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LIPID ABNORMALITIES AND CARDIOVASCULAR PREVENTION (ED MICHOS, SECTION EDITOR)

Keto is Trending: Implications for Body Weight and Lipid Management

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Abstract

Purpose of Review Very-low-carbohydrate (VLC) and ketogenic diets (KDs) have been used for weight loss and more recently in patients with insulin resistance and type 2 diabetes. The impact of VLC and KDs on lipids/lipoproteins is a concern. The purpose of this review is to discuss the impact of KDs on body weight and lipids/lipoproteins.

Recent Findings VLC/KDs contribute to greater weight loss in the short term (< 6 months) compared to higher carbohydrate diets, but there is typically no difference between the diets by 12 months. Triglyceride and high-density lipoprotein cholesterol levels generally improve, but there is a variable response in low-density lipoprotein cholesterol levels, with some individuals experiencing a dramatic increase, particularly those with latent genetic dyslipidemias.

Summary Healthcare professionals should educate patients on the risks and benefits of following VLC/KDs and encourage the consumption of carbohydrate-rich foods associated with positive health outcomes.

Keywords Ketogenic diet · Carbohydrate restriction · Energy expenditure · Lipids · Lipoproteins · Weight loss

Introduction

Most health care professionals are familiar with the ketogenic diet (KD). The KD was developed in the 1920s as a dietary pattern for the treatment of epilepsy. Derivatives of the KD have been used for weight loss since the 1960s. The contemporary KD has been advocated for use by patients with insulin resistance and metabolic syndrome, as well as an aid in type 2 diabetes (T2D) management. The macronutrient composition of the classic KD was strictly divided into 3% total daily energy (TDE) from carbohydrate, 7% from protein, and 90% from fat [1]. The current variations of popular carbohydrate-restricted dietary patterns can be classified according to carbohydrate content as described in Table 1 [2•, 3].

The purpose of this review is to discuss: 1) the impact of the KD, and other carbohydrate-restricted diets, on body weight and weight loss maintenance; 2) the impact of the KD on the circulating lipoprotein lipid profile; and 3) factors for healthcare professionals to consider when counseling patients who choose to follow the KD or other carbohydrate-restricted dietary patterns.

Impact of Carbohydrate-Restricted and Ketogenic Diets on Body Weight and Composition

Weight Loss Several randomized controlled trials (RCTs), as well as systematic reviews and meta-analyses, have examined the effectiveness of low-carbohydrate, high-fat diets (LCHF) (> 30% TDE from fat) compared to high-carbohydrate, low-fat diets (HCLF) (< 30% TDE from fat) for weight loss in individuals with overweight or obesity (reviewed in [2•]). Results from these studies suggest that short-term

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Table 1 Diet classification based on amount of total daily energy and grams per day from carbohydrate [2•, 3]

Diet Description	Ketogenic	Calories/Day	CHO % TDE	Protein % TDE	Fat % TDE
VLCHF/KD	Yes	> 1,000	< 10* (< 20–50 g/day)	~ 10–20% TDE (1.2–1.5 g/kg)	70–80% TDE
Low-CHO	No	> 1,000	10–25** (38–97 g/day)	10–30% TDE	45–80% TDE
Moderate-CHO	No	> 1,000	26–44** (98–168 g/day)	10–30% TDE	25–65% TDE
High-CHO	No	> 1,000	45–65** (169–244 g/day)	10–30% TDE	5–45% TDE
Very-high-CHO	No	> 1,000	> 65** (> 244 g/day)	10–30% TDE	5–25% TDE
Classic KD	Yes	Varies	3	7	90

(Adapted from: Kirkpatrick et al. Clin Lipidol 2019:13(5):689–711, with permission from Elsevier) [2•]

VLCHF Very-low-carbohydrate, high-fat, *KD* Ketogenic Diet, *CHO* Carbohydrate, *TDE* Total Daily Energy

*Typically the amount of CHO required to induce ketosis in most people [3]

**Based on 1,500 cal/day, an energy intake considered hypocaloric for most individuals

(≤ 6 months) weight loss may be greater with a hypocaloric LCHF diet compared to a hypocaloric HCLF diet. However, long-term (> 6 months) weight loss is similar between hypocaloric LCHF diets and hypocaloric HCLF diets. Based on these findings, the National Lipid Association (NLA) Nutrition and Lifestyle Task Force recommended counseling patients to reduce energy intake by limiting multiple energy sources in the diet instead of a single energy source, such as carbohydrate. However, a LCHF diet may be a "reasonable option for some patients for a limited period of time (2–6 months) to induce weight loss" [2•].

One reason LCHF diets may not be superior to other hypocaloric diets with a higher quantity of carbohydrate is the difficulty of long-term adherence to the diet. Results from most longer-term clinical trials have shown that carbohydrate intake exceeds the targeted limit by the end of the follow-up period, particularly with very-low-carbohydrate (VLC)/KDs designed to achieve < 10% TDE from carbohydrate [4, 5]. Attrition in LCHF diet interventions is also typically high (~ 30%), although this is similar to the attrition rate in LFHC diet interventions. Due to the issues with sustained adherence to a dietary pattern characterized by severe carbohydrate restriction, the NLA recommends a more moderate carbohydrate intake (at least 30% TDE) for long-term weight loss and weight maintenance [2•].

Body Composition Achieving ketosis is purported to be required for the benefits of a KD. Typically, in order to achieve ketosis, an individual needs to consume a VLC diet (< 50 g/d), which results in the loss of body water due to glycogen depletion and the diuretic effects of ketones. As glycogen is utilized to maintain blood glucose levels, there is a loss of approximately 3 g of water for every gram of glycogen [2•, 6]. Considering that there are approximately 100 g of glycogen stores in the liver and 400 g in the muscle, this could result in an initial weight loss of ~ 1 kg (2.2 lb) of water due to the downward adjustment of glycogen stores [6]. The low circulating insulin level associated with a reduced-carbohydrate diet also contributes to increased fluid loss, since insulin promotes renal tubular reuptake of sodium and water [2•, 7].

During weight loss, it is desirable to primarily lose fat mass while preserving lean body mass (LBM). Evidence from several RCTs suggests low-carbohydrate diets (< 41.4% energy) result in greater initial loss of fat mass compared to diets with higher carbohydrate content [8]. However, there is also a greater loss of LBM compared to diets with a more balanced macronutrient intake [2•, 6, 8]. The greater loss of LBM may in part be explained by decreased insulin levels. Insulin is a growth factor and promotes protein synthesis [9]. Thus, the lower insulin levels that occur with VLC/KDs reduce the anabolic stimulus from insulin and can result in loss of LBM. Increasing the protein content of a low-carbohydrate diet may help minimize LBM loss [8, 10], but this can be challenging with KDs, which often restrict protein due to the gluconeogenic impact of some amino acids [11]. To preserve LBM during weight loss, the NLA recommends a higher protein intake (1.0–1.5 g/kg/d) for patients choosing a low-carbohydrate weight loss diet [2•]. Increasing physical activity and engaging in resistance exercise can also help to minimize loss of LBM during weight loss [10].

Energy Expenditure Beyond body water loss, the primary mechanisms proposed for the effectiveness of low-carbohydrate diets for weight loss are increases in energy expenditure (EE) and appetite suppression, resulting in negative energy balance and loss of body fat. Results from recent meta-analyses and well-controlled clinical trials demonstrated relative increases in EE when some dietary

carbohydrate is replaced by dietary fat [12, 13•], although the amount of the increase in EE and the clinical relevance has been vigorously debated [14–16]. Hall et al. found that EE was significantly greater when subjects consumed a very-low-carbohydrate, high-fat diet (5% TDE carbohydrate, 80% TDE fat) for four weeks compared to a high-carbohydrate diet (50% TDE carbohydrate, 35% TDE fat). The relative increase in EE was 57 kcal/d, as measured by a metabolic chamber and 151 kcal/d higher using a doubly labeled water method [2•, 12].

However, a recent re-analysis of a 29-study meta-analysis found that changes in EE with low- carbohydrate diets may depend on the duration of the intervention as the body adapts to changes in dietary carbohydrate content [13•]. The researchers found low-carbohydrate diets reduce EE initially (< 2.5 weeks) by a mean of 14.5 kcal/d for each 10% reduction in energy from dietary carbohydrate. However, in studies > 2.5 weeks, there was an increase in EE by a mean of 50.4 kcal/d for every 10% reduction in energy from dietary carbohydrate.

Despite this evidence suggesting an increase in EE with low-carbohydrate diets, the mechanisms contributing to these changes are poorly understood. Hall et al. reported significant alterations in thyroid hormones, as well as leptin and norepinephrine, suggesting a potential role of hormonal responses in the alteration of EE [12]. A higher level of leptin may increase activation of the sympathetic nervous system, contributing to an increase in EE and greater release of norepinephrine [17].

Appetite Suppression The results of most studies using low-carbohydrate diet interventions demonstrate reduced appetite [2•]. The mechanisms contributing to appetite suppression are not completely understood but could include the effects of ketones, effects of carbohydrate restriction per se, and/or the influence of increasing intakes of fat and/or protein [2•, 6, 18, 19].

Most studies that include individuals in ketosis report a reduction in hunger, although direct or indirect mechanisms to explain the reduced hunger are unclear [2•, 18]. Results from acute studies in humans suggest the addition of exogenous ketones to the diet, even in the absence of a low-carbohydrate intake, can suppress hunger and the desire to eat [20], but longer-term studies are needed to determine whether this will impact body weight and composition.

Carbohydrate restriction, even in the absence of ketosis, also appears to have some impact on appetite suppression. As mentioned previously, low-carbohydrate diets may influence hormones impacting appetite, such as ghrelin and leptin, but studies to date have not reported consistent results [2•]. A decreased carbohydrate intake typically results in increased protein and/or fat intake, which may contribute to greater satiety and reduction in hunger [2•, 6, 18, 21]. The effect of protein on appetite appears to be influenced by the amount of protein consumed with the most consistent impact observed when at least 30 g of protein is consumed during an eating occasion [22–24]. KDs often limit protein since higher protein intakes can increase gluconeogenesis and thus interfere with the development of ketosis [2•, 6, 11, 18]. Results from studies that compared high-protein, ketogenic diets to high-protein, non-ketogenic diets demonstrated greater appetite suppression with the high-protein, ketogenic diet, supporting an independent effect of ketosis on appetite [2•, 18]. Although a higher intake of carbohydrate, especially foods and beverages containing refined starches and added sugars, may result in increased appetite, a moderate carbohydrate intake with an emphasis on fiber-rich foods can be helpful for appetite control [25–27].

Impact of Carbohydrate-Restricted and Ketogenic Diets on Lipids and Lipoproteins

Atherosclerotic cardiovascular disease (ASCVD) accounts for > 30% of deaths globally [28•] and professional organizations recognize a 'heart-healthy dietary pattern' as fundamental for ASCVD prevention throughout the lifespan [29–33]. Given the knowledge that elevated atherogenic lipids/lipoproteins (low-density lipoprotein cholesterol [LDL-C], non-high-density lipoprotein cholesterol [non-HDL-C], and triglyceride [TG]-rich lipoproteins) are well-established causal factors in the development of an atherosclerotic plaque [34, 35], the impact of VLC/KDs on lipids/lipoproteins must be scrutinized for downstream effects and possible unintended consequences. Despite improvements in glycemic control and weight loss over short- to intermediate-term periods (< 6 months), there is inconsistency regarding the effects of VLC/KDs on lipids/lipoproteins, including significant variability in LDL-C, non-HDL-C, and apolipoprotein B (Apo B) responses, but results are more consistent in showing potentially favorable effects on HDL-C and TG levels (Table 2).

One mechanism of action for the impact of VLC/KDs on lipids/lipoproteins is increased lipolysis in fat tissue (adipocytes) [28•]. Decreased carbohydrate intake is associated with lower insulin levels. Lower circulating insulin promotes TG hydrolysis, liberating free fatty acids and glycerol, thus triggering hepatic production of ketone bodies (3-beta hydroxy butyrate, acetoacetic acid, and acetone) by the liver. These are ultimately utilized in the Krebs cycle for generation of adenosine triphosphate (Fig. 1) [28•, 36]. Additionally, VLC/KDs induce hepatic gene expression favoring lipid oxidation and reducing lipogenesis and lipoprotein assembly. This is manifested by increased levels of Fibroblast Growth Factor 21 (FGF21), which is known to

Table 2 Effects of low-carbohydrate and very-low-carbohydrate diets versus high-carbohydrate, low-fat diets on cardiometabolic risk markers [2•]

Cardiometabolic Risk Factor	Overweight or Obese Adults with or without Prediabetes or T2D	Comments
Weight	↓ ↔	Greater weight loss with LCHF diets in short-term (<6 mo.) and if hypocaloric; **generally nonsignificant at 1 year**
LDL-C	↓ ↑ ↔	Inconsistent effects that varied by population and diet composition
HDL-C	↑	Significant increase with LCHF diets; clinical significance is unknown
TG	↓	Significant decrease with LCHF diets
HbA1c	↓ ↔	Significant decrease with LCHF in short-term (<6 mo.); **generally nonsignificant at 1 year**
SBP and DBP	↓ ↔	Most studies showed small, nonsignificant reductions

Abbreviations: LCHF=low-carbohydrate, high-fat; LDL-C=low-density lipoprotein cholesterol; HDL-C=high-density lipoprotein cholesterol; TG=triglycerides; HbA1c=hemoglobin A1c; SBP=systolic blood pressure; DBP=diastolic blood pressure
(Adapted from: Kirkpatrick CF, et al. Clin Lipidol 2019:13(5):689-711, with permission from Elsevier) [2•].

coordinate lipid homeostasis and energy balance through induction of hepatic oxidation of lipids, ketogenesis, lipolysis, and enhanced clearance of circulating TG [36].

TG clearance is mediated by low-carbohydrate diets due to the central role of glucose and insulin as signaling mechanisms in the regulation of lipid metabolism [36]. Dietary carbohydrate restriction reduces availability of substrates, such as glucose and fructose, with concomitant increased fatty acid oxidation, as well as decreased lipogenesis. The result is a reduction in very-low-density lipoprotein (VLDL) particle formation and secretion, as well as secretion of smaller, less TG-rich VLDL particles. Research results have consistently demonstrated decreased TG and increased HDL-C levels with VLC/KDs [2•]. Tay et al. found that a hypocaloric, low-carbohydrate, low-saturated fat diet not only improved glycemic control in patients with diabetes, but also led to greater improvement in TG and HDL-C levels compared to a high-carbohydrate diet with similar fat content [37]. Additionally, the magnitude of benefit was greatest in those with the lowest baseline HDL-C. However, individuals with lipoprotein or hepatic lipase deficiency are at risk of severe elevations of TGs with resultant chylomicronemia when consuming a VLC/KD. Although lipase deficiencies are relatively uncommon, such individuals need to restrict total dietary fat intake because they have impaired clearance of TG and TG-rich lipoprotein particles and can develop pancreatitis due to TG elevation with chylomicronemia if a LCHF diet is consumed [2•, 38].

Both increases and decreases in LDL-C and Apo B-containing lipoproteins have been demonstrated with

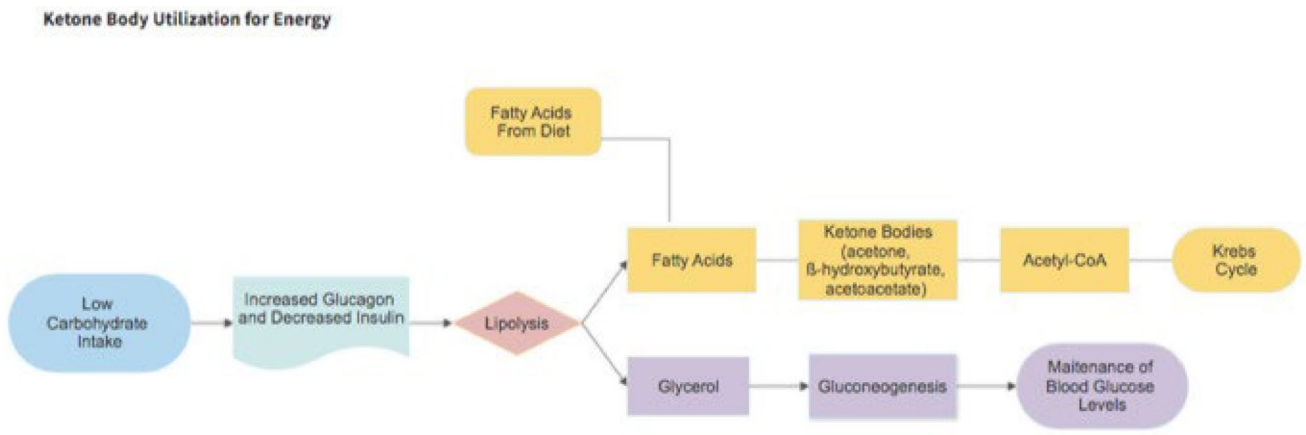

Fig. 1 Ketone body utilitization for energy. (Reprinted from: D'Souza MS, et al. Am J Med 2020:133(10):1126–1134, with permission from Elsevier) [28•]

VLC/KDs [2•, 28•, 39]. Decreased LDL-C levels may be due to the lower insulin levels associated with VLC/KDs, which inhibits HMG-CoA reductase activation and activates HMG-CoA lyase, an enzyme involved in ketone body production, thus favoring ketogenesis and reduced endogenous cholesterol synthesis [6, 28•, 36]. Weight loss will also tend to lower LDL-C, so levels may decline as body weight and body fat are reduced [40–42]. The effect on LDL-C may also be mitigated by the overall composition of the VLC/KD, including the amount of saturated fatty acids (SFAs) and dietary cholesterol, as well as protein content and quantity in the diet. VLC/KDs containing a high amount of SFAs and dietary cholesterol tend to be associated with increased levels of LDL-C [2•, 11], whereas those with a low amount of SFAs are associated more consistently with stable or lower levels of LDL-C [11, 37].

Because dietary patterns, such as VLC/KDs, may have inconsistent effects on LDL-C level, it is imperative to monitor for undesirable elevations in atherogenic lipoproteins that may occur with the use of these diets [2•, 43]. There have been several case study reports published in which the consumption of VLC/KDs unmasked genetically-influenced dyslipidemias [43••, 44••]. Harmon et al. identified five patients with baseline elevated LDL-C (average 124 mg/dL) who experienced a dramatic 295% increase in LDL-C from baseline after following a VLC/KD for ~ 8 months. In these patients, the median LDL-C rose from 124 mg/dL to 394 mg/dL. Moreover, following cessation of the VLC/KD, the LDL-C remained higher than baseline (average 137 mg/dL) at a follow-up interval of 9 months [44••]. The concern, therefore, is that individuals with a genetic predisposition to higher levels of LDL-C and/or family history of premature vascular disease may respond in an exaggerated fashion to a VLC/KD. Hyper-responders may have an increase in LDL-C by 50–100% or more from their pre-VLC/KD baseline levels [43••].

Some evidence points to an increase in LDL particle size (i.e., a shift toward larger, more buoyant LDL particles) with the consumption of VLC/KDs high in SFA content [39, 45•]. The clinical relevance of the shift in LDL particle size is unclear, given total Apo B-containing lipoprotein concentration has also been shown to increase with VLC/KDs high in SFA content [46]. Thus, importantly, although larger, more buoyant LDL particles may be less atherogenic, the available evidence supports the view that the total circulating concentration of Apo B-containing particles is a stronger determinant of ASCVD risk than LDL density or particle size [47–49]. Since Apo B is often not measured clinically, the best correlate of Apo B-containing particle concentration in the standard lipoprotein lipid profile is non-HDL-C, which integrates changes in cholesterol carried by LDL and TG-rich lipoprotein particles [30–32, 42].

To summarize, VLC/KDs are generally associated with reduced TG levels with a concomitant increase in HDL-C levels (Table 2). LDL-C responds variably, which is potentially mitigated by the SFA and dietary cholesterol contents of the VLC/KDs [37]. Also, it is likely that a subset of the population may have a substantially adverse lipoprotein lipid response to a VLC/KD. If patients choose to follow a VLC/KD, the lipid response should be monitored to identify those who may experience a dramatic increase in atherogenic lipids/lipoproteins. Achieving and maintaining weight loss will generally improve the cardiometabolic risk factor profile, including dyslipidemia. Therefore, it is important for healthcare professionals to work closely with patients to identify an approach to sustainable weight loss representing the best fit for each individual in order to ensure long-term success.

Factors to Consider for Working with Patients Who Choose to Follow Carbohydrate-Restricted and Ketogenic Diets

When discussing the use of VLC/KDs with patients, it is essential for healthcare professionals to consider the balance between successful weight loss (and maintenance) and the potential unintended consequences of such an eating pattern on lipids/lipoprotein levels. The overall ASCVD risk for each patient must be in the forefront of consideration. Ideally, a shared decision-making conversation will occur with patients before initiation of a VLC/KD, which would allow an individualized discussion about the potential risks and benefits of the diet. The shared decision-making conversation should include the following points.

- It is essential to identify motivating factors for the patient's interest in a VLC/KD. It can be helpful to identify and discuss ambivalence and assess and build self-efficacy and confidence with patients. Counseling skills, such as motivational interviewing, can be useful when working with patients beginning any kind of lifestyle change [30], including VLC/KDs
- Assess the patient's current carbohydrate intake and identify an appropriate level of carbohydrate based on the patient's needs. Many patients can achieve the benefits of carbohydrate restriction with a moderate carbohydrate intake, which will increase the likelihood of long-term adherence and success in achieving their health goals, i.e., weight loss and/or maintenance, decreased TG level, and/or improved glycemic control.
- If a patient chooses to follow a VLC/KD, there should be an emphasis on replacing carbohydrate with foods rich in unsaturated fatty acids versus SFAs. Achieving < 10% TDE from SFAs is possible [37, 50, 51], but does require knowledge about food sources of unsaturated fatty acids

and SFAs. Facilitate a conversation to identify sources of foods rich in SFAs in the patient's current diet, such as protein foods, fats for cooking (e.g., butter, coconut products, lard), and others (e.g., processed foods). Discuss replacing foods rich in SFAs and cholesterol with lean protein foods (both animal- and plant-based choices), lower fat dairy products, foods rich in unsaturated fatty acids, such as avocado, nuts, and seeds, and non-tropical oils in place of solid fats.

- Discuss the importance of overall quality of the dietary pattern with the patient. Evidence from observational studies demonstrates that a higher adherence to healthy dietary patterns with high-quality foods is associated with a 10–20% lower risk of CVD and CVD mortality [52, 53]. Healthy dietary patterns generally emphasize consumption of fruits, vegetables, whole grains, nuts, seeds, legumes, and non-tropical oils.
- Assess other lifestyle habits, including physical activity, adequate quantity and quality of sleep, smoking cessation, if applicable, and the importance of stress management.
- Refer patients to a registered dietitian nutritionist, when feasible, for medical nutrition therapy and lifestyle counseling to improve cardiometabolic risk and encourage the consumption of high-quality carbohydrate foods (vegetables, fruits, nuts, seeds, legumes, and whole grains) within the context of a carbohydrate-restricted diet.

Conclusion

Based on the current evidence, there is not a specific macronutrient distribution that is superior for weight loss or for the management of T2D; therefore, it is important to consider individual patient preference in the identification of an optimal dietary pattern. Well-designed studies are needed with moderate restrictions of carbohydrate that do not induce ketosis to determine the potential effects on appetite and body weight with dietary carbohydrate at levels that may promote better long-term adherence and consumption of recommended dietary patterns that are associated with health benefits (e.g., healthy US dietary pattern, Mediterranean dietary pattern, plant-based dietary patterns) [29–33].

VLC/KDs may improve TG and HDL-C levels. However, while some patients may experience no adverse effect on LDL-C, others may experience an increase, even a dramatic one, which may unmask an underlying genetic dyslipidemia. The quantities of SFAs and cholesterol in a VLC/KD will affect the LDL-C response. Additionally, in the relatively uncommon circumstance of a lipase deficiency, VLC/KDs may induce significant TG elevation, chylomicronemia, and pancreatitis. Based on these factors, it is important to obtain baseline and follow-up lipid/lipoprotein assessments to identify patients who may experience an excessive increase in LDL-C and/or TG levels. Guidance should be provided regarding dietary fat and carbohydrate quality. This can be achieved through an emphasis on consuming recommended foods, including fruits, vegetables, whole grains, seeds, and legumes, at levels appropriate for the target intake of carbohydrate, and through emphasis on consuming lean protein sources, foods rich in unsaturated fatty acids, such as nuts and avocados, non-tropical oils.

A shared decision-making discussion is important if a patient is considering following a VLC/KD, which should include assessing the risk/benefit ratio. If a patient chooses to follow a VLC/KD, education should include an emphasis on transition after a period of time to a recommended healthy dietary pattern, in addition to addressing physical activity and other lifestyle habits (e.g., sleep, stress management, and smoking cessation, when applicable). It is essential to meet patients where they are in their behavior change journey to facilitate successful adoption and maintenance of recommended nutrition and lifestyle interventions.

Compliance with Ethical Standards

Conflict of Interest Dr. Maki reports grants from General Mills, Hass Avocado Board, National Dairy Council, and Beef Checkoff, during the conduct of the study. Dr. Kirkpatrick and Dr. Willard declare that they have no conflict of interest.

Research Involving Human and Animal Participants This article does not contain any studies with human or animal subjects performed by any of the authors.

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