



# Low-Carbohydrate and Very-Low-Carbohydrate Diets in Patients With Diabetes

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Low-carbohydrate diets have been advocated as an effective method for promoting weight loss in overweight and obese individuals and preventing and treating type 2 diabetes. This article reviews the differences between various low-carbohydrate eating plans and discusses the benefits and drawbacks of such a diet based on available evidence. It also offers practical pointers for clinicians.

Obesity is a growing epidemic; almost 40% of adults worldwide are overweight, and more than 650 million people are obese. This number has tripled since 1975 (1). The increasing prevalence of type 2 diabetes has paralleled the increase in obesity. Elevated body weight increases the risk of type 2 diabetes and mortality (2,3). The development and progression of obesity and type 2 diabetes can be delayed with exercise, diet, and weight loss of 5–10% (4–6). Because type 2 diabetes is largely a lifestyle-mediated chronic disease, there has been growing emphasis on dietary modifications and on determining the optimal eating plan for combatting obesity, diabetes, and their comorbidities.

Guidelines from the American Diabetes Association (ADA) and the Academy of Nutrition and Dietetics recommend that overweight adults with type 2 diabetes reduce energy intake to promote weight loss (7–10). Macronutrient distribution should be tailored to patients' eating patterns, preferences, and metabolic goals.

Very-low-carbohydrate diets were the mainstay of diabetes therapy before the development of exogenous insulin, with a goal of minimizing glucosuria (11,12). In the late 1940s, high-fat diets were found to correlate with high cholesterol levels, leading to the promotion of low-fat diets (LFDs) rather than low-carbohydrate diets (LCDs) for people with risk factors for cardiovascular disease (CVD), including those with diabetes (13). However, the obesity and diabetes epidemics continued to progress. In the 1970s, studies linked high-carbohydrate diets to obesity, type 2 diabetes, and metabolic syndrome, and the paradigm began to shift from LFDs to LCDs (14,15). The article reviews the recent

literature on LCDs for patients with type 1 or type 2 diabetes who are overweight or obese.

## Physiology of LCDs and Ketosis

After about 4 days without carbohydrate consumption, glycogen is depleted and the body begins breaking down protein and fat for energy. Hormone-sensitive lipase is thought to be responsible for fatty acid release (16). From partial degradation of long-chain fatty acids, the liver generates ketone bodies (acetoacetate,  $\beta$ -hydroxybutyrate [BHB], and acetone) (17). Ketones are taken up by tissues in need of energy, converted first to acetyl-CoA and then to adenosine triphosphate (18).

Skeletal muscle, the myocardium, and the liver can use fatty acids for energy, but almost all tissues can also use ketones. The central nervous system depends on ketones during glucopenia because fatty acids do not cross the blood-brain barrier (19,20). Ketogenesis requires glucopenia because glucose is a potent stimulator of insulin secretion, and insulin suppresses fatty acid release. Therefore, ketogenesis is abruptly stopped by administering insulin or glucose (17,21).

Ketone catabolism releases more energy than pyruvate in glycogenolysis because ketones are more reduced. At best, 185.7 kcal/mol can be liberated from pyruvate, but 243.6 kcal/mol can be liberated from BHB—31% more calories (22). This energy difference has been observed in vitro using rat heart models, and human studies have echoed this finding (23). Serum levels of BHB reach 1–2 mmol/L after 2 days of fasting or 90 minutes of intense exercise (24,25) and increase

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to 6–8 mmol/L with prolonged starvation (20). BHB may stay consistently above 2 mmol/L on a ketogenic diet (26). Ketosis can be measured by blood BHB levels and in the urine as acetoacetate (27,28).

Although ketosis at moderate levels (typically defined as up to 3 mmol/L), deemed “nutritional ketosis,” does not appear to be intrinsically harmful, clinicians often avoid ketosis because, at higher levels, it can signal dangerous states such as diabetic and alcoholic ketoacidosis, in which metabolic acidosis occurs (29). However, research indicates that ketone bodies may serve as more than an alternative fuel source; there is emerging evidence supporting their signaling properties and physiologic impact, which may include reducing inflammation and improving insulin sensitivity (18).

### Types of Weight Loss Diets

A typical American diet consists of 2,200 kcal/day, with roughly 35% from fat, 15% from protein, and 50% (~275 g) from carbohydrate (30). Dietary approaches for weight loss commonly emphasize one of the following: decreased carbohydrate intake, decreased fat intake, or decreased calories/portions (Table 1) (31). This review focuses on the approaches that reduce carbohydrate intake, especially those that emphasize maintaining nutritional ketosis.

#### LCDs

There are a wide variety of LCDs, which typically consist of 60–130 g/day carbohydrate (26–45% of daily caloric intake) but do not seek to promote ketosis (32). Popular LCDs include the South Beach Diet and the Zone Diet (33,34).

### Very-Low-Carbohydrate Ketogenic Diets

Ketogenic diets were originally used in the early 20th century to combat epilepsy in children but have since been adapted for weight management. Typically, very-low-carbohydrate ketogenic diets (VLCKDs) are characterized by reducing dietary carbohydrate intake to 20–50 g/day (<26% of a 2,000-kcal/day diet) (35). This goal is based on reducing carbohydrate to produce ketosis (36). Many of these eating plans include an induction phase, and most do not advocate calorie restriction, operating on the premise that higher percentages of protein and fat in the diet, and potentially circulating ketones, promote satiety (36–38). Examples of ketogenic eating plans include the Atkins (37), Protein Power (39), and Sugar Busters (40) diets.

In research and clinical practice, ketosis can be measured as BHB in blood on fingerstick or acetoacetate in urine (28). Ketone meters are available for home use to monitor ketones and have also been used to monitor adherence in studies (41,42). Variations of the Atkins diet are commonly used in research and practice, so it is described in more detail below.

#### Atkins Diet

This VLCKD was first popularized by R.C. Atkins in the 1972 book *Dr. Atkins’ Diet Revolution* and was later updated in *Dr. Atkins’ New Diet Revolution* (37,38). The eating plan begins with an induction phase that limits carbohydrates to 20 g/day for 2 weeks and allows meat, poultry, fish/shellfish, eggs, 1 cup of vegetables, and 1 cup of salad vegetables per day but avoids fruit, bread, grains, starchy vegetables, and dairy products other than cheese, cream, and butter. Induction is

**TABLE 1** Common Calorie and Macronutrient Content in Various Dietary Approaches

	Total Energy, kcal/day	Carbohydrate Content, g (%)	Fat Content, g (%)	Protein Content, g (%)	Examples
Typical American diet	2,200	275 (50)	85 (35)	82.5 (15)	—
Low-carbohydrate or very-low-carbohydrate, high-fat, high-protein	1,414	Low-carbohydrate: 120–225 (26–45) Very-low-carbohydrate: 20–60 (<26)	94 (60)	105 (30)	Dr. Atkins’ Diet Revolution, Protein Power!, Life Without Bread
Moderate fat with balanced nutrient reduction	1,450	275–300 (55–60)	Unspecified (20–30)	Unspecified (15–20)	USDA Food Pyramid, DASH diet, Weight Watchers
Low-fat or very-low-fat, very-high-carbohydrate, moderate protein	1,450	350–400 (70–77)	Low-fat: unspecified (<30, with <10 from saturated fat) Very-low-fat: unspecified (<10%)	Unspecified (13–20)	Dr. Dean Ornish’s Program for Reversing Heart Disease, Eat More Weigh Less, The New Pritikin Program

Adapted from refs. 8 and 31. DASH, Dietary Approaches to Stop Hypertension; USDA, U.S. Department of Agriculture.

meant to rapidly deplete glycogen stores and thus induce fat oxidation (43). Carbohydrates are added gradually while maintaining ketosis until the carbohydrate level that can maintain the goal weight is identified (37). The diet emphasizes urine ketone examination to identify a level of carbohydrates that will maintain ketosis.

### *Low-Carbohydrate Mediterranean Diet*

Initially described in the 1960s, the Mediterranean diet has since been linked to lower mortality (44) and improved A1C and fasting blood glucose (FBG) in patients with diabetes (45). Low-carbohydrate Mediterranean diet (LCMD) plans focus on consuming an abundance of plant-based foods (fruits, vegetables, cereals, potatoes, beans, nuts, and seeds), moderate fish and poultry, fat principally from olive oil, low levels of saturated fat, and limited sweets and red meat (46). They often incorporate breads, cereals, and potatoes but are still lower in carbohydrate than the typical American diet or LFDs. LCMDs emphasize the types of proteins and fat found in the Mediterranean diet while reducing carbohydrates by varying amounts to <50% of daily intake, resulting in weight loss, A1C and triglyceride reductions, and increased HDL cholesterol (45,47).

### *Paleolithic or Hunter-Gatherer Diet*

In 1984, O'Dea (48) studied 10 Aboriginal people with type 2 diabetes who lived for a 7-week period as hunter-gathers. Fasting glucose, postprandial glucose clearance, insulin response to glucose, and triglyceride levels all improved (48). Although no standard definition exists, Paleolithic-style diets encourage the consumption of foods that were prevalent before the agricultural revolution, including grass-fed meat, wild fish, fruits, vegetables, and nuts, and avoidance of processed foods, refined sugars, legumes, dairy products, grains, and cereals (49). A Paleolithic diet is typically lower in carbohydrate than the typical American diet or LFDs.

## **Impact on Glucose Management in Type 1 Diabetes**

### *Glycemic Control*

A systematic review (50) evaluated the effects of LCDs (<45% of total energy) on glycemic control in eight studies of adults and children with type 1 diabetes. The heterogeneity and small size of the studies precluded overall conclusions, but statistically significant improvements in A1C were seen in three of the eight studies. Studies by O'Neill et al. (51) and Nielson et al. (52) found the largest absolute average decrease in A1C, each with reductions of 1.3%, representing roughly a 17–19% reduction from baseline.

The remaining five studies showed stable glucose levels. Two studies lacked standardized insulin protocols, which is a potential confounder.

### *Medication Management*

Insulin dose reduction in patients with type 1 diabetes lowers the risk for complications of hyperinsulinemia, including hypoglycemia, weight gain, and metabolic syndrome (53,54). In the systematic review (50), LCDs reduced total daily insulin dose in all five studies that reported medication use, although in only two studies did the reduction reach statistical significance. Ireland et al. (55) found the daily insulin dose decreased by an average of 5.1 units/day with an average intake of 87 g/day carbohydrate over a 2-week study period. Krebs et al. (56) found an average reduction in total insulin dose of 22.2 units/day over a 12-week study period using an eating plan averaging 100 g/day carbohydrate.

Dietary fat and protein also cause postprandial hyperglycemia in patients with type 1 diabetes (57). High-fat, high-protein meals require more than double the amount of insulin than lower-fat, lower-protein meals with the same carbohydrate content (58). The ADA recommends that patients with type 1 diabetes who have mastered carbohydrate counting learn to incorporate estimates of dietary fat and protein into their insulin dosing (59).

## **Impact on Glucose Management in Type 2 Diabetes**

### *Short-Term Glycemic Control (≤8 Weeks)*

Boden et al. (60) studied 10 obese patients with type 2 diabetes who consumed an Atkins-modeled diet for 2 weeks in a strictly supervised setting. Mean fasting plasma glucose (FPG) levels decreased from 7.5 mmol/L (135 mg/dL) on the first day to 6.3 mmol/L (113 mg/dL) on the final day. Mean 24-hour serum insulin levels were significantly lower at the end of the VLCKD. Insulin sensitivity improved by 75% when measured via euglycemic-hyperinsulinemic clamp; mean A1C improved from 7.3 to 6.8% in 14 days. This study used gold-standard methods to highlight the immediate metabolic impact of a ketogenic eating pattern in people with type 2 diabetes.

### *Intermediate-Term Glycemic Control (3–6 Months)*

In a single-arm pilot study by Yancy et al. (61), patients with type 2 diabetes who consumed <20 g/day carbohydrate for 16 weeks reduced mean fasting glucose by 17% and A1C from 7.5 to 6.3%. In a study by Westman et al. (62), adults with obesity and type 2 diabetes were randomized to a <20 g VLCKD or a reduced-calorie, low-glycemic-index

diet (LGID) with a 500 kcal/day deficit over 24 weeks. Although both groups experienced improved glycemic control, a greater improvement was seen in the VLCKD group, with a mean change in A1C of  $-1.5\%$  versus  $-0.5\%$  in the low-calorie LGID group. In a 3-month study by Saslow et al. (63) comparing a VLCKD to a low-fat moderate-carbohydrate (150 g) calorie-restricted diet (MCCR), A1C remained stable in the MCCR group but declined significantly by  $0.4\%$  in the VLCKD group.

### *Long-Term Glycemic Control ( $\geq 1$ Year)*

#### **1-Year Outcomes**

Several recent studies have followed patients on a VLCKD over 1 year. Davis et al. (64) randomized a group of overweight adults with type 2 diabetes to a VLCKD (2-week restriction to 20–25 g carbohydrate and then reintroduction of 5 g carbohydrate and per week while maintaining ketosis) and an LFD modeled after the Diabetes Prevention Program (fat intake 25% of daily energy) (4). Dietary intake was measured by 24-hour recall at baseline, 6 months, and 12 months, and participants were encouraged to keep food logs. The LFD and VLCKD groups had similar reductions in A1C in the first 3 months. Neither group maintained these improvements at 1 year, but dietary changes were also not maintained according to self-reported dietary intake. Mayer et al. (65) compared overweight and obese adults with type 2 diabetes on a VLCKD (initially  $<20$  g/day carbohydrate without calorie restriction) versus peers on an LFD with orlistat (fat  $<30\%$  of energy, saturated fat  $<10\%$  of energy, and an energy deficit of 500–1,000 kcal). Patients following the VLCKD had an improvement in A1C of  $0.7\%$  compared with an increase of  $0.2\%$  in patients on the LFD. Saslow et al. (66) randomized overweight patients with prediabetes or type 2 diabetes to a VLCKD (20–50 g carbohydrate with a goal BHB of 0.5–3 mmol/L) or an MCCR (45–50% of calories from carbohydrate) over 1 year. Participants attended 19 classes over the 12-month study period and were taught behavioral strategies and mindful eating. Adherence was assessed with 24-hour dietary recall obtained at baseline and at 3, 6, and 12 months. The VLCKD group had a greater reduction in A1C than the MCCR group (decreased from 6.6 to 6.1% vs. from 6.9 to 6.7%,  $P = 0.007$ ), despite greater reductions in diabetes medications. Hallberg et al. (42) conducted a study of overweight and obese adults with type 2 diabetes who self-selected to follow a VLCKD and were closely followed by a telemedicine platform used to upload weight, blood glucose, and BHB levels with daily feedback from the care team. These participants were compared with patients receiving usual care. Blood BHB was monitored daily using a home meter. The carbohydrate goal

was individualized to maintain nutritional ketosis (goal BHB 0.5–3.0 mmol/L) but typically was  $<30$  g/day. BHB measurement confirmed continued nutritional ketosis with a threefold elevation above baseline at 70 days and a twofold elevation at 1 year. There was a decrease in A1C of 17%, from 7.6 to 6.3%, with an improvement in fasting glucose of 22% from baseline. Adherence was a strength of this study; 83% of participants remained in the intensive intervention arm at 1 year, but it was not a randomized study.

#### **2-Year Outcomes**

DIRECT (Dietary Intervention Randomized Controlled Trial) (67) randomized participants to a VLCKD (2-month induction of  $<20$  g/day carbohydrate with potential to increase to 120 g without limitation in calories or other macronutrients), the Mediterranean diet (1,500 kcal/day for women and, 1,800 for men with  $<35\%$  from fat), and an LFD (1,500 kcal/day for women and 1,800 for men, with 30% of calories from fat and 10% from saturated fat) in obese patients and evaluated glycemic control in a subgroup of participants with diabetes. Participants met with a dietitian 18 times during the 2-year study period, and adherence was assessed with a food questionnaire at 6, 12, and 24 months with two repeated 24-hour dietary recalls in a subgroup of participants. FPG decreased at 12 months by 18.1 mg/dL in the VLCKD group and by 23.4 mg/dL in the Mediterranean diet group but increased by 3 mg/dL in the LFD group. At 24 months, the LFD group had an increase in FPG of 12.1 mg/dL from baseline compared with an increase of 1.2 mg/dL in the VLCKD group and a decrease of 32.8 mg/dL in the Mediterranean diet group. A1C had decreased at 24 months by  $0.4 \pm 1.3\%$  in the LFD group,  $0.5 \pm 1.1\%$  in the Mediterranean diet group, and  $0.9 \pm 0.8\%$  in the VLCKD group. The changes were significant ( $P < 0.05$ ) only in the VLCKD group.

Tay et al. (68) compared A1C effects in obese individuals on a VLCKD that was high in unsaturated fat and low in saturated fat (14% carbohydrates [ $<50$  g daily increased to 70 g after 2 months], 28% protein, 58% total fat) or an isocaloric, high-carbohydrate LFD (53% carbohydrate, 17% protein,  $<30\%$  total fat) consistent with the current dietary guidelines. Adherence to the VLCKD was assessed with plasma BHB, which increased to three times that of the LFD group and then decreased toward baseline over the study period. Over 2 years, the study noted similar improvements in body weight, FBG, and A1C. The VLCKD group experienced reduced glycemic variability and had more favorable lipoprotein profile changes. However, the study was limited by a 53% attrition rate in both groups.

Athinarayanan et al. (69) published a 2-year follow-up to the study by Hallberg et al. (42) in which participants' biomarkers were monitored via telemedicine and carbohydrate intake was adjusted to maintain nutritional ketosis consistent with patients' personal health goals. At 2 years, A1C improved by an average of 0.9% from baseline in the VLCKD arm; fasting glucose declined by 29.1 mg/dL for the VLCKD arm and increased by a mean of 21.7 mg/dL in the usual care arm. At 2 years, 74% of participants in the intervention arm and 78% of those in the control arm remained enrolled in the study, and BHB remained 50% higher than baseline in participants pursuing ketosis.

### Medication Management

#### Short-Term Medication Reduction (<3 Months)

McKenzie et al. (41) studied patients on individualized diets designed to maintain nutritional ketosis, with most patients eating <30 g/day carbohydrate. Over the 10-week study period, 51% of patients were able to decrease their insulin dose, with 36% discontinuing insulin entirely. A striking 90% of patients discontinued sulfonylureas, 86% discontinued a sodium–glucose cotransporter 2 (SGLT2) inhibitor, 57% discontinued a dipeptidyl peptidase 4 inhibitor, and 75% decreased doses of a thiazolidinedione. Another 38% discontinued a glucagon-like peptide 1 receptor agonist, with 44% using a decreased dose and 26% using an increased dose at the end of the study period. This study highlights the necessity of frequent medication adjustments in the early stages of a VLCKD.

#### Intermediate-Term Medication Reduction (3–6 Months)

The majority of the 21 participants in the 16-week study by Yancy et al. (61) had diabetes medications either discontinued ( $n = 7$ ) or reduced ( $n = 10$ ) on a VLCKD. In the study by Westman et al. (62) of obese adults with type 2 diabetes randomized to a VLCKD and an LGID over 24 weeks, 95.2% of the VLCKD participants had an elimination or reduction in diabetes medication, compared with 62.1% of the LGID participants. Four individuals in the VLCKD group and one in the LGID group who were taking at least 20 units of insulin at baseline no longer required insulin at the study's conclusion. Two of the 13 patients in the MCCR arm of the 3-month study by Saslow et al. (63) were able to reduce, but not stop, diabetes medications, whereas two of 11 patients in the VLCKD arm were able to stop diabetes medications entirely.

#### Long-Term Medication Reduction ( $\geq 1$ Year)

Several long-term studies have noted significant reductions in diabetes medications with a VLCKD. Although changes

in A1C were not significantly different, Davis et al. (64) found that insulin doses decreased by a mean of 10 units in the VLCKD arm but increased by a mean of 4 units in the LFD arm. Mayer et al. (65) found that the LCD led to a greater reduction in antihyperglycemic medications using a medication effect score based on medication potency and total daily dose; 70.6% of those in the LCD group compared with 30.4% of those in the LFD group decreased their medication effect score by  $\geq 50\%$ . In the study by Tay et al. (68), more than twice the number of VLCKD participants had a reduction of  $\geq 20\%$  in medication effect score compared with LFD participants. Finally, Hallberg et al. (42) found that 40% of patients with type 2 diabetes who started a 1-year VLCKD study period on insulin were able to eliminate this medication. The remaining insulin users decreased their daily insulin dose from a mean of 105.2 to 53.8 units.

### Diabetes Remission

Diabetes remission is difficult to define because glycemic control exists along a continuum (70). Yancy et al. (71), Hallberg et al. (42), and Athinarayanan et al. (69) defined remission as an A1C <6.5% while off medication or on metformin alone. In the 48-week study by Yancy et al. (71) comparing group medical visits emphasizing weight loss using a VLCKD (20–30 g/day carbohydrate without caloric restriction) compared with standard group visits emphasizing medication intensification, 11.5% of participants in the weight management group achieved remission compared with no patients in the standard visit group. In the 2-year study by Athinarayanan et al. (69), 53% of participants on the VLCKD achieved sustained A1C <6.5% off of all medications except metformin compared with no patients in the control arm. Furthermore, 6.7% of participants on the VLCKD had complete diabetes remission, defined as normoglycemia of at least 1 year's duration without medication and an A1C <5.7% on two separate occasions, compared with no patients in the usual care group. A 4-year study by Esposito et al. (72) showed that an LCD can help with diabetes remission in newly diagnosed patients with type 2 diabetes who have never been exposed to diabetes medications. Remission was defined as patients transitioning from meeting diabetes criteria to either meeting prediabetes criteria ("partial remission") or normalization ("complete remission"), as defined by FBG and A1C levels. In comparing an LCMD (<50% carbohydrate) to an LFD, the LCMD participants were significantly more likely to have partial or complete remission than those in the LFD group. There are no studies of long of enough duration to examine the effect of LCDs on prolonged diabetes

remission >5 years as defined by a 2009 ADA consensus statement (70).

### **Impact on Weight Loss**

The impact of LCDs on weight has been studied in the short term, but studies longer than 2 years are limited. Yancy et al. (61) found an average weight loss of 6.6% from original body weight for patients adhering to a VLCKD for 16 weeks; interestingly, weight change did not predict change in A1C. In a study by Hussain et al. (73), in which patients were given the opportunity to choose between a low-calorie eating plan or a VLCKD, those with diabetes lost significantly more weight over the 24-week period on the VLCKD than on the low-calorie diet (−12 vs. −7% of original body weight). Hallberg et al. (42) also found a 12% mean weight loss on the VLCKD over the 1-year period of their study.

Some studies have shown significant weight loss favoring the VLCKD over other eating plans (64,73,74), but others have not shown a difference (63,75). None of the comparison diets have demonstrated greater weight loss. Tay et al. (68) found that both a VLCKD and an LFD combined with exercise led to weight loss, although there was no significant difference in weight loss between the two eating plans. In a meta-analysis (76), LCDs (<130 g/day carbohydrate) for patients with type 2 diabetes significantly reduced body weight compared with baseline, but results were mixed as to whether greater weight loss was achieved compared with other eating plans.

### **Impact on Diabetes Complications**

#### *Microvascular Complications*

To our knowledge, there have been no human studies looking at the impact of VLCKDs on microvascular complications of diabetes. A study of mouse models with either type 1 or type 2 diabetes (77) showed that albuminuria was reversed by maintaining the ketogenic diet for 2 months. Histologic evidence of nephropathy was only partially reversed. Another study (78) transitioned mice who had developed evidence of impaired glucose tolerance from a high-fat diet to a ketogenic diet. The mice fed a high-fat diet developed increased sensitivity to painful stimuli, which improved after transition to a ketogenic diet. The mice on a ketogenic diet also had increased neurite outgrowth. This study indicates that a ketogenic diet may help reverse small-fiber neuropathy and distal symmetric sensorimotor polyneuropathy in diabetes and prediabetes.

The presence of microvascular complications such as nephropathy is often an exclusion criterion in human

studies of LCDs. Several studies of VLCKDs did not report worsening of serum creatinine (61,62,68,73), and a case report noted reversal of nephropathy and stabilization of retinopathy in a patient who lost 19 kg and experienced a 2% decrease in A1C on a VLCKD (79). We were unable to find any evidence that LCDs and VLCKDs worsen microvascular complications of diabetes.

#### *Macrovascular Complications and Risk Factors*

#### **Lipids**

LCDs and VLCKDs can have significant effects on serum lipids, even in the short term. In a monitored study of an Atkins-type diet (60), serum triglyceride levels decreased by 35%, and LDL cholesterol decreased by 10% at the end of the 2-week VLCKD period compared with baseline. A meta-analysis of nine studies (76) including 734 patients with type 2 diabetes on diets containing <130 g/day carbohydrate for study periods ranging from 3 months to 2 years found a significant reduction in serum triglyceride levels and an increase in serum HDL cholesterol, but no significant change in total or LDL cholesterol. In a 1-year study of a VLCKD (80), the average 10-year risk for atherosclerotic CVD decreased by 11.9%. The effects of LCDs and VLCKDs on LDL cholesterol levels may be variable, with some patients developing increased LDL cholesterol (81). Therefore, serum lipids should be monitored in patients using an LCD, and management of lipid levels should be individualized.

#### **Blood Pressure**

In the study by Westman et al. (62) comparing a VLCKD and an LGID, both groups had a significant decrease in blood pressure from baseline, but there was no difference between groups. Davis et al. (64) and Guldbbrand et al. (75) found similar results with insignificant blood pressure variations between randomized LFD and LCD groups over 1 year. It appears that a VLCKD lowers blood pressure in people with diabetes, but not more than other weight loss strategies.

#### **Effect on Mortality**

There are limited randomized controlled trials of LCDs and VLCKDs lasting longer than 2 years. These two eating plans can be high in red meat and low in fruits, vegetables, and whole grains, which has prompted concern about cardiovascular effects. Several observational studies have evaluated the impact of low dietary carbohydrate intake on mortality. Two cohort studies (82,83) reported that lower dietary carbohydrate and higher protein intake were associated with increased cardiovascular and all-cause mortality. Each study evaluated a few hundred deaths

and did not evaluate the sources of dietary protein and fat. Fung et al. (84) analyzed two large cohorts and found a modest increased risk for all-cause mortality in individuals who consumed animal-based diets with low carbohydrate content but not vegetable-based diets. This finding is consistent with the results reported in an analysis of the Iowa Women's Health Study (85). It is unclear whether people who reported lower carbohydrate intake in these studies were specifically following LCDs. Furthermore, these observational studies were dependent on self-reported information, so interpretation of results is limited by potential confounding and self-report bias.

## Clinical Use and Practical Pointers

### *Potential Side Effects and How to Avoid Them*

A study comparing a VLCKD and an LFD in patients with obesity (rather than diabetes) (74) found that adverse effects occurred more commonly in the VLCKD group. These side effects included constipation (68%), headache (60%), halitosis (38%), muscle cramps (35%), diarrhea (23%), weakness (25%), and rash (13%). Other studies in patients with diabetes have not reported adverse effects (68,75). Clinical experience suggests that adequate fluid and sodium intake can be preventive with regard to side effects (7).

Sparse literature is available in adults with diabetes, but nephrolithiasis has been reported at rates of 3–10% in children being treated with a VLCKD for refractory seizures (86–88). This effect tends to occur 14–24 months after diet initiation. Studies of children who presented with nephrolithiasis have noted low serum bicarbonate and hypercalciuria, hypocitraturia, and hyperuricosuria (86,88). Fluid liberalization and urinary alkalization helps prevent further stone formation and are viable treatment options (86). Nephrolithiasis has not been mentioned frequently as a side effect of VLCKDs in adults, and we were unable to find case reports, although articles in the lay press mention a potential risk of this condition.

The most commonly reported adverse effect in adults is hypoglycemia resulting from inadequate reduction of insulin or antihyperglycemic medications (61,89). However, Yancy et al. (71) found a 50% decrease in hypoglycemic events in patients on a VLCKD who underwent protocolized medication reduction compared with peer control subjects who received medication intensification to improve glycemic control. It therefore appears that hypoglycemia can be avoided with careful medical management.

## *Strategies for Medication Reduction*

Given the risk of hypoglycemia from VLCKDs in patients with type 2 diabetes, some studies decreased doses of insulin by half and discontinued sulfonylureas at the initiation of the eating plan (61,64). There have been case reports of the development of euglycemic diabetic ketoacidosis in patients who use an SGLT2 inhibitor and follow a VLCKD, likely resulting from increased lipolysis and ketone formation (90,91). For this reason, the National Lipid Association recommends against concurrent use of a VLCKD and an SGLT2 inhibitor (81). Most clinicians discontinue SGLT2 inhibitors at the initiation of a VLCKD; however, some patients may tolerate concomitant VLCKD and SGLT2 inhibitor without incident. Patients with diabetes who are taking medications known to increase the risk of hypoglycemia or SGLT2 inhibitors who are undertaking a VLCKD should have close medical supervision with an emphasis on frequent blood glucose monitoring and proactive (and ongoing) adjustment of diabetes medications.

## *Strategies for Increasing and Monitoring Dietary Adherence*

The studies that show long-term clinically significant weight loss, medication reductions, and improvement in glycemic control are those that also closely monitored adherence to the eating plan (42,68,69). A study of adults using long-term nutritional ketosis for seizure reduction in epilepsy found that blood BHB levels correlate better than urine ketones with a reduction in seizure frequency (27).

## *Areas of Controversy*

There is concern among some experts that LCDs are potentially deficient in vitamins E, A, thiamin, B6, folate, calcium, magnesium, iron, potassium, and dietary fiber based on the foods allowed, but studies documenting such deficiencies are lacking (31). Many protocols address this concern by encouraging attention to well-balanced micro-nutrients and a daily multivitamin supplement.

Cardiac complications have not been well described in the literature. A pediatric case series found prolonged QTc developed after diet initiation in 3 of 20 patients. This finding correlated with low serum bicarbonate and high BHB. Three patients had cardiac chamber enlargement; one patient with severe dilated cardiomyopathy and prolonged QTc had reversal of these conditions with diet discontinuation (92). A prospective cohort study with a 20-year follow-up showed an increased risk of incident atrial fibrillation with lower self-reported carbohydrate intake (93). We have not found evidence of arrhythmia in the randomized trials of LCDs and VLCKDs.

## Future Research Directions

A global trend has emerged toward using low-carbohydrate dietary interventions to treat diabetes and obesity, especially given the documented benefits with regard to weight, insulin, and medication reduction. Patients with type 2 diabetes often present with long-term complications, including nephropathy, retinopathy, neuropathy, established CVD, and nonalcoholic steatohepatitis. Many of the studies of LCDs, however, excluded patients with these common comorbid conditions, so caution should still be used when using these eating plans in the setting of these complications. Furthermore, the safety and efficacy of these eating plans has not been studied in pregnant patients or patients with a history of disordered eating, so the safety of such diets in these populations is uncertain. Long-term studies are needed to evaluate the effects of LCDs in these circumstances. Finally, challenges with sustained adherence are important considerations for any long-term dietary interventions in diabetes and obesity.

## Summary

LCDs and VLCKDs can be attractive options for treating patients with diabetes and obesity. These eating plans are associated with at least as much weight loss as other diet strategies, but have the added benefit of being associated with significant reductions in the need for insulin and other diabetes medications. Patients attempting a low-carbohydrate dietary strategy should be closely followed so their medication regimen can be appropriately decreased as needed. This dietary strategy appears to be safe and effective in most patients; however, more studies are needed to evaluate the long-term effects of LCDs and VLCKDs on microvascular and macrovascular complications of diabetes.

## DUALITY OF INTEREST

W.S.Y. consults for dietdoctor.com and Guideline Central. No other potential conflicts of interest relevant to this article were reported.

## AUTHOR CONTRIBUTIONS

J.D.M., D.S., N.K., S.L., and A.I.S. researched and wrote the manuscript. W.S.Y. researched and wrote the manuscript and provided editing guidance. All authors are the guarantors of this work and, as such, take responsibility for the accuracy of the data analysis.

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