Very low carbohydrate ketogenic diets and diabetes

Pamela Dyson
PhD, RD, OCDEM, Oxford University NHS Foundation Trust, Oxford, UK; and NIHR Biomedical Research Centre, Oxford, UK

Abstract
Very low carbohydrate ketogenic diets (VLCKD) have been widely promoted for the management of diabetes. There is confusion among people with diabetes and health professionals about the efficacy and safety of these diets and this review aimed to explore the role of VLCKD for people with diabetes.

An electronic search of English language articles was performed using MEDLINE (1980 to January 2020), EMBASE (1980 to January 2020) and the Cochrane Central Register of Controlled Trials (1980 to January 2020). Randomised controlled trials (RCTs) >12 weeks duration comparing VLCKD, defined as <50g carbohydrate/day, with higher carbohydrate intakes in people at risk of or with diagnosed diabetes were included. Primary outcomes included HbA1c and weight and secondary outcomes were lipid concentrations.

There were no RCTs examining the role of VLCKD for diabetes prevention. Two RCTs in diagnosed type 2 diabetes reported significant weight loss, but outcomes for glycaemic control and lipid concentrations were inconsistent. There were no RCTs in people with type 1 diabetes, although observational trials reported lower HbA1c, with a high prevalence of dyslipidaemia and hypoglycaemia.

A lack of high-quality evidence limits the use of VLCKD in people with diabetes.

Key words
very low carbohydrate ketogenic diet; diabetes

Introduction
The search for the optimal diet for the treatment of diabetes has caused much controversy and debate, resulting in confusion and uncertainty for both people with diabetes and health professionals alike. Recent dietary guidelines have concentrated on evidence-based recommendations and concluded that individualisation is key, and that there are a variety of dietary strategies that are suitable for people with diabetes including low-fat healthy eating, Mediterranean-style diets, low energy diets, carbohydrate management and, for those with type 2 diabetes, low carbohydrate diets.1,2 There have been calls for low carbohydrate diets to be used as the default strategy in people with type 2 diabetes,3 although current available evidence indicates that despite significant improvements in both glycaemic control and body weight, there is no evidence of superiority of low carbohydrate diets over other dietary strategies over the longer term.4 It may be that this lack of superiority is related to the degree of carbohydrate restriction, and that very low carbohydrate ketogenic diets (VLCKD) providing <50g carbohydrate/day are more effective than standard low carbohydrate diets (50–130g carbohydrate/day). This supposition is supported by two recent meta-analyses of low carbohydrate diets reporting that those studies with the lowest daily carbohydrate intake found the largest reduction in HbA1c.5,6 In addition, some recent reviews have made the case for VLCKD in the prevention and treatment of both type 1 and type 2 diabetes, although most authors recognise that there is heterogeneity in studies investigating diabetes.7–10

This review aims to investigate the role of VLCKD in the prevention and treatment of diabetes.

Definition of VLCKD
There is no formal definition of VLCKDs,11 but they are characterised by a severe reduction in carbohydrate intake, leading to the presence of circulating ketone bodies, primarily β-hydroxybutyrate, which are produced by fat oxidation for energy production in the absence of available glucose. In addition, there is no consensus at present on the
level of ketone concentrations that indicate dietary ketosis, or acceptable levels of ketosis in those with type 1 diabetes. Physiological studies have demonstrated that diets providing <50g carbohydrate/day will induce ketosis, although this is highly variable and some individuals require as little as <20g/day before ketosis occurs. In order to achieve ketosis, most VLCKDs recommend complete avoidance of all starchy and sugary carbohydrates, limited amounts of low carbohydrate fruit and vegetables and unlimited amounts of protein (meat, fish, eggs and cheese) and fats. Dairy products containing carbohydrate (milk, yogurt, ice cream) are usually avoided, although cheese and butter are included as they contain little or no carbohydrate. In common with other analyses, this review considers that VLCKDs are defined as those providing <50g carbohydrate/day.

**Methods**

**Data sources and search strategy**

This review was conducted with reference to the Cochrane Handbook for Systematic Review of Interventions and reported according to PRISMA guidelines, although only a single investigator screened the literature and selected the studies for inclusion. An electronic search of English language articles published since 1980 (as HbA1c was not commonly reported before this time) was performed using MEDLINE (1980 to January 2020), EMBASE (1980 to January 2020) and the Cochrane Central Register of Controlled Trials (1980 to January 2020). In addition, recently published meta-analyses of low carbohydrate diets were hand-searched to identify any additional VLCKD interventions included in the analyses.

**Eligibility criteria**

The selection criteria included randomised controlled trials (RCTs) >12 weeks comparing interventions evaluating VLCKD (<50g carbohydrate/day) with higher carbohydrate intakes in people at risk of type 2 diabetes or with diagnosed type 1 or type 2 diabetes. As ketosis occurs at levels <50g carbohydrate/day, only those studies reporting actual intakes of <50g/day were included. Primary outcomes included weight and HbA1c and secondary outcomes included lipid concentrations, adverse events and medication changes.

**Data extraction**

Data extraction was carried out by the author and reported on a specially designed spreadsheet. Extracted information included: study details (duration); characteristics of the study participants (demographic, anthropometric and biochemical); descriptions of the intervention and comparator diets (amount of carbohydrate and other macronutrients); outcomes (HbA1c, weight, lipid concentrations, rates of attrition, dietary adherence); changes in medication and adverse events. As only two studies met the inclusion criteria and they were heterogeneous in terms of mode of delivery of the intervention, pharmacological treatment, the diets used for comparison and length of followup, risk of bias was not assessed and a meta-analysis was not performed.

**Results**

The flow diagram illustrating the search and selection of studies is shown in Figure 1. The initial database search returned 123 results and 14 full-text articles were retrieved for eligibility testing. Only two studies met the inclusion criteria and both were conducted in people with type 2 diabetes. Characteristics of these two studies are shown in Table 1, and the primary outcomes in Table 2a. Both studies reported significantly greater reductions in body weight in the intervention group compared to control (9.6kg and 4.2kg), but only one study demonstrated significantly greater reduction in HbA1c (-5mmol/mol). Table 2b summarises changes in lipid concentrations and shows that there are small changes from baseline to follow-up. One study reported significantly greater reductions in triglyceride concentrations (-0.6mmol/L), and the other greater increases in HDL concentrations, although as the reported difference between the two groups was just 0.1mmol/L, the clinical relevance of this is questionable.

In common with most dietary intervention studies, attrition rates were relatively high, with one study reporting that 46% of the control group dropped out of the study, compared with 8% of the intervention group. The second study had higher rates of attrition at 53% and 41% respectively. One study reported greater reductions in medication in the
intervention group compared to the control group, and the other included only those taking metformin and reported no difference in medication changes between groups. 16

Discussion
Prevention, remission treatment of type 2 diabetes
There is a lack of evidence for the role of VLCKD in the prevention and remission of type 2 diabetes. One small pilot study investigating prevention in 22 subjects reported mean weight losses of 5.2% at 12 months follow-up, and these data will be used to plan a full RCT. 18 There is no evidence of VLCKD on remission of type 2 diabetes, but a pilot study investigating a low energy, low carbohydrate diet (<26% energy) reported remission in four out of 21 participants (19%). 19

In terms of treatment, two studies met the inclusion criteria and the results are presented above. In summary, outcomes were inconsistent in terms of glycaemic control and changes to medication, although both studies reported significantly greater weight loss in the intervention group. Observational trials, case reports and audits in people with type 2 diabetes have reported positive significant effects of VLCKD for both glycaemic control (-9 to -33mmol/mol) and for weight loss (7.5 to 14kg), although conclusions are limited by the lack of a comparator group. In addition,
in many of these reports, the intervention was self-selected by the participants and this may explain the positive outcomes. It is intuitive that a diet that is self-selected will be better tolerated and lead to greater adherence.\textsuperscript{25} It has been argued that data from observational studies such as these are of more use than evidence from RCTs, which is not applicable to dietary interventions as it does not allow for the many critical influences on personal choice;\textsuperscript{30} despite this, RCT evidence is still considered of the highest grade and re- sults from RCTs have been shown to be more robust and generalisable than observational studies lacking a comparator group.\textsuperscript{40,41} The majority of observational, or case series reports or RCTs have reported that current \( \text{HbA}_1\text{c} \) concentrations were \( 39\pm6\text{mmol/mol} \).\textsuperscript{43} Conclusions from both these studies are limited by the lack of a comparator group and data about baseline \( \text{HbA}_1\text{c} \) values before the VLCKD was instigated. In the majority of studies reporting positive glycaemic outcomes in type 1 diabetes, the participants tend to be highly motivated, have self-selected a VLCKD, and are willing to adopt tight glycaemic targets and to monitor blood glucose concentrations frequently. Consequently, it is not clear how this can be translated to general populations of people with type 1 diabetes.\textsuperscript{43}

**Medication changes**

The majority of observational studies of VLCKD in people with type 2 diabetes that described changes in medication reported reductions in both glucose-lowering and antihypertensive medication,\textsuperscript{3} and in those with type 1 diabetes, insulin requirements were significantly reduced.\textsuperscript{41}

**Adverse events**

Concern has been expressed about the long-term health effects of low carbohydrate diets generally\textsuperscript{44} and VLCKD specifically.\textsuperscript{45,46} The most commonly reported side effects are gastrointestinal and include constipation and diarrhoea.\textsuperscript{47} Short-term
KEY POINTS

- The role of very low carbohydrate ketogenic diets (VLCKD) for people with diabetes is unclear
- There is little high-quality evidence for VLCKD; two randomised controlled trials (RCTs) in people with type 2 diabetes reported significantly greater weight loss, but inconsistent effects on glycaemic control and medication
- Observational trials and case reports suggest that VLCKD improved glycaemic control in type 1 diabetes, but conclusions are limited by the absence of RCTs
- Reported adverse events included dyslipidaemia and hypoglycaemia in type 1 diabetes
- There is insufficient high-quality evidence to support the use of VLCKD

adverse events include headaches, muscle cramps and weakness, often called ‘keto flu’, but these symptoms usually resolve after a few days. The main longer-term health issues are related to increased risk of cardiovascular disease (CVD) associated with high saturated fat intakes, insufficient intake of micronutrients, and specifically for those with diabetes, increased risk of diabetic ketoacidosis and hypoglycaemia. In terms of CVD risk, a recent review claims that although nutritional ketosis is widely regarded as a normal metabolic state, in fact ketone bodies are more harmful than glucose for activating inflammatory processes and contributing to CVD risk. Lipid concentrations are established CVD risk factors, and although many studies reported significant reductions in triglyceride concentrations, this was accompanied by increased LDL concentrations and often by increased total cholesterol. In the majority of studies in people with type 2 diabetes, where energy restriction led to significant weight loss, only small and insignificant changes in lipid concentrations were reported. Weight reduction improves CVD risk factors and in the presence of significant weight loss there is no difference between different high or low carbohydrate diets for primary prevention of CVD. Conversely, in studies of VLCKD in those with type 1 diabetes, higher fat intakes were recommended for energy balance and weight maintenance and this appeared to result in significant dyslipidaemia. Two observational studies reported dyslipidaemia in >80% and >62% of those with measured lipid concentrations. Supporters of VLCKD often make the case that the increases in LDL, which are associated with low triglyceride concentrations, may reflect the presence of large, buoyant lipoprotein particles, and that this is a low-risk sub-type. However, in those using VLCKD, the long-term cardiovascular outcomes of this high LDL/low triglyceride lipid profile is unknown.

Micronutrient deficiencies that may be associated with VLCKD consist of those nutrients found in unprocessed carbohydrate food (whole grains, milk, fruit and starchy vegetables), including various vitamins, minerals, dietary fibre and phytochemicals with antioxidant properties. Few studies have reported micronutrient intake or nutrient deficiency, although a systematic review concluded that the dietary interventions used in many low carbohydrate studies had a potential risk of micronutrient inadequacy and that supplementation should be considered.

In the absence of medication adjustment, a VLCKD increases the risk of hypoglycaemia in the case of those with type 1 and type 2 diabetes, and may increase the risk of euglycaemic diabetic ketoacidosis in those with type 2 diabetes and diabetic ketoacidosis in type 1 diabetes. Hypoglycaemia was rarely recorded in studies of participants with type 2 diabetes, and this was partly due to both proactive and reactive reduction in glycaemia medication (usually insulin and sulphonylurea). There have been case reports of euglycaemic diabetic ketoacidosis in those with type 2 diabetes using sodium-glucose cotransporter 2 (SGLT2) therapy who adopted a VLCKD, and the general consensus is that VLCKD should be avoided in those treated with SGLT2 inhibitor.

In two observational studies in those with type 1 diabetes who self-selected a VLCKD, one recorded low annual rates of hospitalisation for either hypoglycaemia (1%) or diabetic ketoacidosis (1%), although 69% reported at least one episode of symptomatic hypoglycaemia per month. In the second study, participants were fitted with continuous glucose monitors for seven days and higher rates of hypoglycaemia (<3.0mmol/L) were observed with participants experiencing a median (range) of 0.9 (0.0–2.0) episodes per day. It is important to remember that the participants in these studies all self-selected a VLCKD, and were likely to be highly motivated and display other attributes related to glycaemic control such as frequent blood glucose monitoring and insulin adjustment, and under the circumstances it is of interest that rates of hypoglycaemia are as high as reported.

Conclusions

Low carbohydrate diets providing <130g carbohydrate/day are now generally accepted as a viable strategy for the management of type 2 diabetes, but evidence for more stringent carbohydrate restriction is lacking. The majority of studies in those with type 2 diabetes reported that the participants were unable to adhere to the severe carbohydrate restriction, thus limiting conclusions, although significant weight loss is reported. High quality evidence is lacking in people with type 1 diabetes, and although observational trials reported low HbA1c concentrations, this is offset by increased dyslipidaemia and hypoglycaemia. Studies of people with type 1 diabetes have relied on those who had already self-selected a VLCKD, and this lack of data from high quality trials prevents the translation of these results to wider populations of people with type 1 diabetes. Although it may be true that VLCKDs are useful in people with diabetes, more rigorous well-designed studies are essential to establish the evidence base before these diets can be generally recommended.
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NARRATIVE REVIEW

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References

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