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REVIEW

Does a Ketogenic Diet Have a Place Within Diabetes Clinical Practice? Review of Current Evidence and Controversies

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ABSTRACT

Carbohydrate restriction has gained increasing popularity as an adjunctive nutritional therapy for diabetes management. However, controversy remains regarding the long-term suitability, safety, efficacy and potential superiority of a very low carbohydrate, ketogenic diet compared to current recommended nutritional approaches for diabetes management. Recommendations with respect to a ketogenic diet in clinical practice are often hindered by the lack of established definition, which prevents its capacity to be most appropriately prescribed as a therapeutic option for diabetes. Furthermore, with conflicted evidence, this has led to uncertainty amongst clinicians on how best to support and advise their patients. This review will explore whether a ketogenic diet has a place within clinical practice by reviewing current evidence and controversies.

Keywords: Ketogenic diets; Low carbohydrate diets; Type 2 diabetes; Type 1 diabetes; Obesity

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Key Summary Points

Ketogenic diets has gained significant popularity recently however controversy still exists whether this should be used as a first line treatement for people with diabetes.

Ketogenic diets have favourable metabolic and weight reduction effects in the short term in people living with diabetes, primarily in type 2 diabetes (T2D) with emerging evidence in type 1 diabetes.

Systematic reviews and meta-analyses reiterate that ketogenic diets are not superior but not inferior in terms of metabolic advantages for diabetes management.

There is an urgent unmet need for long-term data of health outcomes comparing conventional and ketogenic diets.

There remains an absence of a univocal definition of a ketogenic diet which continues to hinder research and clinical implementation of ketogenic for diabetes management.

INTRODUCTION

Diabetes is a complex chronic disease characterised by inadequate glucoregulatory control resulting in hyperglycaemia [1]. The global prevalence of diabetes has quadrupled from 108 million in 1980 to an estimated 462 million in 2017 [2, 3] with many more currently undiagnosed, making diabetes one of the most widespread chronic diseases. The ultimate goal of type 2 diabetes management is managing a person's glycaemia within target range of a glycated haemoglobin (HbA1c) of less than 7% (53 mmol/mol) [4] as recommended by clinical guidelines or even to support the achievement of drug-free remission [5, 6], and in doing so reduce the risk of diabetes associated micro- and macrovascular complications [7].

From a dietary and nutrition management perspective it is key that people living with diabetes are supported to make healthier food choices using an individualised approach, appreciating that no one size fits all. Advice has to consider the person's cultural, ethnic, social, and economic factors [8]. Evidence-based guidance for type 1 diabetes (T1D) and type 2 diabetes (T2D) management surrounding nutrition and lifestyle changes globally are similar; Diabetes UK recommends an individualised approach taking personal and cultural preferences into consideration. A diet rich in vegetables, fruits, wholegrains, fish, nuts and pulses is recommended simultaneous with reduced consumption of processed meat, refined carbohydrates and artificially sweetened beverages. The American Diabetes Association endorse a balance of macronutrients including nutrient-dense fruits, vegetables, legumes and whole grains.

More recently the target goal of remission has been introduced for people with T2D following the publication of the DiRECT trial [9, 10] and along with other research and analyses [11, 12]. These programmes used either a formula low energy diet or a low carbohydrate diet. However, not everyone wishes to follow such a plan and therefore alternative dietary options need to be offered.

For people living with T2D, intensive lifestyle management, including increased physical activity and a hypocaloric diet alongside behaviour change, is the cornerstone of diabetes management, with the ultimate aim being to induce weight reduction of at least 15 kg which correlates to improved glucoregulatory control [13, 14]. However, lifestyle intervention typically results only in short-term and modest weight reduction, of around 5% of body weight [15] which is usually insufficient to induce a significant improvement in glycaemic control, particularly with respect to achieving diabetes remission [13, 16].

Recently, there has been an increasing interest in the use of very low carbohydrate diets, otherwise known as ketogenic diets, as an alternative or adjunctive therapeutic option to

other dietary methods and anti-diabetic pharmacotherapy as individuals seek to improve their glucose control and achieve remission [17]. Ketogenic diets have a longstanding history of efficacy in treating various metabolic conditions such as drug-resistant epilepsy [18, 19] and were a mainstay of diabetes therapy (both T1D and T2D) before the development of insulin [20]. However, only recently have they been included for the first time within the American Diabetes Association Guidelines as a possible therapeutic option [21]. Despite this, much controversy remains about their use within clinical practice and whether they are safe for people living with diabetes. This review will therefore explore the current evidence and controversies surrounding the use of ketogenic diets within clinical practice with the aim to help guide clinicians on their use with people living with diabetes. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

A database search of PubMed, Scopus and Medline for original research articles was performed using combinations of terms 'very low carbohydrate', 'low carbohydrate' and 'ketogenic' until 01 August 2023. A review of the available data was undertaken to help inform clinical practice. Studies were examined and critically appraised to help clarify the current status of research within the area ketogenic diets.

CURRENT GUIDANCE FOR DIABETES MANAGEMENT

Multiple dietary approaches have been suggested to help people with diabetes to manage their glucose control. At present, UK National Institute for Health and Care Excellence (NICE) guidelines promote (which have not been updated since 2009) 'general healthy eating' for T2D management, encouraging high fibre, low-glycaemic index sources of carbohydrates and to limit saturated fat intake; the same advice as for the general population [4]. Until recently, both Diabetes UK and American Diabetes Association (ADA) issued broad advice for diabetes management in individuals with T2D with the overarching aim to induce weight loss due to the lack of evidence-based dietary guidelines for diabetes management. Interestingly, this advice was also applicable to the 10% of individuals with T2D who are considered to be a healthy weight (BMI 18.5–24.9 kg/m^2), in people with T1D and gestational diabetes as weight loss in these cohorts improves glycaemic control [22]. This ambiguity has led to uncertainty amongst healthcare professionals with 'prescribing' a specific dietary type or pattern as a therapeutic approach for diabetes [23] as a consensus has yet to be reached for the ideal dietary distribution for people with diabetes [21].

It can be argued that urgent revision of existing conventional dietary strategies to prevent and improve diabetes management is required, especially considering the continued increasing global prevalence of diabetes [24]. Carbohydrate restriction is increasingly gaining acceptance for diabetes management within the UK and advocacy started to emerge with Diabetes UK in 2011 for individuals with T2D [25] and websites such as Diabetes.co.uk, which established the Low Carb Programme [26], an evidence-based digital health intervention app launched in 2015 and supported by the UK National Health Service (NHS). This has driven the recognition of a low carbohydrate diet as a therapeutic approach in general practice for T2D management and remission. People with T2D completing the programme reported greater HbA1c improvements (− 9.1 mmol/mol versus 1.7 mmol/mol, $P < 0.001$) and a third of patients reduced usage of anti-diabetic medications [26]. It is important to note, however, that this is a short-term (15-week) intervention and does not aim to induce nutritional ketosis.

Subsequently, the Scientific Advisory Committee on Nutrition (SACN) in 2021 reviewed existing data on low carbohydrate diets for people with T2D [27]. Despite the evident favourable short-term metabolic effects of a lower carbohydrate diet, SACN reported inconsistent and inconclusive results for long-term therapeutic benefits due to lack of comprehensive long-term data and concluded that a low

carbohydrate diet is not superior but also not inferior compared to other dietary patterns. However, it is important to note that the SACN review only includes ranges of carbohydrate intake from 50 to 130 g a day and therefore a ketogenic diet of 20–50 g of carbohydrate a day remains to be extensively reviewed until which time it cannot be advocated for diabetes management, as this fell outside the scope of this particular SACN review.

WHAT IS A KETOGENIC DIET?

There are many variations of carbohydrate limited or restricted diets, ranging from moderate to very low carbohydrate diets, and a strict definition remains to be agreed; however, Feinman [28] provided the most commonly used categories of carbohydrate-focused diets. A moderate carbohydrate diet is between 130 and 230 g per day or 26–45% of daily energy intake based on a 2000 kcal/day. A low carbohydrate diet is > 130 g or < 26% of daily energy intake and a very low carbohydrate diet, or ketogenic diet, is 20–50 g per day or 10% of daily energy intake.

One of the issues in using percentage energy from carbohydrate based on total energy intake is that this is based on the assumption an individual eats 2000 kcal per day. This means that if an individual's energy intake varies from this amount so does the amount of carbohydrate and therefore whether nutritional ketosis is induced or not. For example, if an individual consumes 3000 kcal/day, 10% of the daily energy would result in consuming 75 g of carbohydrate and therefore would not be defined as a ketogenic diet. Therefore, it would seem more appropriate to use absolute grams of carbohydrate as a defining criteria for carbohydrate restriction to allow greater comparison in dietary methods.

Further discrepancies surround whether definitions should be centred on the actual amount of carbohydrates permitted (i.e. < 50 g) or percentage of daily energy intake [29]. This is important as the varying definitions of a ketogenic diet with a range of carbohydrate intakes will yield significantly varying levels of nutritional ketosis. Also, variations of whether net carbs or total carbs should be measured is another factor which remains unanswered. At present, US guidelines use net carbohydrates, whereas UK and EU guidelines use total carbohydrates. These factors make evaluation of scientific studies difficult.

Ketogenic diets might be considered to be a very restrictive dietary pattern, primarily consisting of high fat, moderate protein, and a very low carbohydrate intake [30]. It is termed 'ketogenic' with the overarching aim being to restrict carbohydrate intake enough to induce nutritional ketosis (Table 1). This is a metabolic state which imitates the biological adaptations seen in starvation, without severely limiting caloric intake and a blood ketone level of between 0.5 and 3 mg/dL [31]. Foods such as grains, potatoes, rice, fruit, starchy vegetables, legumes and bread are substituted with other food sources high in fat, concomitant with an increase protein (typically animal-based).

It is important to note that in a ketogenic diet, carbohydrates are not the only macronutrient that has to be restricted or measured and a common misconception is that a ketogenic diet translates to unlimited or excessively high consumption of animal-based protein. In a state of caloric restriction, excess protein intake will be converted to glucose by gluconeogenesis, which can impact reaching ketosis. Therefore, it is recommended that daily protein intake of a minimum of 0.8 g per kg of body weight and should not exceed 1.75 g per kg of body weight.

During ketosis, ketone bodies (beta-hydroxybutyric acid, acetoacetate and acetone) are formed by the liver from fatty acids by ketogenesis, which act as an energy source as a substitute for the severe reduction of glucose, primarily from carbohydrates [32]. Further physiological responses to limited carbohydrate availability include lipogenesis (the conversion of glycerol into fatty acids and triglycerides), reduced adipose tissue storage and lipolysis of fat depots is increased as a result of low circulating insulin levels [33].

Although the precise physiological mechanisms are unknown, the therapeutic effects of ketogenic diets are partially credited to the rapid and effective weight loss which is the

Table 1 Definitions of ketogenic diets available

Diet name	Fat	Protein	Carbohydrate
Standard ketogenic diet	70–80% of daily caloric intake 2000 kcal diet = 165 g fat	10–20% of daily caloric intake 2000 kcal diet = 75 g protein	5–10% of daily caloric intake 2000 kcal diet = 40 g carbs
Well-formulated ketogenic diet	Unlimited until satiety	1.2 and 2.0 g/kg reference weight (approx. 15% daily expenditure)	20–30 g per day on average
Modified ketogenic diet	50% of daily expenditure	30% of daily expenditure	15–20 g per day (approx. 20% daily expenditure)
Medium chain triglyceride diet	40–45% of daily calories obtained from MCT oil (supplemented) and 30% from long chain dietary fats	10% of daily energy expenditure	15% daily expenditure
Very low-calorie ketogenic diet	> 10 g per day	1–1.5 g of protein/kg of ideal body weight	< 50 g per day on a 600–800 kcal diet

g grams, % percent, *g/kg* grams per kilogram, *MCT* medium chain triglycerides, *kcal* kilocalories

most significant predictor of T2D remission [34]. Proponents suggest that the potential metabolic advantage behind ketogenic diets in inducing greater and more sustained weight reduction compared to other conventional diets can be attributed to the decreased metabolic adaptations following weight loss [35]. Comparatively, ketogenic diets have been reported to lead to greater satiety [36] and decreased appetite due to an increase in anorexigenic hormones such as glucagon-like peptide 1 [37] and leptin [38] and cholecystokinin [39] and suppression of the appetite hormone, ghrelin [40]. Others suggest that the superior efficacy could also be due to the anorexigenic effects of ketone bodies themselves. Supporting evidence has shown that exogenous consumption of a ketone ester drink, concomitant with increased blood ketone levels, resulted in greater reductions in ghrelin and appetite compared to a dextrose drink [41]. However, to date there is no substantive evidence that weight loss is any better than with other dietary methods in the long term despite often better short-term outcomes [42].

EVIDENCE SUPPORTING THE USE OF KETOGENIC DIETS FOR DIABETES MANAGEMENT

The short-term benefits of ketogenic diets on glycaemia, insulin sensitivity and diabetes management have been under investigation for several decades, yet their use remains controversial. Not one single reason can explain this but it is likely driven by the inconsistencies of efficacy due to the aforementioned heterogeneity of methodology, carbohydrate and other macronutrient intake, patient population and other confounding variables. In 2017 [43] Saslow et al. provided supporting evidence in a

small cohort ($n = 23$) randomised controlled trial comparing a ketogenic diet compared to the conventional 'Plate Method' that is broadly recommended for T2D management in people living with overweight. At 32 weeks, participants who underwent a ketogenic diet had significantly lower HbA1c levels (with 55% achieving a HbA1c less than 6.5% mmol/l) and greater weight loss. Another study [44] also revealed that 86% of individuals with T2DM who completed a 12-month low carbohydrate diet were able to reduce or completely discontinue insulin use. However, there is an urgent unmet need for long-term data of health outcomes comparing conventional and ketogenic diets.

A recent systematic review and meta-analysis [45] revealed that both low carbohydrate and ketogenic diets produce beneficial effects on glucose control compared to other diets in people with T2D. However, it was shown that ketogenic diets result in significantly greater efficacy in reduction of HbA1c (− 1.45%) compared to low carbohydrate diets (− 0.27%). However, some inconsistencies remain in this review regarding its superiority of weight reduction compared to other diets, with pooled analysis revealing no significance in BMI reduction between ketogenic diets and controls diets.

Reports reveal that high blood pressure affects 50% of people with diabetes and, therefore, it is important to highlight other positive effects of the ketogenic diet, including improvements in blood pressure. A 2015 study showed that in 377 patients with a BMI between 27 and 37 kg/m^2 who followed a ketogenic diet for 1 year, systolic and diastolic blood pressure significantly improved after 12 weeks. However, no changes in blood pressure were observed after 1 year, which may correlate to the plateau of weight loss between 12 weeks and 1 year [46].

Other ancillary benefits of ketogenic diets reveal anti-inflammatory and anti-oxidant effects with significant improvements in inflammation and oxidative stress, both of which are pathogenic factors and play a role in diabetes and its complications [47–49]. For example, a 12-week randomised controlled trial investigating the effects of a well-formulated ketogenic diet versus a whole-food diet showed a significant decrease in high-sensitivity C-reactive protein (hsCRP) [50].

One of the other, and arguably most important, benefits of ketogenic diets in people living with diabetes is improvement in reported quality of life. A recent study in patients living with T2D and obesity comparing the effects of 12 weeks of energy-restricted ketogenic diet compared to a conventional diet revealed significant improvements not only in metabolic parameters but also in mental health, physical functioning and pain [51]. Health-related quality of life plays a pivotal role in diabetes and its management due to its potential deleterious effects on the physical, social and psychological well-being of patients, all of which can lead to reduced self-care and subsequent glycaemic control [52].

Many studies investigating ketogenic diets for diabetes management have been conducted in people living with overweight and obesity who represent the majority of those living with T2D [34]. However, there is limited research investigating their effect in the 10–15% of individuals with T2D who have a healthy BMI (20–24.9 kg/m^2) and do not necessarily require weight loss intervention. This leads to the fundamental question, which frequently arises in the scientific literature [34], of whether ketogenic diets provide additional benefits beyond weight loss (and independent of other macronutrient changes) or whether greater weight loss is the attributing factor for glucoregulatory improvement as, although typically unintended, the ketogenic diet is typically a caloric deficit diet, compared to the typical 'western diet'.

To establish if there is superiority of low carbohydrate diets compared to a commonly prescribed hypocaloric yet nutritionally balanced diet, a 52-week study found that a hypocaloric very low carbohydrate diet (VLCD; 15%, 28% and 58% of dietary intake from carbohydrate, protein and fat, respectively) and high carbohydrate diet (53%, 17%, 30%) yielded equal body weight reductions and HbA1c in people with T2D and obesity [53]. However, of note, the composition of the VLCD used in this study was low in saturated fat yet high in

unsaturated fat, whereas, typically, ketogenic diets are relatively high in saturated fat which could explain its associated deleterious health outcomes that are observed, which will be discussed later. At the end of this study participants on the VLCD had greater improvements in lipid profiles and reduced dependence on anti-diabetic agents due to greater improvements in glucoregulatory control. Similarly, a 6-week randomised controlled trial [54] revealed that weight loss improved pancreatic beta cell (β cell) function independently of carbohydrate intake in those with T2D with both groups reducing their body weight by 6%, suggesting that body weight reduction, and its maintenance, is the key determinant of improvement of glucoregulatory control, regardless of how weight loss is achieved. The DIETFIT study [55] is a key study not only demonstrating deterioration in adherence during a ketogenic diet but also highlighting the frequently found results of no significant difference in weight loss between a healthy low fat and healthy low carbohydrate-based diet. This study also highlights the intra-variability in response to ketogenic diets; however, it affirmed that neither genotype pattern nor baseline insulin secretion affects weight loss.

However, it has been extensively argued that the metabolic benefits of ketogenic diets are due to a greater reduction of energy intake and longer duration of a calorie deficit, due to the impact of ketosis on appetite control and satiety, and elimination of refined carbohydrates and sugar sources that are ultra-processed, lack nutrients and are poor in quality. This group of food (high fat and high sugar) can often be linked with a high glycaemic index and glycaemic load (the quantity of carbohydrate) [56], a deleterious combination that diminishes insulin sensitivity, leads to insulin resistance and subsequently increases the risk of T2D when consumed long term in high quantities according to meta-analyses [57, 58]. Therefore, it may be proposed that revised recommendations and guidelines for diabetes management should focus attention on the quality of carbohydrates and their glycaemic index (GI) and load, rather than the quantity [59]. However, one review in 2009 investigating low GI diets for diabetes [60] reveals clinically insignificant reductions in HbA1c (− 0.5%), nevertheless indicting improved glycaemic control.

Emerging evidence suggests that there may be greater preservation of muscle mass and more favourable changes in body composition during ketogenic diets compared to other conventional low-fat hypocaloric diets [61–64]. Studies using dual-energy x-ray absorptiometry scans [63, 65] reveal ketogenic diets lead to greater reductions in fat mass and visceral adipose tissue, which may provide additional metabolic advantages compared to non-ketogenic diets. However, evidence is inconclusive and conflicting data remains with a recent meta-analysis [66] revealing that ketogenic diets may have a deleterious effect on fat free mass due to adherence issues. Studies investigating this potential benefit of a ketogenic diet are typically in combination with physical resistance exercise, in athletes [63], or are very short-term studies and should be interpreted with this in mind. The metabolic benefits of other conventional diets may be reduced as a result of the well-established loss of muscle mass concomitant with weight reduction [67]. The elevated intake of protein likely negates this muscle mass loss and may play a key role in the metabolic advantage of a ketogenic diet, as muscle plays a crucial part in glucose metabolism, glucoregulatory control and energy expenditure [68].

SIDE EFFECTS/HEALTH OUTCOMES OF KETOGENIC DIET

Much of the resistance to use ketogenic diets in practice has stemmed from the potential link to side effects and potential issues that might arise from increased consumption of fat with a person's diet. Recently studies are beginning to shed light on the health outcomes of long-term ketogenic diet use which further raise concern regarding its suitability for its prescription for diabetes management. Further reports of significant early changes in bone and calcium metabolism amongst adults [69] and children [70, 71] are observed as a result of ketogenic diet. This has been postulated to be due decreased conversion of inactive to biologically

active vitamin D as a result of chronic ketoacidosis which also poses the risk of osteopenia and bone fractures [72] particularly amongst elderly and postmenopausal women—an age group most affected by diabetes.

The health consequences of a long-term increase in saturated dietary fat intake remain largely unknown and whether the ketogenic diet should be recommended, particularly as those with diabetes are already at a significantly greater risk of cardiovascular disease, remains up for debate [73, 74]. Despite a lack of data specifically on ketogenic diets, it is well established in Mendelian randomisation studies [75] which reveal not only that dietary saturated fat increases LDL cholesterol (LDLc) but also the subsequent deleterious impact of LDLc as a risk factor of coronary disease. Further, prospective studies using quartiles of carbohydrate intake revealed that participants who had the lowest carbohydrate intake have the highest risk of cardiovascular disease (RR 1.13), cancer (RR 1.08) and overall mortality (RR 1.22) [76], suggesting that caution should be taken when initiating such diets. However, conflicting studies reveal ketogenic diets can lead to improvements in triglycerides and HDL levels and their ratio. Notably, 24 weeks of a ketogenic diet in people living with obesity (BMI > 35 kg/m^2) led to significant reductions in total cholesterol, LDLc and triglycerides with a simultaneous increase in HDLc, concomitant with reductions in body weight and glycaemia levels [77].

The health benefits of unprocessed, high-quality sources of carbohydrates such as legumes, whole grains, fruits and vegetables are well established [78, 79] and limiting these has been linked to mineral and vitamin deficiency [80]. There is also an abundance of contrary evidence demonstrating that vegetarian and vegan dietary patterns, which are nutrient dense, moderate-high in carbohydrates and fibre, also result in significant beneficial glycaemia-lowering effects along with reduction in cardiovascular risk in those with T2D when compared to ADA nutritional guidelines for diabetes management [73, 81]. Studies investigating vegetarian and vegan low carbohydrate diets are starting to emerge; a low carbohydrate vegan diet (with high protein meat replacement products) was compared with a moderate carbohydrate vegetarian diet [82]. Both diets produced a significant reduction in body weight and improved HbA1c levels, indicating their suitability for potential clinical implementation for both vegetarians and vegans. Similar to the literature on animal-based ketogenic diets, there is inconclusive data for the metabolic and glycaemic benefits of plant-based ketogenic diets, particularly for diabetes management. Emerging evidence reveals that [83] a plant-based high-carbohydrate, low-fat diet in people with overweight led to reductions in body weight and insulin resistance. This greater weight loss is likely to be due to lower consumption of energy-dense foods coupled with the appetite suppressant effects of a high-fibre diet. This also provides further evidence in support of the beneficial role of carbohydrates, specifically those that have a low glycaemic index, for diabetes management.

Despite the abundance of promising short-term evidence in supporting the use of ketogenic diets for diabetes management, especially for T2DM, there is a still a paucity of research to support the long-term efficacy and safety in a variety of cohorts to broadly recommend as a therapeutic approach for diabetes management at a population level. For balance it is important to point out this is true for all dietary approaches for diabetes management due to the logistic problems in long-term studies. The lack of adherence and non-compliance is a limiting factor of ketogenic diets which is one contributor to the lack of long-term studies for diabetes management. It has been shown [84] that adherence can be improved through intervention of psychological support and reinforcing mindful eating and other behavioural adherence strategies. A study highlights [85] the importance of adequate lifestyle support from healthcare professionals when individuals embark on a ketogenic diet to improve diabetes management, with an increase of non-adherence and dropout rates when lifestyle support was stopped. The social impact of reducing a main source of food for many is a major contributor to non-adherence as many social events revolve around consuming carbohydrate-rich food.

Non-adherence may also be attributable to the side effects experienced from ketogenic diets, a temporary experience so common it has been coined "keto flu" [86]. This phenomenon primarily includes neurological symptoms such as headache, brain fog and dizziness and gastrointestinal symptoms such as nausea and constipation [87, 88] which is positively related to the degree of nutritional ketosis reached.

TYPE 1 DIABETES

There is even greater uncertainty and ambiguity surrounding the suitability of a ketogenic diet as a prescription for individuals living with T1D. Unlike other types of diabetes, T1D is generally not a condition that can be reversed metabolically [34] because of the autoimmune response which leads to deterioration of β cell function and subsequent insulin secretion [89]. As a result, T1D treatment primarily consists of a generalised approach of insulin therapy [90] and there is an accepted consensus that a nutritional approach, including ketogenic diets, to solely 'treat' T1D is unlikely to be efficacious and is arguably dangerous because of concerns surrounding greater risk of diabetic ketoacidosis (DKA) and hypoglycaemia [88]. In support, the position statement from SACN and Diabetes UK stated that a low carbohydrate or ketogenic diet in people with T1D is not recommended because of the lack of evidence regarding its safety and efficacy [42].

Nevertheless, a recent 2021 review has highlighted that few small-population studies revealed that ketogenic diets may improve HbA1c and may also improve biochemical and physical markers of cardiovascular risk. For example, one study revealed that in 316 patients with T1D who averaged 36 ± 15 g of carbohydrates per day for an average duration of 2.2 ± 2.9 years, an average HbA1c of 5.7% ± 0.66% resulted; however, this study included both children and adults. Despite the low rates of acute diabetes-related complications in some studies in this review, Buehler et al.'s study [91] reiterates the potential serious risks of unmonitored ketosis in patients particularly with T1D and suggests that a continuous glucose monitor (CGM) may be used to prevent any hypoglycaemic or DKA episodes when embarking on a ketogenic diet.

Similar to T2DM, one of the key issues with establishing T1D and ketogenic diet safety is the limited data with respect adherence to the diet long-term; in a 4-year study investigating low carbohydrate diets in people with T1D, less than 50% of participants adhered to the diet diminishing from 2 years onwards, reverting to a normal diet concomitant with increases in mean HbA1c [92]. This finding supports the idea that a ketogenic diet is most suitable for short-term use. Nevertheless, it is well established that exogenous insulin therapy use in individuals with T1D and in those with T2D [93, 94] typically results in some weight gain, which may, in contradiction, weaken the ability of improved blood glucose [95].

The risk of weight gain and living with obesity is becoming increasingly prevalent in people with T1D, with up to 36% of those with T1D now living with overweight or obesity [96] and therefore weight reduction is starting to be encouraged in this cohort. Similarly, as many individuals living with T1D are a normal weight, it remains up for debate whether weight loss observed when undertaking a ketogenic diet should be encouraged for the majority of those with T1D. This particular population remains significantly underinvestigated, as unlike individuals with T2D, insulin resistance per se is not the root cause of β cell dysfunction in this cohort and it may be argued whether a ketogenic diet would result in clinically significant improvements in insulin sensitivity. Further studies are warranted to investigate whether weight loss in people with T1D living with obesity improves HOMA-β (Homeostatic Model Assessment) and subsequently insulin function. Similarly, as it has been shown that the prevalence of kidney disease is significantly higher in people with T1D (16%) compared to those with T2D (9%) [97], concerns remain about recommendation of a diet very high in protein which is a potential risk for exacerbation of chronic kidney disease due to hyperfiltration [98]. Early studies have previously suggested a deleterious effect of high-protein diets on general kidney health; however, this

has largely been disproven by more recent studies [99–104].

GESTATIONAL DIABETES

Gestational diabetes (GDM) is a type of diabetes that first develops or is diagnosed during pregnancy [105]. GDM affects up to 18% of all women and, similar to T2D, the first-line approach is lifestyle intervention [106] as up to 70% of individuals with GDM can adequately control blood sugar levels with lifestyle and nutrition modifications alone. Notably, 33% of women who experience gestational diabetes progress to postpartum T2D [107]; therefore, clinically, it is important to help women prevent this happening. There is currently no evidence, including randomised controlled trials, to support the use of the ketogenic diet in pregnancy or as a treatment for those with gestational diabetes [108].

Emerging studies have shown that higher animal protein intake during pregnancy (> 42.2 g/day), particularly red meat, is associated with an increased risk of gestational diabetes [109]. Further concerns surround the impact of long-term maternal nutritional ketosis and its potential negative impact on foetal neural development and organ damage [108, 110, 111]. Additionally, as with any caloric deficit diets undertaken during pregnancy, it is important to reiterate that sufficient gestational weight gain is required for optimal foetal growth and postnatal health outcomes [108]. In women with a normal BMI (18.5–24.9) a weight gain of 11.5–16 kg is expected during pregnancy. Individuals living with overweight (BMI 25–29.9) or obesity (BMI > 30) should gain 7–11.5 kg and 5–9 kg, respectively. However, it is important to highlight that the guidance for gestational weight management does not cover those who have conditions such as T1D or T2D. Other concerns of this dietary practice surround the limitations of fibre and micronutrient-rich foods of a ketogenic diet [112], including fruit and vegetables, that have been suggested to be beneficial for postnatal outcomes and reduced adverse pregnancy events in epidemiological studies [113].

Similar to T2D, there are no clinical guidelines surrounding optimal carbohydrate intake for people with gestational diabetes. However, a meta-analysis from multiple reports suggests an optimal carbohydrate intake of 47–70% of daily energy intake supports normal foetal growth [114]. Similarly, the NHS recommends that carbohydrates should make up just over a third of an individual's dietary intake during pregnancy [115], with a reduction of saturated fat also recommended. On the other hand, it has been suggested that a ketogenic diet during pregnancy in those with gestational diabetes may even worsen insulin sensitivity due to observations of increased inflammation and suppression of lipolysis (a marker of insulin resistance in adipose tissue) [116, 117].

As aforementioned, similar to individuals with T2D, it is likely, irrespective of a particular dietary strategy, that in those with gestational diabetes improving nutritional quality will ultimately improve glucoregulatory control. This is evidenced in a recent meta-analysis [114], in which it was shown that a range of dietary approaches, including both low carbohydrate (33–40% of daily energy intake) and higher carbohydrate diets (60–70% of daily energy intake), that have a low glycaemic index and low added sugars can help control maternal glycaemia.

CHALLENGES OF THE UNIVERSAL APPLICATION OF A KETOGENIC DIET

A key barrier that healthcare professionals face with recommending, counselling about and 'prescribing' ketogenic diets for diabetes management is that there are considerable inconsistencies of its definition in the scientific literature, with no international consensus reached. There are many variants of diets that primarily focus on carbohydrate restriction; however, the precise amount of carbohydrates to define a diet as 'low' or 'very low' and the range of carbohydrates allowed differs substantially within studies, resulting in difficulty drawing conclusions within the literature [118].

The search for the correct definition of ketogenic diets' suitability for prescription is further complicated by the fact that the optimal distribution and intake of the other macronutrients (protein and fat) for individuals with diabetes also remains inconclusive. Therefore, the varying guidelines of permitted quantities of other macronutrients [88, 119] create further heterogeneity within studies making it challenging to interpret and compare findings. Consequently, the significant alteration of other macronutrients within a ketogenic diet (fat and protein) results in confounding variables which make distinguishing the accrediting factor of a ketogenic diet on glucoregulatory control challenging. Until there is consistency of a definition, the recommendation of a ketogenic diet for diabetes management cannot be endorsed for public health.

The most practical definition of a ketogenic diet should, in theory, be a dietary pattern that promotes nutritional ketosis, i.e. the formation of ketone bodies. A ketone concentration > 0.5 mmol/l or 0.5 Mm is typically defined as reaching nutritional ketosis [120]; however, there is further conflicting evidence surrounding the optimal ketone concentration in nutritional ketosis for diabetes management. The only way to show a person has reached nutritional ketosis is through assessing it by a urine or blood sample. Therefore, individuals who follow the ketogenic diet may think they are achieving ketosis but may require further carbohydrate restriction. On the other hand, some individuals may not need to restrict < 50 g carbohydrates to achieve ketosis which will be discussed later. This is evidenced in a study whereby ketone analysis at 12 and 24 months revealed that individuals have difficulty sustaining nutritional ketosis with many rarely exceeding 0.5 mmol/l [121]. As previously mentioned, it is important to note that excessively high protein intake in the absence of carbohydrates will lead to excess amino acids that can be converted to carbohydrates and fat which can lead to issues reaching clinical ketosis.

Nevertheless, the most common definition used is called a 'classic ketogenic diet' and is the most widely studied out of all the variations. A well-formulated ketogenic diet was adapted by Phinney and Volek, from the 'standard ketogenic diet', in order to address some of the limitations to promote long-term sustained nutritional ketosis through enhanced adherence. The aim is for this diet to be used as a long-term dietary approach for diabetes management which optimises health outcomes, whilst also reducing the undesired side effects such as constipation and loss of energy. This is achieved through advocating adequate fruit and vegetable intake compared to a 'standard ketogenic diet' which is arguably more beneficial for patients to meet all nutritional needs. Further variants of ketogenic diets include 'modified ketogenic diet' which is more flexible by permitting greater intake of carbohydrates simultaneous with decreased fat intake and 'medium chain triglyceride ketogenic diet' which utilises dietary supplements of medium chain triglycerides (which are more ketogenic than long chain triglycerides) that assist in inducing ketosis without the need for as greater restriction of carbohydrates as a traditional ketogenic diet. Although not usually intended, ketogenic diets typically induce an energy (caloric) deficit; however, 'very low-calorie ketogenic diets' are also a subtype, restricting calories to between 800 and 100 kcal/day [122]. A typical hypocaloric diet reduces average energy intake below what is typical for the individual, averaging a deficit of 500 kcal.

Similar to other therapeutic approaches for diabetes management, it will be difficult to determine an optimal 'one-size-fits-all' diet let alone a single approach to achieving ketogenic diets that have broad applicability for prescription at a population level as there is significant inter-individual variability which will alter its suitability, safety, and efficacy [118, 123]. Diabetes is a heterogenous disease due to differences in duration, insulin sensitivity, β cell function and insulin production [124]. Moreover, other non-dietary factors such as physical activity can alter the degree at which ketosis is reached and influence the physiological response to a ketogenic diet [125]. People who are physically active will achieve ketosis more rapidly due to the accelerated depletion of glucose and glycogen—for example, ultra-

endurance athletes can still achieve nutritional ketosis on approximately 82 g of carbohydrate per day [62, 126]. Other factors such as age, BMI, sex and ethnicity remain to be investigated and whether they have an impact on the level of carbohydrate restriction required to reach nutritional ketosis.

Various inter-individual factors such as phenotype and genetics may further influence the efficacy of ketogenic diets [127] and risk of potentially harmful adverse effects when used for diabetes management, particularly for those individuals who are unaware of genetic abnormalities. Particular concern surround those with apolipoprotein E/B genetic variants, due to their key role in lipid and cholesterol metabolism [128]. Thus, as a result of the nature of the ketogenic diet, this could result in significantly elevated low density lipoprotein (LDL) levels concomitant with an increased risk of hypertension and atherosclerotic cardiovascular disease. A case report series found that hypercholesterolemia developed whilst on ketogenic diets in five patients with and without underlying genetic abnormalities related to APOE E2/E2 genotype. On the contrary, certain genotype/single nucleotide polymorphisms (SNPs) such as the angiotensin 2 receptor (AGTR2) may enhance the response of the ketogenic diet by affecting the individual's fat metabolism resulting in greater weight loss and body fat percentage reduction concomitant with improved glycaemia [127, 129]. As it is highly unlikely that population-level screening can occur to check each patient for genetic abnormalities, any nutritional based intervention should be personalised under medical supervision on a case-by-case basis [127].

Similarly, as the vast majority of people with T2D are living with overweight or obesity, doubts remain whether a diet high in saturated fat and processed meat should be promoted because of their elevated risk of other comorbidities such as cardiovascular disease [130], cancer [131] and chronic kidney disease [132]. Studies have shown that ketogenic diets may lead to exacerbation or progression these conditions due to deleterious changes in lipid profiles such as elevated LDLc [133, 134] and increased inflammation [135]. However, some studies reveal beneficial changes of ketogenic diets on LDLc and high density lipoprotein in those living with obesity [77]. As the data is still inconclusive for this particular patient cohort, healthcare professionals should conduct individual medical assessments of comorbidities and risk factors to determine whether a ketogenic diet is suitable for the patient. Careful monitoring throughout the duration of the ketogenic dietary intervention will also be crucial to prevent adverse health outcomes.

These concerns are also relevant in the older population, whereby 33% are affected by T2D [136]. Cancer Research UK [137] and the NHS Food Guidelines encourage less consumption of red and processed meat [138] and The British Heart Foundation advise against the ketogenic diet because of the high saturated fat content, coupled with restrictions on fruits and vegetables but also as a result of limited research and long-term studies [139]. The National Lipid Association has published a scientific statement [23] which reviewed current evidence on the effects on low carbohydrate and very low carbohydrate diets (including ketogenic diets) stating that ketogenic diets are not superior to other weight loss diets and also promotes caution of the ketogenic diet due to the severe restriction of food sources associated with cardioprotective benefits and encourage foods associated with deleterious cardiovascular outcomes (i.e. processed meats). Against all this a large meta-analysis from Liverpool [140] which concluded that "Large randomized controlled trials of at least 6 months duration with carbohydrate restriction appear superior in improving lipid markers when compared with low-fat diets. Dietary guidelines should consider carbohydrate restriction as an alternative dietary strategy for the prevention/management of dyslipidemia for populations with cardiometabolic risk."

Another key issue can relate to ethical, cultural and religious beliefs which may prevent people living with diabetes from being able to follow a prescribed conventional animal-based ketogenic diet. Vegetarians and vegans exclude foods derived from animals with plant-based diets consisting of grains, legumes, fruit and vegetables. However, adaptations of the

ketogenic diet to suit those with ethical, religious and cultural beliefs include substituting animal-based protein for high-fat and high-protein alternatives such as nuts, seeds, tofu and other plant protein. Plant-based diets have been linked to a reduced risk of both obesity and T2D [141]. Similar evidence reveals that [83] a plant-based high-carbohydrate, low-fat diet in people with overweight led to reductions in body weight and insulin resistance. This also provides further evidence in support of the beneficial role of carbohydrates, specifically those that are high in fibre and a low glycaemic index (the rate of carbohydrate digestion) for diabetes management.

From a dietary perspective it is key that people living with diabetes are supported to make healthier food choices using an individualised approach, appreciating that no one size fits all. Another fundamental question that has yet to be answered is the duration of which ketogenic diets should be prescribed for, and whether the ketogenic diet should be 'prescribed' as a short-term solution or a lifelong prescription for diabetes management. Studies report that the initial metabolic improvements of a ketogenic diets diminish at 6 months, which are likely to be correlated to reduction in dietary adherence, which is evident in many studies [142]. However, a meta-analysis [143] reveals that benefits of a ketogenic diet, including decreased triglyceride levels, increasing HDL cholesterol levels, and reduction of anti-diabetic medications usage can be observed for up to 12 months. The findings surrounding improvements in lipid profiles can lead us to suggest that ketogenic diets can improve physical markers of cardiovascular risk and other metabolic outcomes. It can therefore be suggested that, at present, a ketogenic diet can be prescribed as a short-term solution for up to a year for glycaemic and health outcome improvement. In the absence of any evidence or logical physiological mechanism of harm it is possible they could be safe for rather longer.

In the same vein, an important question also remains about what the correct prescription is if patients achieve remission of T2D. There is an unmet need for research to investigate the physiological adaptive effects when carbohydrates are reintroduced from a ketogenic diet and whether remission can remain. Studies [62] have found that rapid reintroduction of carbohydrates may cause deleterious effects on lipid profiles, suggesting that a gradual reintroduction of carbohydrate should be encouraged. Similar to other diet-induced methods of weight loss, it is likely that the beneficial effects will only last as long as the individual remains on a ketogenic diet, concomitant with sustained weight reduction [34]. As a result, it is possible that patients who transition from a ketogenic diet to moderate carbohydrate diet may experience a decline in glycaemic control and loss of diabetes remission is likely to occur [34]. Therefore, it is likely that a ketogenic diet, if used as a "prescription" for diabetes management, is a continuous treatment that requires exceptional adherence to maintain its therapeutic benefits. As a result, there is a risk of periodic "yo–yo" cycles of a ketogenic diet to induce weight loss and subsequent diabetes improvement.

RECOMMENDATIONS

It is evident from the scientific literature that the ketogenic diet can be an effective short-term treatment for diabetes management; however, the diet is as such and should be promoted as a long-term lifestyle with care due to the unknown surrounding long-term health outcomes. Unfortunately, no long-term evidence exists for the current guideline-driven approaches either so all long-term dietary strategies for diabetes management remain an 'evidence-free zone.' This might be compounded by those who generate guidelines including SACN and NICE only accepting data from randomised controlled trials and meta-analyses as evidence, which omits the data from well-conducted case-series which may not meet the threshold for evidence of efficacy but may be useful in indicating safety and tolerability. Additionally, until a recognised definition of a ketogenic diet/VLCD is established, prescription and advocacy at a public health level will be challenging.

From the available data ketogenic diets appear to not be superior but are also not

inferior in terms of metabolic advantages for diabetes management [27], but it is generally agreed that the advantage of a ketogenic is due to a longer duration of a caloric deficit diet. In short, the optimal diet for diabetes management is the one that an individual can adhere to induce significant weight loss and involves lifelong change. Like other nutritional interventions, a personalised nutrition approach for diabetes management is required, with support of a dietician, to fine-tune the optimal dietary pattern to improve long-term adherence and minimise side effects [144] whilst also considering individuals' lifestyle.

Finally, it is crucial that individuals with T2D taking medication should first seek medical guidance for a personalised assessment before implementing any significant carbohydrate restrictive diet to ensure appropriate safety and ensure that any pharmacotherapies are appropriately managed. However carbohydrate restriction in those taking the most commonly prescribed medication, metformin, does seem to be safe [145].

CONCLUSION

It is clear that ketogenic diets have favourable metabolic and weight reduction effects in the short term and a growing number of official nutritional guidelines are recognising and promoting the short-term metabolic benefits of this diet. Equally there is no long-term evidence for our conventional guidelines as such studies are very difficult to fund and run. It is evident that there is an urgent unmet need for long-term analysis of health outcomes of both conventional and ketogenic diets. Nevertheless, the maintenance of significant weight loss remains the key driver for improved diabetes management and healthcare professionals should advocate a healthy dietary pattern that an individual will have the greatest adherence to [34]. The limiting factor of the absence of a univocal definition of a ketogenic diet continues to hinder research and clinical implementation of ketogenic diets for diabetes management at a public health level will be challenging.

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Declarations

Conflict of Interest. Adrian Brown reports honoraria from Novo Nordisk, Office of Health Improvement and Disparity, Johnson and Johnson and Obesity UK outside the submitted work and is on the Medical Advisory Board and shareholder of Reset Health Clinics Ltd. David Unwin is an advisor for Diabetes Digital Media who have developed the Low Carb app. Duane Mellor has worked as an investigator on meal replacement studies which have had commercial support. Chloe Firman has no conflicts of interest.

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