻¹ (<6.5%)	>1 year	
ABCD/PCDS ²⁹	Remission	Cessation of all diabetes medication	Fasting glucose < 7.0 mmol L ⁻¹ HbA1c < 48 mmol mol ⁻¹	>6 months	Occurs along with weight loss

bariatric surgery, the ADA definition of partial remission will be used,³⁰ whereas, for formula low energy diets (LED) also described as total diet replacement (TDR), the DiRECT definition will be applied.⁵ If alternative definitions are used, we have highlighted these along with the potential implications that this could have for implementation of these approaches in routine clinical management of people with T2DM.

BARIATRIC SURGERY AND REMISSION OF T2DM

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 h 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 or biliopancreatic diversion are far greater than those achieved by traditional best medical care.^{14–16} These values, however, are reduced in individuals with T2DM managed with insulin.³⁷

The exact mechanisms by which bariatric surgery elicits these improvements to glycaemia are not completely understood, although energy restriction,³⁸ vagal tone,³⁹ gut hormones,⁴⁰ bile acid metabolism⁴¹ and reprogramming intestinal glucose metabolism have all been implicated.⁴² To date, the data on durability appears to favour bariatric surgery because this is the only approach to remission that has data demonstrating 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 study³³ 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 4 years duration consumed a formula VLED (600 kcal day⁻¹) for 8 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, and a mean weight gain of 3.1 kg was found. The fasting and 2-h 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 for 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, although 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 (approximately 826–850 kcal day⁻¹). The restoration of β -cell function and the export of very low-density lipoprotein 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 body mass index of 27–45 kg m⁻² were randomised to either an intensive weight management programme using a LED or standard care. The primary outcomes were two-fold, achieving 15 kg or more weight loss and/or remission of T2DM (Table 1). Although this comprises a successful approach, caution needs to be taken as a result of 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 15 kg 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 1.0 kg within the control group, showing that formula LED is an effective treatment in achieving T2DM remission and weight loss in this patient population. The 2-year data have 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 (7.6 kg) compared to the control group (2.3 kg), despite a mean weight regain of 2.3 kg, whereas 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 a Middle Eastern and North African origin. In this study, also delivered in primary care, 61% of participants achieved remission, whereas 33% achieved normoglycaemia [$\text{HbA1c} < 5.7\%$ ($< 39 \text{ mmol mol}^{-1}$)]. The mean body weight loss was 11.98 kg compared to 3.98 kg 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 partly driven by the characteristics of the study population being predominantly male, younger, with a diagnosis of T2DM within the last 24 months, and demonstrating mostly good glycaemic control, which has been shown to predict remission.³²

Therefore, high-quality data are 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. Although a 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 investigating 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-month remission were fewer anti-diabetes medication, lower gamma-glutamyl transferase levels and better quality of life. A 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 is more likely to be effective within a clinical setting if implemented within 6 years of diagnosis of T2DM and ideally within 2 years, in those on less medication, with 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' being 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 although the definitions proposed by Feinman et al.⁵¹ have become commonly used in practice (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 the ability to achieve T2DM remission.

Several meta-analyses have reviewed the effect of carbohydrate restriction (usually compared to 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 the result of 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.

Although 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. In total, 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 the 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 min, with 26 sessions being delivered over the 12-month period. At 12 months, for those on the continuous care usual care arm 0.20% (2.19 mmol mol⁻¹), the adjusted mean weight loss was 13.8 kg at 12 months, with the usual care losing only 1.1 kg. At 24 months, weight loss was 11.7 kg with 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) because of 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, although, given that the glucose-lowering effect of metformin can be in the order of 9–11 mmol mol⁻¹,⁵³ 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 to 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 because of methodological differences, it should be noted that the mean duration of T2DM in this study was 8.4 years²⁴ 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 study⁵ which excluded people taking IT and only included people with T2DM diagnosed within the previous 6 years. Given the tendency for β -cell function to decline with duration of T2DM, this might partly explain the differences in the 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 the ability to follow the diet. The ketone data at

TABLE 2 Suggested consensus for carbohydrate restriction^{50,51}

Definition	Carbohydrate (g day ⁻¹)	Carbohydrate (% of energy) ^a
Very low carbohydrate or ketogenic diet	20–50 g	6%–10%
Low carbohydrate	<130 g	<26%
Moderate carbohydrate	130–225 g	26%–45%
High carbohydrate	>225 g	>45%

^aBased on 2000 kcal day⁻¹ diet.

both 12 and 24 months show that patients struggled to maintain nutritional ketosis, with concentrations rarely exceeding the recommended 0.5 mmol L^{-1} , with a mean of 0.3 mmol L^{-1} .^{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 noting 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 National Health Service (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 that used carbohydrate restriction and weight loss to manage T2DM, in an attempt to achieve remission.^{22,23,60} These data can be challenging to interpret because often there are no published dietary protocols, and participants vary in terms of baseline characteristics, including the duration of T2DM, initial HbA1c, and type and amounts of medications, with much of the data being 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 the Norwood Surgery (9500 patients in Merseyside, UK), who 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-min 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, on average, a median improvement using routine clinical measurements of HbA1c of $17.5 \text{ mmol mol}^{-1}$ and 46% remission rate at 23 months for those choosing the low carbohydrate approach. Surprisingly a subcohort ($n = 45$) of participants who had T2DM longer than 6 years did better with an average improvement in HbA1c of 24 mmol mol^{-1} , which did not appear to be associated with a 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 that 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 being 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 in primary care have been shown 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 because 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 because 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 could be of little or no importance to an individual who can and is willing to maintain carbohydrate restriction, and who also benefits from reduced risks of complications as a result of 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} Although 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 a 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 a 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 4, with approximately 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 5 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, similar to 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 1 year were associated with greater remission.⁴⁴

The potential of the Mediterranean diet has also been explored, with a lower carbohydrate Mediterranean diet being compared against a low-fat diet. Participants following a Mediterranean diet achieved greater remission rates across all years over a 6-year follow-up.⁶⁷ At the end of the first year, any remission (partial or complete, according to the ADA definition³⁰) 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 to be partly related to the weight regain observed over the study period. These data are difficult to directly compare with other remission studies because the initial aim was the introduction of anti-hyperglycaemia medications in people with newly diagnosed T2DM specifically and not remission. Furthermore, the degree of carbohydrate restriction was modest, at 40% of dietary energy from carbohydrate, compared to other studies that 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 sessions⁶⁸ to achieve T2DM remission. These have been conducted in a variety of different patient populations and show that T2DM remission is achievable with intensive intervention, with 17.8%–53.3% of patients achieving partial or complete remission at 12 months.^{46,68} However, because these studies utilised weight loss to facilitate remission, this provides evidence for intensive education supporting dietary energy restriction as an effective strategy for improving glycaemia and inducing 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 regarding these approaches, as well as a negative view of their palatability, safety and side effects.⁷⁰ Although 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, 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 describing interventions that led to remission, there was significant heterogeneity in the intervention components meaning that firm conclusions are difficult to define.^{5,18,20,55,59–64,66–68,71–74} 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 allows direct assessment of 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 1 year (25% and 23%) between interventions delivering a total of 36 h⁷³ compared to 46 h,⁴⁶ respectively. However, remission rates of 46% have also been reported within in a real-world setting^{22,60} with a low intensity intervention of approximately 5 h in total over a 2-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 investigating 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 a 10-kg weight loss at 4 years.⁷⁵ Because weight loss appears to be the primary driver of T2DM remission,³² this may imply that contact time is 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 programme⁷⁴ using a TDR intervention showed promising outcomes. Patients achieved a weight loss of 16.6 kg and a reduction in HbA1c of 24.3 mmol mol⁻¹, with 44% of patients being reported to have achieved remission. On further review, because they were continued on metformin (as a result of advice from a general practitioner), they did not meet 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 enable the suggestion 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 participants 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 reported 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 sites⁷⁷ to offer 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 (800 kcal day⁻¹), 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 LED may be more time-consuming and require greater skilled dietary intervention to ensure nutritional adequacy, which are 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 facilitating 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, although this one-off cost is less than 1 year of T2DM medications for an individual⁸⁰ and thus represents a worthwhile investment.

Most remission interventions have been developed and delivered by a multidisciplinary team that is either already experienced in the delivery of the dietary approach being assessed or is trained to do so. The professional background of educators reported in the literature comprised 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 conducted 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 to using formula TDR programmes, but also for any planned dietary intervention that has the potential to reduce body weight or alter a patient's 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 also can 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, anti-hypertensive agents and diuretics were withdrawn on commencing the TDR.⁸⁴ If the approach is one involving a low carbohydrate diet, insulins, sulphonylureas and meglitinides will usually need to be reduced or stopped to avoid hypoglycaemia.⁸⁵ Sodium-glucose cotransporter 2 inhibitors 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, and 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, although ethnicity and culture are not synonymous, there are 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⁻¹); 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 the 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, because all the interventions reported remission rates, savings from de-prescribing would be evident. Also, because 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, although modelling suggests this could be achieved at 6 years, assuming that 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 et al.⁹² emphasise 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. Because 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 the 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 because 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, as well as 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 regard 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 that permit continued prescribing of metformin. This may impact on the reported remission rates as a result of differences in de-prescribing protocols rather than differences in the effectiveness of the intervention. For example, in one study, metformin was only discontinued because of contra-indication, 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.

CONCLUSIONS

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.

Similar to 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) is 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 of at most 2–4 years, although there are some data from 5 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, has 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.

ACKNOWLEDGMENTS

We acknowledge the support of the British Dietetic Association in helping to arrange and facilitate the meeting of this group and Diabetes UK for hosting the initial discussions. In addition, we acknowledge the contributions of the others in attendance at this meeting (Andrew Burman, Thomas Embury, Dr Pamela Dyson, Dr Nicola Guess and Douglas Twenefour).

AUTHOR CONTRIBUTIONS

DM was responsible for the study conceptualisation. AB, PMcA, JT, DU, JU, TD, CM, AM and DM were responsible for the methodology. AB, PMcA, JT, DU, JU, TD, SW, CM, AM and DM were responsible for original draft. AB, PMcA and DM were responsible for the reviewing and editing. JT, DU, SW, CM and AM contributed to the reviewing and editing.

CONFLICT OF INTERESTS

AB has worked as an investigator on TDR studies which have had commercial support. JT works for Medtronic, a company which manufactures and supplies diabetes pumps. CM and DU are advisors for Diabetes Digital Media who have developed the Low Carb app. TD and SW work for XPERT Health which is a charity providing diabetes education. DM has worked as an investigator on meal replacement studies which have had commercial support.

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REFERENCES

- Ilkova H, Glaser B, Tunçkale A, Bagriçak N, Cerasi E. Induction of long-term glycaemic control in newly diagnosed type 2 diabetic patients by transient intensive insulin treatment. *Diabetes Care*. 1997;20(9):1353–6.
- Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ*. 2000;321(7258):405–12.
- Davies MJ, D’Alessio DA, Fradkin J, Kernan WN, Mathieu C, Mingrone G, et al. Management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetologia*. 2018;61(12):2461–98.
- Chatterjee S, Khunti K, Davies MJ. Type 2 diabetes. *Lancet* 2017; 389(10085):2239–51.
- Lean ME, Leslie WS, Barnes AC, Brosnahan N, Thom G, McCombie L, et al. Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial. *Lancet*. 2018;391(10120):541–51.
- Sjöström L, Peltonen M, Jacobson P, Ahlin S, Andersson-Assarsson J, Anveden Å, et al. Association of bariatric surgery with long-term remission of type 2 diabetes and with microvascular and macrovascular complications. *JAMA*. 2014;311(22):2297–304.
- Taylor R, Barnes AC. Translating aetiological insight into sustainable management of type 2 diabetes. *Diabetologia*. 2018;61(2):273–83.
- Deakin T, McShane CE, Cade JE, Williams RD. Group based training for self-management strategies in people with type 2 diabetes mellitus. *Cochrane Database Syst Rev*. 2005;2:Cd003417.
- Oggers-Jewell K, Ball LE, Kelly JT, Isenring EA, Reidlinger DP, Thomas R. Effectiveness of group-based self-management education for individuals with type 2 diabetes: a systematic review with meta-analyses and meta-regression. *Diabet Med*. 2017;34(8):1027–39.
- Chrvala CA, Sherr D, Lipman RD. Diabetes self-management education for adults with type 2 diabetes mellitus: a systematic review of the effect on glycaemic control. *Patient Educ Couns*. 2016;99(6):926–43.
- Khunti K, Gray LJ, Skinner T, Carey ME, Realf K, Dallosso H, et al. Effectiveness of a diabetes education and self-management programme (DESMOND) for people with newly diagnosed type 2 diabetes mellitus: three year follow-up of a cluster randomised controlled trial in primary care. *BMJ*. 2012;344:e2333.
- Deakin TA, Cade JE, Williams R, Greenwood DC. Structured patient education: the Diabetes X-PERT Programme makes a difference. *Diabet Med*. 2006;23(9):944–54.
- Dyson PA, Twenefour D, Breen C, Duncan A, Elvin E, Goff L, et al. Diabetes UK evidence-based nutrition guidelines for the prevention and management of diabetes. *Diabet Med*. 2018;35(5):541–7.
- Buchwald H, Estok R, Fahrenbach K, Banel D, Jensen MD, Pories WJ, et al. Weight and type 2 diabetes after bariatric surgery: systematic review and meta-analysis. *Am J Med*. 2009;122(3):248–56.
- Khorgami Z, Shoar S, Saber AA, Howard CA, Danaei G, Sclabas GM. Outcomes of bariatric surgery versus medical management for type 2 diabetes mellitus: a meta-analysis of randomized controlled trials. *Obes Surg*. 2019;29(3):964–74.
- Buchwald H, Avidor Y, Braunwald E, Jensen MD, Pories W, Fahrenbach K, et al. Bariatric surgery. A systematic review and meta-analysis. *JAMA*. 2004;292(14):1724–37.
- Taylor R. Banting Memorial Lecture 2012. Reversing the twin cycles of type 2 diabetes. *Diabet Med*. 2013;30(3):267–75.
- Purnell JQ, Selzer F, Wahed AS, Pender J, Pories W, Pomp A, et al. Type 2 diabetes remission rates after laparoscopic gastric bypass and gastric banding: results of the Longitudinal Assessment of Bariatric Surgery Study. *Diabetes Care*. 2016;39(7):1101–7.

19. Lips MA, de Groot GH, van Klinken JB, Aarts E, Berends FJ, Janssen IM, et al. Calorie restriction is a major determinant of the short-term metabolic effects of gastric bypass surgery in obese type 2 diabetic patients. *Clin Endocrinol.* 2014;80(6):834–42.
20. Lean MEJ, Leslie WS, Barnes AC, Brosnahan N, Thom G, McCombie L, et al. Durability of a primary care-led weight-management intervention for remission of type 2 diabetes: 2-year results of the DiRECT open-label, cluster-randomised trial. *Lancet Diabetes Endocrinol.* 2019;7(5):344–55.
21. Sjöholm K, Carlsson LMS, Taube M, le Roux CW, Svensson P-A, Peltonen M. Comparison of preoperative remission scores and diabetes duration alone as predictors of durable type 2 diabetes remission and risk of diabetes complications after bariatric surgery: a post hoc analysis of participants from the Swedish obese subjects study. *Diabetes Care.* 2020;43(11):2804–11.
22. Unwin D, Unwin J. Low carbohydrate diet to achieve weight loss and improve HbA1c in type 2 diabetes and pre-diabetes: experience from one general practice. *Pract Diabetes.* 2014;31(2):76–9.
23. Nielsen JV, Joensson E. Low-carbohydrate diet in type 2 diabetes. Stable improvement of bodyweight and glycaemic control during 22 months follow-up. *Nutr Metab.* 2006;3(1):22.
24. Hallberg SJ, McKenzie AL, Williams PT, Bhanpuri NH, Peters AL, Campbell WW, et al. Effectiveness and safety of a novel care model for the management of type 2 diabetes at 1 year: an open-label, non-randomized, controlled study. *Diabetes Ther.* 2018;9(2):583–612.
25. MyWay DigitalH. Diabetes My Way: Diabetes Remission. 2020. [cited 2021 July 3]. Available from: <https://diabetesmyway.nhs.uk/resources/internal/diabetes-remission/>
26. Huntriss RE, Jones L, Harvie M, McDiarmid S, Johnson, et al. Manchester Intermittent versus Daily diet Diabetes App Study (MIDDAS): evaluation of medication cost. *Diabet Med.* 2021; 38(S1):e8_14555. https://onlinelibrary.wiley.com/doi/10.1111/dme.8_14555?af=R
27. O'Sullivan JB, Hurwitz D. Spontaneous remissions in early diabetes mellitus. *Arch Intern Med.* 1966;117(6):769–74.
28. Captieux M, Prigge R, Wild S, Guthrie B. Defining remission of type 2 diabetes in research studies: a systematic scoping review. *PLoS Med.* 2020;17(10):e1003396.
29. Nagi D, Hambling C, Taylor R. Remission of type 2 diabetes: a position statement from the Association of British Clinical Diabetologists (ABCD) and the primary care diabetes society (PCDS). *Br J Diabetes.* 2019;19:73–6.
30. Buse JB, Caprio S, Cefalu WT, Ceriello A, Del Prato S, Inzucchi SE, et al. How do we define cure of diabetes? *Diabetes Care.* 2009;32(11):2133–5.
31. Taheri S, Zaghoul H, Chagoury O, Elhadad S, Ahmed SH, El Khatib N, et al. Effect of intensive lifestyle intervention on bodyweight and glycaemia in early type 2 diabetes (DIADEM-I): an open-label, parallel-group, randomised controlled trial. *Lancet Diabetes Endocrinol.* 2020;8(6):477–89.
32. Thom G, Messow C-M, Leslie WS, Barnes AC, Brosnahan N, McCombie L, et al. Predictors of type 2 diabetes remission in the Diabetes Remission Clinical Trial (DiRECT). *Diabet Med.* 2020;21:e14395.
33. Lim EL, Hollingsworth KG, Aribisala BS, Chen MJ, Mathers JC, Taylor R. Reversal of type 2 diabetes: normalisation of beta cell function in association with decreased pancreas and liver triacylglycerol. *Diabetologia.* 2011;54(10):2506–14.
34. Steven S, Hollingsworth KG, Al-Mrabeh A, Avery L, Aribisala B, Caslake M, et al. Very low-calorie diet and 6 months of weight stability in type 2 diabetes: pathophysiological changes in responders and nonresponders. *Diabetes Care.* 2016;39(5):808–15.
35. Taylor R, Al-Mrabeh A, Zhyzhneuskaya S, Peters C, Barnes AC, Aribisala BS, et al. Remission of human type 2 diabetes requires decrease in liver and pancreas fat content but is dependent upon capacity for β cell recovery. *Cell Metab.* 2018;28(4):547–56, e3.
36. Pories WJ, Swanson MS, MacDonald KG, Long SB, Morris PG, Brown BM, et al. Who would have thought it? An operation proves to be the most effective therapy for adult-onset diabetes mellitus. *Ann Surg.* 1995;222(3):339–50.
37. Brown A, Guess N, Dornhorst A, Taheri S, Frost G. Insulin-associated weight gain in obese type 2 diabetes mellitus patients: what can be done? *Diabetes Obes Metab.* 2017;19(12):1655–68.
38. Jackness C, Karmally W, Febres G, Conwell IM, Ahmed L, Bessler M, et al. Very low-calorie diet mimics the early beneficial effect of Roux-en-Y gastric bypass on insulin sensitivity and β -cell function in type 2 diabetic patients. *Diabetes.* 2013;62(9):3027–32.
39. Tadross JA, le Roux CW. The mechanisms of weight loss after bariatric surgery. *Int J Obes.* 2009;33(1):S28–32.
40. Cummings DE. Endocrine mechanisms mediating remission of diabetes after gastric bypass surgery. *Int J Obes.* 2009;33(1):S33–40.
41. Noel OF, Still CD, Argyropoulos G, Edwards M, Gerhard GS. Bile acids, FXR, and metabolic effects of bariatric surgery. *J Obes.* 2016;2016:4390254.
42. Saeidi N, Meoli L, Nestoridi E, Gupta NK, Kvas S, Kucharczyk J, et al. Reprogramming of intestinal glucose metabolism and glycaemic control in rats after gastric bypass. *Science.* 2013;341(6144):406–10.
43. Mingrone G, Panunzi S, De Gaetano A, Guidone C, Iaconelli A, Capristo E, et al. Metabolic surgery versus conventional medical therapy in patients with type 2 diabetes: 10-year follow-up of an open-label, single-centre, randomised controlled trial. *Lancet.* 2021;397(10271):293–304.
44. Gregg EW, Chen H, Wagenknecht LE, Clark JM, Delahanty LM, Bantle J, et al. Association of an intensive lifestyle intervention with remission of type 2 diabetes. *JAMA.* 2012;308(23):2489–96.
45. McInnes N, Smith A, Otto R, Vandermeij J, Punthakee Z, Sherifali D, et al. Piloting a remission strategy in type 2 diabetes: results of a randomized controlled trial. *J Clin Endocrinol Metab.* 2017;102(5):1596–605.
46. Ried-Larsen M, Johansen MY, MacDonald CS, Hansen KB, Christensen R, Wedell-Neergaard A-S, et al. Type 2 diabetes remission 1 year after an intensive lifestyle intervention: a secondary analysis of a randomized clinical trial. *Diabetes Obes Metab.* 2019;21(10):2257–66.
47. Kelley DE, Wing R, Buonocore C, Sturis J, Polonsky K, Fitzsimmons M. Relative effects of calorie restriction and weight loss in noninsulin-dependent diabetes mellitus. *J Clin Endocrinol Metab.* 1993;77(5):1287–93.
48. Malandrucchio I, Pasqualetti P, Giordani I, Manfellotto D, De Marco F, Alegiani F, et al. Very-low-calorie diet: a quick therapeutic tool to improve β cell function in morbidly obese patients with type 2 diabetes. *Am J Clin Nutr.* 2012;95(3):609–13.
49. Al-Mrabeh A, Zhyzhneuskaya SV, Peters C, Barnes AC, Melhem S, Jesuthasan A, et al. Hepatic lipoprotein export and remission of human type 2 diabetes after weight loss. *Cell Metab.* 2020;31(2):233–49.
50. McArdle PD, Mellor D, Rilstone S, Taplin J. The role of carbohydrate in diabetes management. *Pract Diabetes.* 2016;33(7):237–42.
51. Feinman RD, Pogozelski WK, Astrup A, Bernstein RK, Fine EJ, Westman EC, et al. Dietary carbohydrate restriction as the first approach in diabetes management: critical review and evidence base. *Nutrition.* 2015;31(1):1–13.
52. McArdle PD, Greenfield SM, Rilstone SK, Narendran P, Haque MS, Gill PS. Carbohydrate restriction for glycaemic control in type 2 diabetes: a systematic review and meta-analysis. *Diabet Med.* 2019;36(3):335–48.
53. Hirst JA, Farmer AJ, Ali R, Roberts NW, Stevens RJ. Quantifying the effect of metformin treatment and dose on glycaemic control. *Diabetes Care.* 2012;35(2):446–54.
54. Meng Y, Bai H, Wang S, Li Z, Wang Q, Chen L. Efficacy of low carbohydrate diet for type 2 diabetes mellitus management: a systematic review and meta-analysis of randomized controlled trials. *Diabetes Res Clin Pract.* 2017;131:124–31.
55. Snorgaard O, Poulsen GM, Andersen HK, Astrup A. Systematic review and meta-analysis of dietary carbohydrate restriction in patients with type 2 diabetes. *BMJ Open Diabetes Res Care.* 2017;5(1):e000354.
56. Bueno NB, de Melo ISV, de Oliveira SL, da Rocha Ataide T. Very-low-carbohydrate ketogenic diet v. low-fat diet for long-term weight loss: a meta-analysis of randomised controlled trials. *Br J Nutr.* 2013;110(7):1178–87.
57. Gardner CD, Trepanowski JF, Del Gobbo LC, Hauser ME, Rigdon J, Ioannidis JPA, et al. Effect of low-fat vs low-carbohydrate diet on 12-month weight loss in overweight adults and the association with

- genotype pattern or insulin secretion: the DIETFITS randomized clinical trial. *JAMA*. 2018;319(7):667–79.
58. Dyson P. Very low carbohydrate ketogenic diets and diabetes. *Pract Diabetes*. 2020;37(4):121–6.
 59. Athinarayanan SJ, Adams RN, Hallberg SJ, McKenzie AL, Bhanpuri NH, Campbell WW, et al. Long-term effects of a novel continuous remote care intervention including nutritional ketosis for the management of type 2 diabetes: a 2-year non-randomized clinical trial. *Front Endocrinol*. 2019;10:348.
 60. Nielsen JV, Joensson EA. Low-carbohydrate diet in type 2 diabetes: stable improvement of bodyweight and glycemic control during 44 months follow-up. *Nutr Metab*. 2008;5(1):14.
 61. Unwin D, Khalid AA, Unwin J, Crocombe D, Delon C, Martyn K, et al. Insights from a general practice service evaluation supporting a lower carbohydrate diet in patients with type 2 diabetes mellitus and prediabetes: a secondary analysis of routine clinic data including HbA1c, weight and prescribing over 6 years. *BMJ Nutr Prev Health*. 2020;3:285–94 [bmjnp-2020-000072](https://doi.org/10.1136/bmjnp-2020-000072).
 62. Unwin D, Unwin J. A simple model to find patient hope for positive lifestyle changes: GRIN. *J Holist Healthc*. 2019;16(2):Summer 18–22.
 63. Unwin D. Successful dietary management of type 2 diabetes: experience from Norwood Surgery in Southport. 2020. [cited 2021 July 2] Available from: <https://www.guidelinesinpractice.co.uk/supplements/successful-dietary-management-of-type-2-diabetes-experience-from-norwood-surgery-in-southport/455723.article>
 64. Saslow LR, Summers C, Aikens JE, Unwin DJ. Outcomes of a digitally delivered low-carbohydrate type 2 diabetes self-management program: 1-year results of a single-arm longitudinal study. *JMIR Diabetes*. 2018;3(3):e12.
 65. American Diabetes Association. Nutrition recommendations and interventions for diabetes. A position statement of the American Diabetes Association. *Diabetes Care*. 2008;31(Suppl 1):S61–78.
 66. Karter AJ, Nundy S, Parker MM, Moffet HH, Huang ES. Incidence of remission in adults with type 2 diabetes: the diabetes & aging study. *Diabetes Care*. 2014;37(12):3188–95.
 67. Esposito K, Maiorino MI, Petrizzo M, Bellastella G, Giugliano D. The effects of a mediterranean diet on the need for diabetes drugs and remission of newly diagnosed type 2 diabetes: follow-up of a randomized trial. *Diabetes Care*. 2014;37(7):1824–30.
 68. Dave R, Davis R, Davies JS. The impact of multiple lifestyle interventions on remission of type 2 diabetes mellitus within a clinical setting. *Obes Med*. 2019;13:59–64.
 69. Astbury NM, Piernas C, Hartmann-Boyce J, Lapworth S, Aveyard P, Jebb SA. A systematic review and meta-analysis of the effectiveness of meal replacements for weight loss. *Obes Rev*. 2019;20(4):569–87.
 70. Maston G, Franklin J, Gibson AA, Manson E, Hocking S, Sainsbury A, et al. Attitudes and approaches to use of meal replacement products among healthcare professionals in management of excess weight. *Behav Sci*. 2020;10(9):136.
 71. Morris E, Aveyard P, Dyson P, Noreik M, Bailey C, Fox R, et al. A food-based, low-energy, low-carbohydrate diet for people with type 2 diabetes in primary care: a randomized controlled feasibility trial. *Diabetes Obes Metab*. 2020;22(4):512–20.
 72. Yancy WS, Crowley MJ, Dar MS, Coffman CJ, Jeffreys AS, Maciejewski ML, et al. Comparison of group medical visits combined with intensive weight management vs group medical visits alone for glycemia in patients with type 2 diabetes: a noninferiority randomized clinical trial. *JAMA Intern Med*. 2020;180(1):70–9.
 73. Saslow LR, Daubenmier JJ, Moskowitz JT, Kim S, Murphy EJ, Phinney SD, et al. Twelve-month outcomes of a randomized trial of a moderate-carbohydrate versus very low-carbohydrate diet in overweight adults with type 2 diabetes mellitus or prediabetes. *Nutr Diabetes*. 2017;7(12):304.
 74. Saslow LR, Mason AE, Kim S, Goldman V, Ploutz-Snyder R, Bayandorian H, et al. An online intervention comparing a very low-carbohydrate ketogenic diet and lifestyle recommendations versus a plate method diet in overweight individuals with type 2 diabetes: a randomized controlled trial. *J Med Internet Res*. 2017;19(2):e36.
 75. Wadden TA, Neiberg RH, Wing RR, Clark JM, Delahanty LM, Hill JO, et al. Four-year weight losses in the look AHEAD study: factors associated with long-term success. *Obesity*. 2011;19(10):1987–98.
 76. Astbury NM, Albury C, Nourse R, Jebb SA. Participant experiences of a low-energy total diet replacement programme: a descriptive qualitative study. *PLoS One*. 2020;15(9):e0238645-e.
 77. NHS Diabetes. Low calorie diets to treat obesity and type 2 diabetes: NHS England; 2020. [cited 2021 July 2]. Available from: <https://www.england.nhs.uk/diabetes/treatment-care/low-calorie-diets/>
 78. Burke LE, Ewing LJ, Ye L, Styn M, Zheng Y, Music E, et al. The SELF trial: a self-efficacy-based behavioral intervention trial for weight loss maintenance. *Obesity*. 2015;23(11):2175–82.
 79. Spahn JM, Reeves RS, Keim KS, Laquatra I, Kellogg M, Jortberg B, et al. State of the evidence regarding behavior change theories and strategies in nutrition counseling to facilitate health and food behavior change. *J Am Diet Assoc*. 2010;110(6):879–91.
 80. Feinmann J. Type 2 diabetes: 5000 patients to test feasibility of ‘remission service’. *BMJ*. 2018;363:k5114.
 81. Summers C, Curtis K. Novel digital architecture of a “Low Carb Program” for initiating and maintaining long-term sustainable health-promoting behavior change in patients with type 2 diabetes. *JMIR Diabetes*. 2020;5:e15030.
 82. Fairburn C, Beglin SJ. Appendix B: eating disorder examination questionnaire. In: Fairburn CG, editor. *Cognitive behavior therapy and eating disorders*. New York, NY: Guildford Press; 2008. p. 309–14.
 83. da Luz FQ, Hay P, Gibson AA, Touyz SW, Swinbourne JM, Roekenes JA, et al. Does severe dietary energy restriction increase binge eating in overweight or obese individuals? A systematic review. *Obes Rev*. 2015;16(8):652–65.
 84. Leslie WS, Ford I, Sattar N, Hollingsworth KG, Adamson A, Snihotta FF, et al. The Diabetes Remission Clinical Trial (DiRECT): protocol for a cluster randomised trial. *BMC Fam Pract*. 2016;17(1):20.
 85. Murdoch C, Unwin D, Cavan D, Cucuzzella M, Patel M. Adapting diabetes medication for low carbohydrate management of type 2 diabetes: a practical guide. *Br J Gen Pract*. 2019;69(684):360–1.
 86. Brown A, Dornhorst A, McGowan B, Omar O, Leeds AR, Taheri S, et al. Low-energy total diet replacement intervention in patients with type 2 diabetes mellitus and obesity treated with insulin: a randomized trial. *BMJ Open Diab Res Care*. 2020;8(1):e001012.
 87. Xin Y, Davies A, McCombie L, Briggs A, Messow CM, Grieve E, et al. Within-trial cost and 1-year cost-effectiveness of the DiRECT/counterweight-plus weight-management programme to achieve remission of type 2 diabetes. *Lancet Diabetes Endocrinol*. 2019;7(3):169–72.
 88. Xin Y, Davies A, Briggs A, McCombie L, Messow CM, Grieve E, et al. Type 2 diabetes remission: 2 year within-trial and lifetime-horizon cost-effectiveness of the Diabetes Remission Clinical Trial (DiRECT)/counterweight-plus weight management programme. *Diabetologia*. 2020;63(10):2112–22.
 89. Jacobs-van der Bruggen MAM, van Baal PH, Hoogenveen RT, Feenstra TL, Briggs AH & Lawson K et al. Cost-effectiveness of lifestyle modification in diabetic patients. *Diabetes Care*. 2009;32(8):1453–8.
 90. Rushing J, Wing R, Wadden TA, Knowler WC, Lawlor M, Evans M, et al. Cost of intervention delivery in a lifestyle weight loss trial in type 2 diabetes: results from the Look AHEAD clinical trial. *Obes Sci Pract*. 2017;3(1):15–24.
 91. Doble B, Wordsworth S, Rogers CA, Welbourn R, Byrne J, Blazeby JM, et al. What are the real procedural costs of bariatric surgery? A systematic literature review of published cost analyses. *Obes Surg*. 2017;27(8):2179–92.
 92. Yau A, Adams J, Monsivais P. Time trends in adherence to UK dietary recommendations and associated sociodemographic inequalities, 1986–2012: a repeated cross-sectional analysis. *Eur J Clin Nutr*. 2019;73(7):997–1005.

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How to cite this article: Brown A, McArdle P, Taplin J, Unwin D, Unwin J, Deakin T, et al. Dietary strategies for remission of type 2 diabetes: a narrative review. *J Hum Nutr Diet.* 2021;1–14.
<https://doi.org/10.1111/jhn.12938>