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Review of current evidence and clinical recommendations on the effects of low-carbohydrate and very-low-carbohydrate (including ketogenic) diets for the management of body weight and other cardiometabolic risk factors: A scientific statement from the National Lipid Association Nutrition and Lifestyle Task Force

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Abstract: Historically, low-carbohydrate (CHO) and very-low-CHO diets have been used for weight loss. Recently, these diets have been promoted for type 2 diabetes (T2D) management. This scientific statement provides a comprehensive review of the current evidence base available from recent systematic reviews and meta-analyses on the effects of low-CHO and very-low-CHO diets on body weight, lipoprotein lipids, glycemic control, and other cardiometabolic risk factors. In addition, evidence on emerging risk

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factors and potential safety concerns of low-CHO and very-low-CHO diets, especially for high-risk individuals, such as those with genetic lipid disorders, was reviewed. Based on the evidence reviewed, low-CHO and very-low-CHO diets are not superior to other dietary approaches for weight loss. These diets may have advantages related to appetite control, triglyceride reduction, and reduction in the use of medication in T2D management. The evidence reviewed showed mixed effects on low-density lipoprotein cholesterol levels with some studies showing an increase. There was no clear evidence for advantages regarding effects on other cardiometabolic risk markers. Minimal data are available regarding long-term (>2 years) efficacy and safety. Clinicians are encouraged to consider the evidence discussed in this scientific statement when counseling patients on the use of low-CHO and very-low-CHO diets.

Introduction

Historically, dietary strategies that restrict carbohydrate (CHO) have been used for weight loss.[1–4] There is growing interest in low-CHO and very-low-CHO diets for patients with prediabetes and type 2 diabetes (T2D) to improve glycemic control and other cardiometabolic risk factors (eg, high blood pressure and atherogenic dyslipidemia).[1–6] There are proposed benefits of these diets for other conditions (eg, acne, cancer, neurological diseases, and polycystic ovary syndrome)[3] and performance enhancement in athletes.[7] There have been anecdotal reports of improved mood, cognitive function, and energy levels with the use of low-CHO and very-low-CHO diets for weight loss, which have not generally been supported by findings from controlled studies.[8–11] In addition, very-low-CHO diets have become popular because of the perception they are healthier than currently recommended dietary patterns.[12]

There are several types of CHO-restricted diets, some of which restrict CHO to very low levels without restricting dietary protein and fat (eg, Atkins-style diet), whereas others allow moderate CHO intake with moderate protein and fat intake (eg, South Beach, Zone). Contemporary very-low-CHO diets limit protein to moderate levels to induce ketosis without restricting fat or total calories.[1] A very-low-CHO ketogenic diet (KD) has been used for the treatment of intractable epilepsy since the 1920s. The classic KD is precisely calculated to induce ketosis while providing adequate nutrition to prevent malnutrition and promote normal growth and development in children.[13,14] Some individuals participate in medically supervised low-CHO and very-low-CHO diets for weight loss and/or T2D management; however, many follow these diets without medical supervision. In a 2018 survey of Americans between 18 and 80 years of age (n = 1009), 16% reported following some type of low-CHO eating pattern in the past year.[15]

There is some evidence that low-CHO and very-low-CHO diets elicit weight loss with *ad libitum* intake and without feelings of deprivation and hunger.[1] In addition, reduced CHO intake results in decreased insulin levels, which has been hypothesized to produce cardiometabolic benefits.[3,4,16] However, low-CHO and very-low-CHO diets that are high in saturated fatty acid (SFA)-rich foods and low in nutrient-dense CHO foods are inconsistent with evidence-based dietary strategies recommended by professional organizations.[17–20]

This National Lipid Association (NLA) Scientific Statement reviews the characteristics of low- and very-low-CHO diets and their impacts on metabolic pathways, examines the evidence on the effects of these diets on weight loss, dyslipidemia, and other cardiometabolic risk factors, and makes recommendations for clinicians about the use of these diets in adults in clinical practice. The specific content of this scientific statement includes:

- a description of CHO-restricted diets;
- a brief review of very-low-calorie KDs;
- the impact of nutritional ketosis on energy and cholesterol metabolism;
- the differential effects of CHO-restricted diets on the determinants of energy balance and body weight;
- the evidence base for short- and long-term effects on weight loss, body composition, and cardiometabolic risk factors;
- safety concerns and adverse effects; and
- points to consider for the clinician-patient discussion on the use of low-CHO and very-low-CHO diets.

Definition of CHO-restricted diets

The terminology and definitions used for CHO-restricted diets vary considerably and are often defined based on the proportion of total daily energy (TDE) from CHO and/or absolute CHO intake. In this review, a CHO-restricted diet is defined as CHO intake below the lower boundary of the acceptable macronutrient distribution range for healthy adults (45–65% TDE).[20,21] A moderate-CHO diet is defined as 26–44% TDE from CHO (130–225 grams CHO/d for a reference 2000 kcal diet), a low-CHO diet as 10–25% TDE from CHO (50–130 grams CHO/d), and a very-low-CHO diet as <10% TDE from CHO (<50 grams CHO/d) (Table 1).

Description of CHO-restricted and ketogenic diets

Low- and moderate-CHO diets can be moderate or high in fat and moderate or high in protein and do not result in

Table 1 Diet classification based on amount of TDE and grams per day from CHO[20,22–24]

Diet description	Ketogenic	Calories/d	CHO % TDE	Protein % TDE	Fat % TDE
VLCHF/KD	Yes	>1000	<10* (<20–50 g/d)	~10% TDE (1.2–1.5 g/kg)	70–80% TDE
Low-CHO	No	>1000	10–25† (38–97 g/d)	10–30% TDE	25–45% TDE
Moderate-CHO	No	>1000	26–44† (98–168 g/d)	10–30% TDE	25–35% TDE
High-CHO	No	>1000	45–65† (169–244 g/d)	10–30% TDE	25–35% TDE
Very-high-CHO	No	>1000	>65† (>244 g/d)	10–30% TDE	25–35% TDE
VLCalD‡	Varies	<800	Varies	Varies	Varies
Classic KD	Yes	Varies	3	7	90

CHO, carbohydrate; VLCHF/KD, very-low-CHO, high-fat ketogenic diet; VLCalD, very-low-calorie diet; PSMF, protein sparing modified fast; TDE, total daily energy.

*Typically the amount of CHO required to induce ketosis in most people.[22]

†Based on 1500 calories/d, an energy intake considered hypocaloric for most individuals.

‡VLCalDs vary in macronutrient composition—some may be ketogenic if CHO content is low enough; others may not be if CHO content is >50 g/d. The PSMF is a subset of VLCalDs and is typically higher in protein to spare LBM with a macronutrient composition of <20 to 50 g CHO/d, 1.2 to 1.5 g/kg protein/d, and <10 to 15% TDE fat.

nutritional ketosis due to higher contents of both CHO and protein.[4,22] Ketosis can be predicted for a CHO-restricted diet based on its ketogenic ratio (the ratio of the sum of ketogenic factors to the sum of anti-ketogenic factors):

KR = (0.9 F + 0.46 P)/(1.0 C + 0.58 P + 0.1 F), where F is grams of fat, P is grams of protein, and C is grams of CHO.[25]

The ratio that consistently induces ketogenesis is ≥2,[25] with 1.5 typically being the lower ketogenic threshold.[25,26] Zilberter and Zilberter[25] reviewed 62 studies that reported on prescribed dietary interventions described as "ketogenic" and found that only 25 of the 62 studies had a ketogenic ratio >1.5, which illustrates the complexity of interpreting the available evidence on KDs, much of which appears to be from investigations that did not truly assess KDs.

Low- and moderate-CHO diets allow the consumption of CHO-containing foods that are components of cardioprotective dietary patterns, including vegetables, fruits, whole grains, nuts, seeds, and legumes.[17–20,27] These foods are important sources of fiber, magnesium, B-vitamins, and bioactive compounds, such as polyphenols, all of which have been associated with lower risks for dyslipidemia, atherosclerotic cardiovascular disease (ASCVD) events, and incident T2D.[17–20,27,28]

Contemporary very-low-CHO KDs have become popular among the lay public,[12,29] as well as some clinicians and nutrition scientists.[1,29] The current popular version is very low in CHO (~20–50 g/d or 5–10% TDE), high in fat (70–80% TDE),[22] and emphasizes the replacement of CHO with fat; thus, it is a very-low-CHO, high-fat (VLCHF) diet,[2] which results in ketosis.[4,22] Achieving ketosis is highly individualized[30] and less than 20 g/d of CHO may be needed in some people.[31] In addition, at a given level of CHO intake, protein quantity appears to influence the degree of ketosis because some amino acids are used for gluconeogenesis and stimulate insulin secretion,[4] which may reduce hepatic ketone production.[30] Therefore, current VLCHF/KDs are typically moderate in protein intake (1.2–1.5 g/kg/d).[4,22] Typically, there is little emphasis on the type of fat that replaces CHO in VLCHF/KDs, which may result in a high intake of SFAs and cholesterol. Furthermore, the severe restriction of CHO in a VLCHF/KD limits CHO intake to nonstarchy vegetables[31] and eliminates fiber-rich starchy vegetables, as well as most fruits, legumes, and whole grains,[30] which are foods that have been associated with reduced cardiometabolic risk.[27]

Medically supervised very-low-calorie ketogenic diets for the treatment of obesity

Medically supervised very-low-calorie diets (VLCalDs) have been used for over 40 years for the treatment of obesity (body mass index [BMI] ≥30 kg/m^2 or a BMI of ≥27 kg/m^2 with one or more comorbidities).[23,32,33] The energy level of a VLCalD has been defined as <800 kcal/d[33,34] The macronutrient composition of VLCalDs is typically 0.8–1.5 g protein/kg ideal body weight to induce rapid weight loss and preserve lean body mass (LBM) and 15–30 g fat/d. An important point is that the CHO content in some VLCalDs is 20–50 g/d, which may induce ketosis, but can be as high as 80 g/d[33]; thus, not all VLCalDs are ketogenic[23] (Table 1). The protein-sparing modified fast (PSMF) is a medically supervised VLCalD with 500–800 kcal/d, primarily from protein (1.2–1.5 g/kg ideal body weight). Fat is restricted to only that found in the protein foods allowed on the diet, such as lean meat, fish and seafood, and poultry. CHO is restricted to 20–50 g/d, resulting in ketosis.[23,33,35] VLCalDs or PSMFs should be prescribed only in limited circumstances by trained clinicians. Patients must be medically supervised due to rapid weight loss and possible

health complications, including possible medication adjustments to avoid hypoglycemia and hypotension.[23] Although some medically supervised programs utilize VLCalDs or PSMFs that are very low in CHO, they are not the focus of this scientific statement. Readers interested in the specific details of VLCalDs and PSMFs for adults are encouraged to read relevant articles.[23,32,33,35]

The impact of nutritional ketosis on energy metabolism

Glucose is typically the sole fuel for the human brain because fatty acids (FA) cannot cross the blood-brain barrier. When CHO intake is adequate, insulin promotes lipogenesis and suppresses ketone production; thus, ketone concentration is very low (<0.3 mmol/L) vs glucose (~4 mmol/L).[4] After a few days of severe CHO restriction (<20 g/d), the body's glucose production from gluconeogenesis becomes insufficient and the central nervous system (CNS) requires an additional energy source. During restricted CHO intake, insulin levels decrease and glucagon levels increase, which impact metabolic pathways in the liver resulting in decreased lipogenesis and increased mitochondrial FA oxidation.[30,36] The increased FA oxidation causes overproduction of acetyl-CoA and the production of ketone bodies in the hepatic mitochondria. Acetoacetate is the main ketone body produced and is converted to β-hydroxybutyrate and acetone. Ketosis is typically defined as a blood level of β-hydroxybutyrate ≥0.3 mmol/L.[37,38] Ketone bodies are used as a source of energy for all tissues, especially skeletal and cardiac muscle, after conversion back to acetyl-CoA, which is used in the tricarboxylic acid cycle.[4] Because ketone bodies have a similar binding affinity (a.k.a., Michaelis-Menten [kM] constant) as glucose for transport to the brain, the CNS begins to use ketone bodies for energy at a plasma concentration of ~4 mmol/L. Ketone levels in healthy people do not generally exceed 8 mmol/L because the CNS efficiently uses these molecules for energy in place of glucose.[3,4,39]

In ketogenesis, glucose levels remain within normal levels via gluconeogenesis from glucogenic amino acids and glycerol from hydrolyzed triglycerides (TG). During the first 3 to 4 days of a KD, the main source of glucose is via gluconeogenesis from amino acids. If the circumstances that promote ketogenesis continue, the contribution of amino acids decreases and the amount of glucose derived from glycerol increases.[4] Based on research examining the effects of fasting and very-low-CHO diets, metabolic adaptation to ketosis takes two weeks or longer to achieve a steady-state ketone level.[16,40,41]

The impact of nutritional ketosis on cholesterol metabolism

Low-CHO and very-low-CHO/KDs appear to have variable effects on low-density lipoprotein cholesterol (LDL-C) levels (discussed in a later section) due, in part, to the hepatocellular effects of low insulin levels. A higher CHO intake increases insulin levels, which activates HMG-CoA reductase and increases hepatic cholesterol synthesis.[3,4] A lower CHO intake decreases insulin levels and inhibits HMG-CoA reductase activation and cholesterol synthesis while activating HMG-CoA lyase, an enzyme involved in ketone body production, thus favoring ketogenesis.[30] There are secondary effects on lipoprotein lipase (and co-factors), as well as LDL-receptor and PCSK9 expression affecting very-low-density lipoprotein (VLDL) and LDL clearance and lipoprotein remodeling. The net impact on serum LDL-C levels is thus mediated by complex mechanisms. It has been proposed that, by lowering insulin levels, low-CHO diets may inhibit hepatic cholesterol synthesis.[3,4,30] Unless this is counteracted by other mechanisms, the expected result would be decreased total cholesterol (total-C) and LDL-C,[3,4,30] especially when intakes of SFA and dietary cholesterol are not increased[4] when CHO consumption is lowered. Thus, LDL-C response cannot be predicted in the individual, and should be evaluated in those who choose to follow a low-CHO or very-low-CHO/KD.

Effects of low-CHO and very-low-CHO diets on determinants of energy balance and body weight

CHO-restricted diets have significant effects on factors that influence energy expenditure (EE) and intake. Results from well-controlled studies have shown that substitution of fat for CHO results in a higher EE. Hall et al.[42] examined changes in EE in 17 men with overweight or obesity consuming an isocaloric habitual high-CHO diet (50% TDE CHO, 15% TDE protein, 35% TDE fat) for 4 weeks followed by a VLCHF/KD (5% TDE CHO, 15% TDE protein, 80% TDE fat) for 4 weeks. Participants spent two consecutive days each week in a metabolic chamber to measure changes in EE using the doubly labeled water method during the last two weeks of each dietary phase. During the VLCHF/KD phase, EE was 57 kcal/d higher as measured by the metabolic chamber and 151 kcal/d higher as measured by the doubly labeled water method.

In a randomized controlled trial (RCT), participants who had lost an average of 12% of body weight were randomly assigned to weight maintenance diets varying in dietary CHO, i.e., low (20% TDE), moderate (40% TDE), or high (60% TDE).[43] Protein intake was held constant and energy from fat was substituted for CHO. Total EE measured with doubly labeled water was 91 kcal/d higher with the moderate-CHO group and 209 kcal/d higher in the low-CHO group compared with the high-CHO group, with a linear trend of 52 kcal/d per 10% reduction in dietary CHO.[43]

Although EE appears to be higher with low-CHO diets and very-low-CHO/KDs, the mechanisms contributing to this are incompletely understood. It has been proposed

that changes in catecholamines and thyroid hormone levels influence the EE of individuals following these diets, but associated changes have not been observed in all studies. In the trial by Hall et al.[42] (discussed previously), there was a significant increase in thyroid-stimulating hormone and free thyroxine (T4) levels, significantly decreased free and total tri-iodothyronine levels, and significantly decreased levels of leptin and norepinephrine in the 17 participants during the VLCHF/KD phase of their study.

Results from controlled investigations have suggested a reduced appetite also occurs with CHO restriction, due to various mechanisms, and contributes to weight loss.[4,38,39,44,45] Westman et al.[45] reported that there was a "spontaneous reduction in calorie intake" in studies that examined the effects of low-CHO diets and very-low-CHO/KDs on appetite and satiety, which may be partly mediated through effects of nutritional ketosis on appetite. Participants report less hunger when they are in ketosis, although the mechanisms of action of ketosis on hunger and appetite suppression are not completely understood and evidence suggests both direct and indirect actions of ketone bodies and their oxidation.[3,30,38,39] The degree to which ketosis contributes to appetite reduction, independent of other variables, such as the quantities of CHO and protein consumed and oxidized, is uncertain.[38] Protein appears to provide greater satiety than CHO.[22,30,38,45,46] However, well-controlled studies that matched protein intake found that a ketogenic, high-protein diet suppressed appetite more than a high-protein diet that was not ketogenic, suggesting that circulating ketone levels have an impact, independent of protein intake.[38] Longer-term, well-controlled studies are needed to assess the degree to which appetite suppression occurs with CHO restriction above the threshold for ketosis, which would allow a higher intake of nutrient-dense CHO foods (eg, vegetables, fruits, whole grains, and legumes) that reflect evidence-based cardioprotective dietary patterns.[38]

Low-CHO diets may reduce hunger by influencing circulating levels of hormones that impact hunger and appetite control, including ghrelin, leptin, and cholecystokinin, but study results have been inconsistent.[37–39,43,44,47] Ghrelin and cholecystokinin levels were mildly decreased during ketosis in participants following a low-CHO, VLCalD/KD,[37] whereas ghrelin and leptin were significantly lower in participants assigned to a low-CHO (but non-ketogenic) weight maintenance diet (20% TDE CHO) compared with participants following a moderate-CHO (40% TDE) or high-CHO (60% TDE) weight maintenance diet.[43] Hu et al.[47] found no difference in change in ghrelin levels or self-reported change in appetite between the participants consuming a very-low-CHO diet (<40 g/d) or a low-fat (<30% TDE), high-CHO (~55% TDE) diet over 12 months. These results illustrate the many potential factors that influence EE and appetite during weight loss with low-CHO diets and very-low-CHO/KDs.

Other possible effects of low-CHO and very-low-CHO diets on energy balance and body weight are: 1) diuretic effects of ketosis[48,49] and reduced insulin concentration[50]; 2) increased adipose tissue lipolysis[4,48,51,52]; 3) reduction in resting respiratory quotient, reflecting a higher proportion of fat being oxidized for energy[4,53–55]; and 4) increased metabolic costs of gluconeogenesis and the thermic effect of protein.[4,32,48,56]

Key points

- Low-CHO diets and very-low-CHO/KDs appear to increase EE. The mechanisms contributing to this effect are incompletely understood.
- Changes in catecholamines and thyroid hormone levels may influence the EE of individuals following low-CHO diets and very-low-CHO/KDs.
- Individuals following low-CHO diets and very-low-CHO/KDs in RCTs reported reduced appetite and hunger. The mechanisms that contribute to this are not clear but may include changes in gastrointestinal hormones.

Evidence for the effect of low-CHO and very-low-CHO diets on weight loss

Weight loss in adults with overweight or obesity

Despite favorable effects of low-CHO and very-low-CHO diets on EE and intake, long-term effects on weight loss may not be superior to more conventional strategies. According to the 2013 American Heart Association/American Cardiology/The Obesity Society (AHA/ACC/TOS) Guideline for the Management of Overweight and Obesity in Adults,[34] research has not demonstrated any advantage of a very-low-CHO diet on weight loss at 6 months compared with a calorie-restricted, low-fat diet. More recently, several systematic reviews and meta-analyses of RCTs have examined the effectiveness of low-CHO, high-fat (LCHF) (>30% TDE fat) vs high-CHO, low-fat (HCLF) diets (<30% TDE fat) for weight loss in individuals with overweight or obesity at 3 to 6 months[57] or 1 to 2 years.[57–60] Participants assigned to both LCHF and HCLF diets achieved clinically meaningful weight loss (Table 2, Fig. 1). However, weight loss was significantly greater with LCHF diets vs HCLF diets when the prescribed diets were hypocaloric,[59] when the prescribed *ad libitum* LCHF diets were hypocaloric (even though not required or encouraged),[60] and the study duration was less than 2 years.[58]

Results for patients with prediabetes[63] and T2D[57,64–67] were similar, with no significant difference for weight loss between the low-CHO and HCLF diet groups in long-term studies (Table 2, Fig. 1). Sainsbury et al.[68] found a significant decrease in weight with low-CHO vs HCLF diets at 3 months (weighted mean difference [WMD] −1.08 kg, 95% CI: −1.93, −0.23, n = 12 studies), but no difference at >6 months (WMD −0.14 kg, 95% CI: −0.94, 0.65, n = 9 studies). van Zuuren et al.[69] reported

Table 2 Effect of low-CHO and very-low-CHO diets compared with HCLF diets on weight, lipids, HbA1c, and blood pressures at 1–2 years follow-up reported in meta-analyses

Author	# of RCTs	Weight WMD (95% CI), kg	LDL-C, WMD (95% CI), mg/dL	HDL-C, WMD (95% CI), mg/dL
Meta-analyses of studies of adults with overweight and/or obesity				
Naude et al. 2014[57]	14	−0.48 (−1.44 to 0.49)	2.71 (−0.39 to 6.19)	1.55 (0.39 to 3.09)
Bueno et al. 2013[58]	13	−0.91 (−1.65 to −0.17)	4.64 (1.55 to 7.73)	3.48 (2.32 to 4.64)
Schwingshackl & Hoffmann 2013[59]	32	0.15 (−0.50 to 0.80); −0.59* (−1.04 to −0.15)	3.11 (1.71 to 4.51)	2.35 (1.29 to 3.42)
Mansoor et al. 2016[60]	11	−2.17 (−3.36 to −0.99)	6.19 (0.12 to 12.8)	5.41 (3.48 to 7.35)
Gjuladin-Hellon et al. 2019[61]	5†	NR	1.55 (−1.55 to 4.64)	3.48 (0.77 to 5.80)
Sackner-Bernstein et al. 2016[62]	17	−2.04‡ (−3.15, −0.93)	8.6‡ (3.6 to 13.7)	5.1‡ (3.5 to 6.7)
Meta-analyses of studies of adults with overweight and/or obesity with pre-diabetes and/or type 2 diabetes				
Naude et al. 2014[57]	5	0.91 (−2.08 to 3.89)	3.87 (−2.32 to 10.44)	0.00 (−3.48 to 3.09)
Schwingshackl & Hoffmann 2014[63]	14§	−0.47 (−1.85 to 0.92)	1.55 (−5.41 to 8.89)	1.55 (0.00 to 3.09)
Meng et al. 2017[64]	9	−0.24 (−2.18 to 1.70)	1.55 (−3.09 to 6.19)	2.71 (1.16 to 4.25)
Snorgaard et al. 2017[65]	10	0.20 (−0.97 to 1.36)	−0.39 (−3.87 to 2.71)	NR
Huntriss et al. 2018[66]	5–7‖	0.28 (−1.37 to 1.92)	1.93 (−3.87 to 7.35)	2.32 (1.55 to 3.48)
Korsmo-Haugen et al. 2019[67]	7–10¶	0.14 (−0.29 to 0.57)	1.16 (−3.87 to 6.19)	2.32 (−0.39 to 5.03)
Sainsbury et al. 2018[68]	25	−0.43 (−0.93 to 0.07)	NR	NR
van Zuuren et al. 2018[69]	2–3**	−0.14 (−1.64 to 1.35)	2.32 (−3.09 to 8.12)	4.64 (2.71 to 6.57)

HCLF, high-carbohydrate, low-fat; RCT, randomized control trials; WMD, weight mean difference; 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; NR, not reported.

If all values in the confidence interval are on the same side of zero (either all positive or all negative), the findings are significant.

In this meta-analysis, 14 RCTs were included in the full meta-analysis, but the number of RCTs varied in the analyses involving only participants with T2D: 5 RCTs were included for SBP, 6 RCTs were included for DBP, 7 RCTs were included for LDL-C, 8 RCTs were included for weight, 9 RCTs were included for HDL-C, and 10 RCTs were included for TG and HbA1c.

*For hypocaloric diet comparisons only.

†In the Gjuladin-Hellon et al.[61] meta-analysis, 8 RCTs were included in the full meta-analysis, but only 5 RCTs were included in the 12 mo + meta-analysis for LDL-C, HDL-C, and TG.

‡The decimal places reported reflect those reported in the published article.

§In the Schwingshackl & Hoffmann[63] meta-analysis, the authors included RCTs of high-fat diets (>30% TDE total fat) of which 6 studies were classified as low-CHO and 4 were classified as moderate-CHO.

‖In the Huntriss et al.[66] meta-analysis, 18 RCTs were included in the full meta-analysis, but only 7 RCTs were included in the 12 mo + meta-analysis for HDL-C, TG, HbA1c, SBP, and DBP, 6 RCTs were included for weight, and 5 RCTs were included for LDL-C.

¶In the Korsmo-Haugen et al.[67] meta-analysis, 23 RCTs were included in the full meta-analysis, but the number of RCTs varied in the 12 mo + meta-analyses, which is what is reported in Table 2: 7 RCTs were included for DBP, 8 RCTs were included for SBP, 9 RCTs were included for LDL-C and TG, and 10 were included for weight, HDL-C, and HbA1c.

**In the van Zuuren et al.[69] meta-analysis, 33 RCTs and 3 clinical control trials were included in the full meta-analysis, but the number of RCTs varied in the 12 mo + meta-analyses, which is what is reported in Table 2: 2 RCTs were included for weight, LDL-C, HDL-C, TG, SBP, and DBP, and 3 RCTs were included for HbA1c.

a significantly greater weight loss at 8–16 weeks (WMD −2.04 kg, 95% CI: −3.23, −0.85; P = .0008; n = 4 studies) with low-CHO vs HCLF diets, but no difference at any other time. In addition, Snorgaard et al.[65] reported no difference in BMI and waist circumference in their meta-analysis.

Points to consider regarding the effects of low-CHO and very-low-CHO diets on weight loss

The results from the meta-analyses discussed previously support the view that low- and very-low-CHO diets are not superior for weight loss compared with diets with a higher quantity of CHO and are difficult to maintain in clinical trials of adults with overweight and obesity, with or without prediabetes or diabetes.[57–60,63,65–69] In the studies included in the meta-analyses, mean CHO intake in the low- and very-low-CHO diet groups at the end of follow-up exceeded 50 g/d in all except one study.[70] Mean CHO intake in the remaining studies was between 33–47% TDE by study end.[58–60] Attrition was ∼30% for both the LCHF and HCLF diet groups in some studies.[60]

Gardner et al.[71] found that when individuals are educated to consume foods with high dietary quality for both low-fat and low-CHO diets, weight loss was similar in both groups. Sacks et al.[72] found that satisfaction was similar among study completers assigned to four different hypocaloric diets (n = 645): low-fat, average-protein; low-fat, high-protein; high-fat, average-protein; and high-fat, high-protein. However, there was substantial variation in weight loss achieved with each of the diet conditions with some individuals in each showing well-above-average weight loss, suggesting that personal preference in the selection of a weight loss diet is important and should be considered.

Table 2 (continued)

TG, WMD (95% CI), mg/dL	HbA1c WMD (95% CI), %	SBP, WMD (95% CI), mm/Hg	DBP, WMD (95% CI), mm/Hg
−5.31 (−12.4 to 2.66)	NR	−2.00 (−5.00 to 1.00)	−0.03 (−1.68 to 1.62)
−15.9 (−23.9 to −7.09)	−0.24 (−0.55 to 0.06)	−1.47 (−3.44 to 0.50)	−1.43 (−2.49 to −0.37)
−8.38 (−13.5 to −3.25)	NR	NR	NR
−23.0 (−32.8 to −13.3)	NR	−1.02 (−2.98 to 0.94)	−1.01 (−2.75 to 0.74)
−9.74 (−15.9 to −2.66)	NR	NR	NR
−28.8‡ (−39.1 to −18.5)	NR	−1.7‡ (−3.5 to 0.2)	NR
−7.09 (−43.4 to 23.0)	0.01 (−0.28 to 0.30)	0.31 (−3.1 to 3.72)	0.09 (−1.95 to 2.13)
−15.9 (−21.3 to −11.5)	−0.17 (−0.39 to 0.06)	−1.35 (0.35 to 2.35)	−1.35 (−1.79 to −0.92)
−29.2 (−39.9 to −18.6)	−0.44 (−0.61 to −0.26)	NR	NR
NR	0.04 (−0.04 to 0.13)	NR	NR
−21.3 (−31.0 to −11.5)	−0.28 (−0.53 to −0.02)	−2.74 (−5.27 to −0.20)	−0.99 (−2.24 to 0.25)
−8.86 (−20.4 to 2.66)	0.00 (−0.10 to 0.09)	−1.39 (−3.20 to 0.43)	−0.55 (−2.17 to 1.06)
NR	−0.09 (−0.21 to 0.03)	NR	NR
−16.8 (−28.3 to −4.43)	−0.02 (−0.37 to 0.41)	1.60 (−1.50 to 4.70)	0.88 (−1.25 to 3.02)

Key points

- Short-term (≤6 months) hypocaloric low-CHO and very-low-CHO diets may result in greater weight loss than hypocaloric high-CHO, low-fat (HCLF) diets.
- Longer-term (>6 months) results suggest that low-CHO and very-low-CHO diets may result in weight loss that is equivalent to that of HCLF diets.
- Very-low-CHO diets are difficult to maintain and are not clearly superior for weight loss compared with diets that

Cardiometabolic risk factor	Adults with overweight or obesity	Adults with overweight or obesity and T2D
Weight	↓**	↑↓*
LDL-C	↑**	↑*
HDL-C	↑***	↑**
TG	↓**	↓**
HbA1c	↓*	↑ ⇔ ↓**
SBP	↓*	↑↓**
DBP	↓**	↑↓**

Figure 1 Effects of low-CHO and very-low-CHO diets vs high-CHO, low-fat diets on cardiometabolic risk markers at 1–2 years follow-up.[57–69] LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; T2D, type II diabetes; TG, triglycerides; HbA1c, hemoglobin A1c; SBP, systolic blood pressure; DBP, diastolic blood pressure. *No significant difference between diet groups. **Mixed results on significant difference between diet groups—some meta-analyses found a significant difference between diet groups, while others did not. ***Significant difference between diet groups.

Key recommendations for weight loss in adults with overweight or obesity*	COR	LOE
Because a specific distribution of CHO, protein, and fat has not been shown to be superior for weight loss, it **is reasonable** to counsel patients on achieving a calorie reduction by limiting the intake of multiple energy sources (ie, CHO, fat) vs limiting calories from a single energy source (ie, CHO).[34,57–60,63–69,71,72]	IIa	B-R
A low-CHO diet (50–130 g CHO/d) or very-low-CHO/KD (~20–49 g CHO/d) **is a reasonable option** for some patients for a limited period of time (2–6 months) to induce weight loss.[57,68,69]	IIa	B-R
Because low-CHO diets or very-low-CHO/KDs are difficult to maintain long-term, a more moderate CHO intake (>130–225 g/d) **is reasonable** for longer-term (>6 months) weight loss and maintenance.[57–60,63,65–69]	IIa	B-R

*The NLA grading system adopted the methodology and classification system used in the 2015 ACC/AHA Clinical Practice Guideline Recommendation Classification System[73] (Table 3). All recommendations were graded by the Class of the Recommendation (COR) and by the Levels of the Evidence (LOE) supporting the Recommendation.

allow a higher amount of CHO in adults with overweight and obesity with or without diabetes.
- Long-term participation in any weight loss intervention is difficult, but adherence to the assigned macronutrient distribution (ie, CHO, protein, and fat) is lower with low-CHO and, especially, very-low-CHO diets.
- Personal preference should be considered when selecting a weight loss diet.

Evidence for the effect of low-CHO and very-low-CHO diets, including ketogenic diets, on body composition changes

Body water loss

The initial weight loss that occurs with low-CHO diets and very-low-CHO/KDs is largely attributable to the loss of body water, not fat loss.[30] This body water loss occurs due to at least two major mechanisms, ketonuria-induced natriuresis and glycogen-depletion, although other mechanisms may also play some role.[48,74,75] Renal losses of sodium and water are also promoted by lower average insulin levels during low-CHO diets, because insulin promotes renal reabsorption of sodium.[76] Glycogen depletion to maintain blood glucose levels results in a loss of body water (3 grams of water per 1 gram stored glycogen).[2,30,48,49,75] Gomez-Arbelaez et al.[75] found that the peak amount of water loss (as measured by multifrequency-bioelectrical impedance) coincided with the phase of maximum ketosis in study participants and, as ketosis decreased, body water was recovered.

Lean body mass or fat-free mass and body fat mass

A concern with any weight loss intervention is the potential to decrease LBM while decreasing fat mass as individuals lose weight.[4] VLCalDs and protein-sparing–modified fast interventions were intended to promote rapid weight loss while preserving LBM.[33] Results from RCTs suggest that a higher protein intake has a protective effect for preserving LBM during weight loss. Adam-Perrot et al.[30] reviewed studies that demonstrated when participants consumed a LCHF diet vs a hypocaloric low-fat diet, they achieved equivalent or higher fat mass loss, but also a higher loss of LBM, unless accompanied by higher protein intake. A hypocaloric high-protein, low-fat diet vs an isocaloric HCLF diet resulted in less LBM loss, suggesting a high-protein diet was more effective at preserving LBM.[30,77]

Krieger et al.[78] conducted a meta-regression analysis of RCTs (n = 87) to examine the effects of varying amounts of protein and CHO intake on body composition during energy restriction (minimum of 1000 kcal/d). After controlling for energy intake, diets with <41.4% TDE from CHO (mean intake 79–97 g/d) were associated with 6.56 kg more body mass loss, 1.74 kg more fat-free mass (FFM) loss, and 5.57 kg more fat mass loss at >12 weeks. When protein intake was >1.05 g/kg/d, there was 1.21 kg more FFM retained compared with protein intake ≤1.05 g/kg/d at >12 weeks.[78] Thus, low-CHO diets that have a higher protein content from partially replacing CHO with protein rather than fat alone appear to promote fat mass loss and result in a lower percentage of LBM lost.[79] Other RCTs with small sample sizes found a greater loss of FFM with very-low-CHO/KDs compared with moderate-CHO (35% TDE; 30% TDE protein)[44] or high-CHO (50% TDE; 15% TDE protein)[42] diets.

Key points

- Ketosis is associated with body water loss.

Table 3 2015 ACC/AHA clinical practice guideline recommendation classification system[74]

CLASS (STRENGTH) OF RECOMMENDATION
CLASS I (STRONG) **Benefit >>> Risk**

Suggested phrases for writing recommendations:
• Is recommended
• Is indicated/useful/effective/beneficial
• Should be performed/administrated/other
• Comparative-Effectiveness Phrases:
  ○ Treatment / strategy A is recommended / indicated in preference to treatment B
  ○ Treatment A should be chosen over treatment B

CLASS IIa (MODERATE) **Benefit >> Risk**

Suggested phrases for writing recommendations:
• Is reasonable
• Can be useful/effective/beneficial
• Comparative-Effectiveness Phrases:
  ○ Treatment/strategy A is probably recommended/indicted in preference to treatment B
  ○ It is reasonable to choose treatment A over treatment B

CLASS IIb (WEAK) **Benefit ≥ Risk**
Suggested phrases for writing recommendations: • May/might be reasonable • May/might be considered Usefulness/effectiveness is unknown/unclear/uncertain or not well established
CLASS III: No Benefit (MODERATE) **Benefit = Risk**
Suggested phrases for writing recommendations: • Is not recommended • Is not indicated/useful/effective/beneficial • Should not be performed/administered/other
CLASS III: Harm (STRONG) **Risk > Benefit**
Suggested phrases for writing recommendations: • Potentially harmful • Causes harm • Associated with excess morbidity/mortality • Should not be performed/administered/other

LEVEL (QUALITY) OF EVIDENCE
LEVEL A
• High-quality evidence from more than 1 RCT • Meta-analyses of high-quality RCTs • One or more RCTs corroborated by high-quality registry studies
LEVEL B-R (Randomized)
• Moderate-quality evidence from 1 or more RCTs • Meta-analysis of moderate-quality RCTS
LEVEL B-NR (Nonrandomized)
• Moderate-quality evidence from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies • Meta-analyses of such studies
LEVEL C-LD (Limited Data)
• Randomized or nonrandomized observational or registry studies with limitations of design or execution • Meta-analyses of such studies • Physiological or mechanistic studies in human subjects
LEVEL C-EO (Expert Opinion)
• Consensus of expert opinion based on clinical experience

Modified from the 2015 ACC/AHA Clinical Practice Guideline Recommendation Classification System

- The initial weight loss that occurs with low-CHO diets and very-low-CHO/KDs is primarily due to loss of body water.
- All weight loss interventions using CHO-restriction appear to result in greater loss of lean body mass (LBM) compared with more macronutrient balanced hypocaloric diets.
- Higher protein content in low-CHO diets may result in less LBM loss during weight loss.

Key recommendation for body weight and composition*	COR	LOE
In patients choosing to lose weight using a CHO-restricted diet, it **is reasonable** to recommend a higher protein intake (1.0–1.5 g/kg/d) to preserve LBM during weight loss.[77,78]	IIa	B-R

LBM, lean body mass.

*The NLA grading system adopted the methodology and classification system used in the 2015 ACC/AHA Clinical Practice Guideline Recommendation Classification System[73] (Table 3). All recommendations were graded by the Class of the Recommendation (COR) and by the Levels of the Evidence (LOE) supporting the Recommendation.

Evidence for the effect of low-CHO and very-low-CHO diets on traditional cardiometabolic risk factors

Effects on blood lipids and lipoproteins

Recent systematic reviews and meta-analyses of RCTs of adults with overweight or obesity without diabetes have reported conflicting results on the effects of low-CHO and very-low-CHO diets on total-C and LDL-C[57–62] (Table 2). In a meta-analysis of 14 RCTs that examined the differences in blood lipids between low-CHO and isocaloric balanced diets, there was a trend in the low-CHO diet groups for a higher total-C (WMD 3.09 mg/dL, 95% CI: −0.77, 6.57, n = 12 studies) and LDL-C (WMD 3.48 mg/dL, 95% CI: 0.0, 6.96, n = 12 studies) at 3–6 months follow-up and 1–2 years follow-up (total-C WMD 2.32 mg/dL, 95% CI: −1.16, 6.19, n = 6 studies; LDL-C WMD 2.71 mg/dL, 95% CI: −0.39, 6.19, n = 6 studies).[57]

A meta-analysis of 8 large RCTs (each n > 100) over 6–24 months examined the effects of CHO-restricted diets vs low-fat (LF) diets on LDL-C and other lipid markers in adults with overweight or obesity.[61] The CHO-restricted diets were divided into two subgroups: moderate-CHO (4 trials; 35–40% TDE CHO or 130–225 g/d) and very-low-CHO (4 trials; <10% TDE CHO or <50 g/d). The LF diets were 50–65% TDE CHO and 20–35% TDE fat, except one study (70% TDE CHO, <10% TDE fat). Overall, significantly higher LDL-C (WMD 2.71 mg/dL; 95% CI, 0.77, 5.03; $P = .009$; n = 8 studies) was reported in the pooled analysis of CHO-restricted diets vs LF diets. However, a subgroup analysis based on CHO content reported no significant difference in LDL-C levels between CHO-restricted vs LF diets (for very-low-CHO: 2.71 mg/dL; 95% CI: −1.93, 6.96; $P = .27$, n = 4 studies; for moderate-CHO: 1.93 mg/dL; 95% CI: −0.77, 4.64; $P = .16$, n = 4 studies).[61]

Contrary to the results from these two meta-analyses,[57,61] four other meta-analyses examining the effects of low-CHO diets vs HCLF diets in adults with overweight or obesity found significantly higher LDL-C levels during the CHO-restricted diets.[58–60,62] Systematic reviews and meta-analyses of RCTs examining the effects of low-CHO and very-low-CHO diets on blood lipids in patients with T2D and prediabetes found no significant difference in total-C[57,63–67,80] and LDL-C levels[57,63–67,69,80] between low-CHO and HCLF diets (Table 2, Fig. 1).

None of the meta-analyses discussed previously examined the effect of low-CHO or very-low-CHO diets on VLDL-C, non–high-density lipoprotein cholesterol (non–HDL-C), apolipoprotein B (apoB), or LDL particle number or size in adults with T2D and there is very little evidence from RCTs of adults with overweight or obesity. Gjuladin-Hellon et al.[61] identified only three large (n > 100) RCTs that examined the impact of CHO-restricted diets on VLDL-C,[81] apoB levels,[82] or LDL-C particle size.[83] Although the results of these large RCTs showed improvement in these variables for the CHO-restricted diet groups vs the HCLF diets groups, results were limited by the CHO restriction in the diet interventions ranging from ketogenic to nonketogenic and the intensive lifestyle interventions provided to participants may have affected the results.

Similar to total-C and LDL-C, recent systematic reviews and meta-analyses of RCTs have found varying results on the effects of low-CHO and very-low-CHO diets on TG and HDL-C levels (Table 2, Fig. 1). In their meta-analysis of adults with overweight or obesity (14 RCTs), Naude et al.[57] reported a significant difference for HDL-C at 1–2 years follow-up, but no significant difference for TG between diet groups. Furthermore, both Naude et al.[57] and Korsmo-Haugen et al.[67] reported no significant differences between diet groups for TG and HDL-C levels at 1–2 years follow-up in adults with overweight or obesity and T2D.

Conversely, other meta-analyses reported significant improvements in both TG and HDL-C levels with low-CHO diets vs HCLF diets at 1–2 years follow-up in adults with overweight and obesity[58–62] and prediabetes or T2D.[63,64,66,69] Gjuladin-Hellon et al.[61] reported a significantly greater decrease in TG levels and a significantly greater increase in HDL-C levels with CHO-restricted diets vs LF diets at 6 and 12 months in adults with overweight or obesity, but no significant difference at 24 months, except in the very-low-CHO diet group, which maintained significantly higher HDL-C levels than the other diet groups at 24 months.

Points to consider regarding the effects of low-CHO and very-low-CHO diets on blood lipids and lipoproteins

The conflicting results of the studies examining the effect of low-CHO and very-low-CHO diets on blood lipids

and lipoprotein levels in adults with overweight or obesity with and without T2D may be due to variations in CHO and fat quantity and quality of the diet interventions in the RCTs, and/or differences in adherence to the prescribed diets over the course of the study periods.[57,63,78,80] Participants began with a CHO-restriction that was ketogenic (<20–50 g/d) at study start in very few studies included in the meta-analyses and adherence to the diet was not maintained to the study end, except in the Brinkworth et al.[70] study; thus, at 2-year follow-up, there was little difference between the diets.[57–61,66,67] In one meta-analysis of RCTs of adults with overweight or obesity without T2D, the TDE SFA in the HCLF diets was ~9.3%, whereas the low-CHO and comparison control diets were ~12.5–15% TDE SFA.[59] Thus, the greater SFA in the low-CHO and control diets may have resulted in higher LDL-C levels vs the HCLF diet. The lack of significant difference between the diet groups in RCTs involving adults with T2D or prediabetes may be attributed to similar SFA content between diets,[66] SFA intake did not increase from baseline in the diet groups,[80] or CHO was replaced with unsaturated fatty acids in the low-CHO diets.[67] Taken together, the available data suggest that controlling SFA intake is crucial to prevent significant increases in LDL-C and for achieving improved cardiovascular (CV) health with low-CHO diets. Furthermore, improvements in TG and HDL-C levels were achieved at a CHO intake considered low (<130 g/d) or moderate (130–225 g/d), but not ketogenic, which may promote more successful adherence.[66]

In addition to the points discussed previously, weight loss can impact lipids and lipoproteins and modifications in macronutrients can influence the response to some extent. Negative energy balance and weight loss, regardless of the dietary strategy, tend to improve TG, LDL-C, and HDL-C.[19] A 3 kg weight loss can decrease TG by at least 15 mg/dL, and a 5 to 8 kg weight loss can decrease LDL-C by ~5 mg/dL and increase HDL-C by 2 to 3 mg/dL.[34] The macronutrient content of the dietary strategy used for weight loss can affect LDL-C levels in that a higher intake of unsaturated fatty acids tends to lower LDL-C, whereas a higher intake of SFA, cholesterol, and *trans* fatty acids tends to raise LDL-C. Higher protein intake, particularly from plant proteins such as soy protein, tends to lower LDL-C relative to protein from animal sources. Thus, the effect on LDL-C is variable and likely depends in part on the net impact of the various factors discussed previously. Weight loss with a low-CHO diet that is also low in SFA, cholesterol, and *trans* fatty acids will tend to reduce LDL-C, but LDL-C may increase with a low-CHO diet that is high in SFA, cholesterol, *trans* fatty acids, and animal proteins.[19] In regard to TG levels, reducing dietary CHO will generally lower TG levels with a resultant decrease in VLDL-C, particularly in individuals with elevated TG. The TG-lowering effect will be enhanced by weight loss and negative energy balance. Lowering TG will generally raise HDL-C once weight has stabilized, but HDL-C may go down during weight loss or negative energy balance. Weight stabilization after weight loss also tends to raise HDL-C. The reduction in TG levels due to weight loss, with or without CHO restriction, will also tend to shift toward larger HDL and LDL particles.[19]

Although the results from some studies may not show a significant difference in lipid and lipoprotein parameters between diet groups, there may be individuals who experience extreme effects of low-CHO and VLCHF diets, which may be related to genetic factors and the variable response to substrate availability and neurohormonal reactivity. Two RCTs[84,85] reported considerable variability in LDL-C levels in adults with obesity consuming a VLCHF diet (4% TDE, 61% TDE total fat, 20% TDE SFA)[84] or adults with a normal weight following a very-low-CHO diet (<20 g/d; *ad libitum* with no restriction on fat or protein intake)[85] compared with a HCLF or control diet. The increase in LDL-C ranged between 5–10% in one RCT[84] and 44% (range 5% to 107%) in the other RCT.[85] In their narrative review on nutrigenetics and blood cholesterol levels, Vazquez-Vidal et al. reviewed gene-nutrient interaction studies that examined inter-individual variability in blood cholesterol responses.[86] Some studies have shown significant associations between the *APOE4* allele and an increased LDL-C response to dietary interventions while others found no association indicating the LDL-C response varies based on different types of dietary interventions (ie, amount and type of fat and cholesterol) or specific foods.[86,87] Thus, it is essential to assess the lipid profile of patients who choose to follow low-CHO or very-low-CHO diets and KDs.

Key points

- Results from meta-analyses demonstrate a variable total-C and LDL-C response to low-CHO and very-low-CHO diets.
- A high saturated fatty acid (SFA) content in low-CHO and very-low-CHO diets is a key factor for an increase in LDL-C.
- Compared with high-CHO, low-fat (HCLF) diets, low-CHO diets generally decrease TG levels.
- Compared with HCLF diets, low-CHO diets generally result in a short-term increase in HDL-C levels, which is typically not maintained for longer durations.
- Improvements in TG and HDL-C levels were achieved at low- and moderate-CHO intakes vs very-low-CHO intakes, which may result in better long-term adherence.
- Genetic factors have been shown to play a role in the individual variability of LDL-C levels with low-CHO and very-low-CHO diets.
- Baseline and follow-up lipid/lipoprotein assessments are essential for individuals following low-CHO and very-low-CHO diets to identify extreme responses.

Effects on glucose, hemoglobin A1c, insulin and insulin sensitivity, and hypoglycemic medication use

Systematic reviews and meta-analyses of low-CHO and very-low-CHO diets compared with HCLF diets in RCTs of adults without T2D[57,60] or that included a small number of adults with T2D[58] found no significant difference for fasting blood glucose (FBG), hemoglobin A1c (HbA1c), and insulin levels between diet groups, although there were trends in favor of the low-CHO diets for these endpoints. However, only one RCT[70] included in the meta-analyses reported CHO intake <50 g/d by the end of study.[58,60]

Systematic reviews and meta-analyses of RCTs comparing low-CHO and very-low-CHO diets to HCLF diets in adults with T2D and prediabetes found no significant difference between glucose levels[57,64] or insulin levels.[80] In short-term (≤6 months) studies, HbA1c was significantly lower with low-CHO diets compared with HCLF diets.[63–69,80] At ≥1 year, HbA1c was similar between the low-CHO and HCLF diet groups,[57,63,65,67–69,80] except in two meta-analyses.[64,66] Meng et al.[64] (WMD -0.44%; 95% CI: −0.61, −0.26; $P = .00$; n = 9 studies) and Huntriss et al.[66] (WMD −0.28%; 95% CI: −0.53, −0.02; $P = .03$; n = 7 studies) reported a significantly decreased HbA1c in the low-CHO diet groups at 1 year (Table 2, Fig. 1).

Although there were no significant differences in HbA1c responses between CHO-restricted and HCLF diets in most meta-analyses of RCTs, a greater reduction in the use of diabetes medications was found in low-CHO diet groups compared with HCLF diet groups at the end of study,[64–69] primarily lower insulin dosages,[64,67] suggesting a clinically relevant impact on glycemic control. In 4 of 5 RCTs examining medication changes in one meta-analysis,[69] there was a dose reduction of glucose-lowering medications. In their meta-analysis of 18 RCTs, Huntriss et al.[66] reported a statistically significant reduction in the use of diabetes medications, including reductions in insulin, oral hypoglycemic agents (OHAs), or a combined diabetes medication score in the low-CHO diet groups. Fourteen RCTs included in the Huntriss et al.[66] meta-analysis reported a reduced requirement for diabetes medications in the low-CHO diet group vs control group, of which 9 studies found a statistically significant reduction in insulin (2 RCTs), OHAs (2 RCTs), or a combined diabetes medication score (5 RCTs) in the low-CHO diet groups. Importantly, the average CHO intake in 12 RCTs included in the overall meta-analysis was 106 g/d indicating that reductions in the use of diabetes medications can be achieved at CHO levels considered low, but not ketogenic.[66]

Effects of dietary patterns on lipids and glycemic control in people with type 2 diabetes

Recent network meta-analyses (NMAs) compared the impact of different dietary approaches in clinical trials on glycemic control[88] (primary outcome was HbA1c; n = 56; 4937 participants) and blood lipids[89] (n = 52; 5360 participants) in patients with T2D. Eight dietary approaches with a minimum intervention period of 12 weeks and compared with a control (minimal intervention or no intervention) were included in the NMAs:

- low-CHO (<25% TDE CHO; high intake animal and/or plant protein, often high fat);
- moderate-CHO (25–45% TDE CHO, 10–20% TDE protein);
- high-protein (20% TDE protein from animal and/or plant sources, <35% TDE fat);
- low-fat (<30% TDE fat; high intake of cereals and grains; 10–15% TDE protein);
- low glycemic index (GI)/glycemic load (GL);
- vegetarian (no meat and fish)/vegan (no animal products);
- Mediterranean (rich in fruit, vegetables, olive oil, legumes, cereals, fish, and moderate intake of red wine during meals); and
- Paleolithic[88] (includes lean meat, fish, shellfish, fruits, vegetables, roots, eggs and nuts; excludes grains, dairy products, salt or refined fats and sugar).[90]

All eight dietary approaches significantly reduced HbA1c vs the control diet. Based on the surface under the cumulative ranking curves (SUCRA), the low-CHO diet reduced HbA1c the most (SUCRA = 84%) followed by the Mediterranean diet (SUCRA = 80%), whereas the Mediterranean diet reduced FBG the most (SUCRA = 88%) followed by the Paleolithic (SUCRA = 71%) and vegetarian (SUCRA = 63%) diets. Subgroup analyses found that low-CHO diets reduced HbA1c more than the other diets in smaller and shorter-term (<12 months) studies that included patients <60 years of age. The Mediterranean, moderate-CHO, low GI/GL, high-protein, and low-fat diets reduced HbA1c more in larger and longer-term studies with patients >60 years of age. Furthermore, univariate meta-regression analysis showed that the mean reduction in HbA1c was significantly related to the mean difference in weight change between dietary approaches.[88]

The NMA by Neuenschwander et al.[89] compared the effect of the eight dietary patterns to a control diet on LDL-C, HDL-C, and TG in patients with T2D. The results demonstrated that moderate-CHO and vegan/vegetarian diets were more effective at reducing LDL-C compared with the control diet, and low-CHO, high-protein, and low-fat dietary patterns. The Mediterranean diet was the only dietary pattern that increased HDL-C. The Mediterranean and low-CHO diets significantly reduced TG levels compared with low-fat and control diets. Based on the SUCRA ranking for the combined effect on LDL-C, HDL-C, and TG, the Mediterranean diet (SUCRA: 79%) had the most beneficial effects with Paleolithic (SUCRA: 73%) and low-CHO (SUCRA: 62%) ranking next. The authors cautioned about interpreting the results

for the Paleolithic SUCRA given their NMA included only one study.[89]

Key points

- Low-CHO diets did not reduce FBG or insulin levels more than high-CHO, low-fat (HCLF) diets in clinical trials.
- Low-CHO diets result in a greater short-term (<6 months) reduction in HbA1c vs HCLF diets, but there was less difference between diets beyond 1 year.
- Low-CHO diets resulted in a reduction in the use of diabetes medications, and reductions in the use of diabetes medications were achieved at CHO intake levels that do not induce ketosis.
- The Mediterranean dietary pattern produced improvements in TG, HDL-C, and HbA1c levels in individuals with T2D compared with low-CHO diets.

Effects on blood pressures

Reductions in systolic blood pressure (SBP) (3 mm Hg) and diastolic blood pressure (DBP) (2 mm Hg) typically occur with a 5% weight loss.[34] Systematic reviews and meta-analyses of low-CHO and very-low-CHO diets compared with HCLF diets in RCTs of adults without T2D[57,60,62] or that included a small number of adults with T2D[58] reported conflicting results for the impact on blood pressure. One meta-analysis reported no statistically significant difference in SBP (WMD −1.47 mm Hg; 95% CI: −3.44, 0.50; $P = .14$; n = 11 studies), but found a significant difference in DBP between diet groups (WMD −1.43 mm Hg; 95% CI: −2.49, −0.37; $P = .008$; n = 11 studies).[58] Other meta-analyses did not find a significant difference between diet groups for either SBP or DBP.[57,60,62]

Similarly, systematic reviews and meta-analyses of RCTs comparing low-CHO and very-low-CHO diets to HCLF diets in adults with T2D and prediabetes found conflicting results for the effect on blood pressure (Table 2, Fig. 1). One meta-analysis found a significant difference in SBP between diet groups in favor of low-CHO diets (WMD −2.74 mm Hg; 95% CI: −5.27, −0.20, $P = .03$; n = 7 studies), but no significant difference in DBP,[66] whereas another meta-analysis found a significant decrease in DBP with high-fat diets (WMD −1.35; 95% CI: −1.79, −0.92; $P < .00001$; n = 6 studies), but not SBP.[63] van Zuuren et al.[69] found a significant decrease in DBP (WMD −1.91; 95% CI: −3.63, −0.18; $P = .03$; n = 4 studies) with low-CHO diets at 6 months, but no significant difference between diet groups for SBP or DBP past 6 months. Two other meta-analyses did not find a significant difference between diet groups for either SBP or DBP.[57,67] A critical review[80] of 12 RCTs reported no difference between low-CHO and HCLF diets, except in two studies: one showed a greater reduction in SBP (−3.03 mm Hg, $P = .04$) in the HCLF group[91] and the other showed a greater reduction in DBP in the low-CHO diet group (−2 mm Hg, $P = .020$, diet × time).[92]

Key point

- Low-CHO and very-low-CHO diets produced inconsistent effects on blood pressures in adults with overweight or obesity with and without prediabetes or T2D compared with high-CHO, low-fat diets.

Key recommendations for cardiometabolic risk factors*	COR	LOE
To achieve an improvement in a patient's cardiometabolic risk factor profile, a weight reduction diet that achieves a clinically significant weight loss (5–10% of body weight) **is recommended.**[18,19,34]	I	A
As part of low-CHO and very-low-CHO diets, it **is reasonable** for a patient to choose unsaturated fatty acids over SFAs.[19,59,66,67,80]	IIa	B-R
In patients with overweight or obesity with or without T2D and with elevated TG levels, a low-CHO diet **is reasonable** for lowering TG levels (and VLDL-C) compared to an HCLF diet.[58–64,66,69]	IIa	B-R
Because substantial variation in lipid responses has been observed in patients choosing to follow low-CHO and very-low-CHO diets, baseline and follow-up lipid profiles **are reasonable.**[57–67,69]	IIa	B-R
In patients with T2D, a low-CHO diet **may be reasonable** to achieve an improvement in glycemic control or a reduction in diabetes medications.[64–69]	IIb	B-R
In patients with overweight and obesity with hypertension, weight loss with a low-CHO or very-low-CHO diet **may be reasonable** as a way to lower blood pressure.[58,63,66]	IIb	B-R

HCLF, high-carbohydrate, low-fat; SFA, saturated fatty acids.

*The NLA grading system adopted the methodology and classification system used in the 2015 ACC/AHA Clinical Practice Guideline Recommendation Classification System[73] (Table 3). All recommendations were graded by the Class of the Recommendation (COR) and by the Levels of the Evidence (LOE) supporting the Recommendation.

Evidence for the effect of low-CHO and very-low-CHO diets on emerging risk factors

Effect on C-reactive protein levels

Few systematic reviews or meta-analyses have examined the effect of low-CHO or very-low-CHO diets on systemic inflammation. A meta-analysis identified 4 RCTs that examined the impact on C-reactive protein (CRP) levels and reported no significant differences despite a WMD in favor of very-low-CHO diets.[58] In adults with either prediabetes and/or T2D, CRP was not significantly different between high-fat diet groups (included 6 RCTs that prescribed a low-CHO diet).[63] In one critical review, only one study reported on CRP, which found no significant difference between the diet groups.[80]

Effect on the gut microbiome

There is a theoretical concern about the adverse effects of a marked CHO restriction for low-CHO diets and very-low-CHO/KDs due to the avoidance of CHO-rich foods that provide dietary fiber for the gut microbiome. However, there are no long-term studies; only short-term RCTs have been conducted to date. These studies have reported unfavorable shifts in microflora composition with an energy-restricted VLCHF/KD[93] and with a higher-fat diet.[94] Although potentially unfavorable shifts in gut microbiota have been observed in some studies with low-CHO diets, the clinical relevance of these shifts is currently uncertain.

Effect on trimethylamine N-oxide production

Another emerging concern with low-CHO and very-low-CHO diets is the potential effect on ASCVD risk due to trimethylamine N-oxide (TMAO) production. Many individuals following low-CHO and very-low-CHO diets consume more animal products, which are associated with an increase in TMAO levels.[95,96] High levels of TMAO have been associated with major adverse cardiac events and increased mortality in secondary prevention patients,[97,98] as well as major adverse cardiac events or all-cause mortality.[99]

Until recently, the impact of low-CHO and very-low-CHO diets on TMAO production has been largely unknown. Park et al.[96] reported the effect of three isocaloric diets (LCHF [Atkins] diet, Mediterranean [South Beach] diet, and a very-low-fat, plant-based [Ornish] diet) consumed by healthy, normolipidemic participants (n = 26) for 4 weeks on levels of systemic TMAO levels and its nutrient precursors in a post hoc analysis of plasma samples from an earlier randomized crossover study. Compared with both the baseline and the low-fat diet phase, the LCHF diet phase was associated with higher levels of TMAO.[96] Thus, short-term exposure to a LCHF diet vs a very-low-fat, plant-based diet was associated with increased TMAO levels, whereas the plant-based diet was associated with decreased levels of TMAO.

Key points

- Weight loss lowers CRP. However, current evidence does not support a difference between low-CHO and very-low-CHO diets compared with high-CHO, low-fat diets on the effects on CRP.
- Research suggests unfavorable gut microbiota changes and fecal metabolite shifts associated with low-CHO and very-low-CHO diets; however, the clinical significance of these changes is unknown.
- Short-term exposure to an LCHF diet vs a very-low-fat, plant-based diet was associated with increased TMAO levels; however, the clinical significance of this change is unknown.

Safety concerns associated with low-CHO and very-low-CHO diets, including ketogenic diets

The possible tolerance and safety concerns of low-CHO diets vary depending on the level of CHO restriction and the characteristics of individuals. With VLCHF/KDs, gastrointestinal complaints tend to be the most common adverse effects, including constipation, nausea, and abdominal pain, which are experienced in the first few weeks.[13] Some individuals may experience symptoms described as the "keto flu" within 2 to 4 days of beginning a VLCHF/KD, which may occur as the body adapts to using ketone bodies for fuel, may last a few days to one week, and include lightheadedness, dizziness, fatigue, difficulty exercising, poor sleep, and constipation.[1] Other adverse effects that have been reported in individuals strictly following VLCHF/KDs include headache,[30,45] skin rash,[45] muscle cramps, weakness, diarrhea, dehydration, hypoglycemia,[100] increased levels of blood uric acid, and vitamin/mineral deficiencies.[30] Increased urination can lead to reduced levels of electrolytes, including sodium, magnesium, and potassium, and may be associated with symptoms of hypovolemia, as well as dizziness related to the need to reduce hypertension and/or hyperglycemia medications.[100] Educating individuals to consume protein from whole foods vs supplements will promote an adequate intake of sodium, potassium, and magnesium.[1] Ensuring adequate fluid and electrolyte intake is essential to avoid symptoms of initiating a VLCHF/KD.[13,100] People with certain diseases and disorders may have additional safety concerns to consider with the use of low-CHO diets and VLCHF/KDs.

Caution in patients with lipid disorders and variability with atherogenic lipoprotein response

As discussed previously, there is a high variability in the LDL-C response to low-CHO diets and very-low-CHO/KDs. Gene-nutrient interaction studies demonstrate that genetics contribute to the individual variability of lipid/lipoprotein responses to dietary interventions.[86] Of considerable concern is the use of VLCHF/KDs in patients with hypercholesterolemia, particularly familial hypercholesterolemia (FH). Patients with known hypercholesterolemia and FH may have a genetic predisposition to increased LDL-C levels with

VLCHF/KDs. VLCHF/KDs are typically not congruent with the medical nutrition therapy recommended for these patients, which includes a reduction in SFAs, *trans* fatty acids, and dietary cholesterol.[101–104] Replacing SFAs with unsaturated fatty acids decreases LDL-C and is associated with reduced ASCVD risk.[17,19,20] Due to the unpredictable response of LDL-C to VLCHF/KDs, all patients who choose to follow these diets should have baseline and follow-up lipoprotein lipid profiles assessed.[85]

Some patients with severe hypertriglyceridemia may have genetic or acquired causes of lipoprotein lipase dysfunction or deficiency, with predisposition to hyperchylomicronemia and acute pancreatitis. In these patients, a VLCHF/KD could cause chylomicronemia and precipitate pancreatitis. Patients with hyperchylomicronemia must adhere to a very-low-fat diet (10–15% TDE or <15–20 g fat/d);[105] thus, a VLCHF/KD is contraindicated in these patients until the chylomicronemia is cleared, and then, only under close observation.

Caution in patients with ASCVD, risk of atrial fibrillation, and a history of heart failure, kidney disease, and liver disease

Based on the previous discussion related to the potential increase in LDL-C and inconsistent effects on HbA1c, SBP, and DBP with low-CHO or very-low-CHO diets, close medical supervision is recommended for patients with established ASCVD who choose to use these diets. The 2013 AHA/ACC/TOS Guideline for the Management of Overweight and Obesity in Adults[34] discussed various beneficial effects on CV risk factors with weight loss in adults with overweight or obesity with or without CV risk. However, Jensen et al.[34] stated, "there is insufficient evidence to comment on the cardiovascular risk factor effects of low-carbohydrate diets," and included the recommendation to, "[p]rescribe a calorie-restricted diet, for obese and overweight individuals who would benefit from weight loss, based on the patient's preferences and health status, and preferably refer to a nutrition professional for counseling. A variety of dietary approaches can produce weight loss in overweight and obese adults."

Recently, Zhuang et al.[106] examined the association between CHO intake and the risk of atrial fibrillation (AF) in Atherosclerosis Risk in Communities (ARIC) study participants (n = 13,852) who did not have AF. They found a U-shaped curve between CHO intake and AF with the lowest observed risk associated with a CHO intake of 39–61% TDE and cautioned against the use of low-CHO diets for weight loss due to the increased risk of AF.[106]

Individuals with chronic illnesses may be more susceptible to adverse effects due to the extreme dietary changes that are inherent with low-CHO diets and very-low-CHO/KDs. Because the effects of these diets on patients with chronic illnesses is unknown, it is recommended that patients with heart failure, kidney disease, and liver disease who choose to follow a low-CHO or very-low-CHO/KD should do so under close medical supervision and receive medical nutrition therapy appropriate for their specific diagnosis from a registered dietitian nutritionist (RDN). A VLCHF/KD is contraindicated in patients with a history of pancreatitis and liver failure.[107]

Caution in patients using medications for diabetes, hypertension, and anticoagulation

Patients and clinicians must be aware that individuals with diabetes who choose to follow a very-low-CHO diet or KD are at an increased risk of hypoglycemia because of the effect of the severe CHO restriction on glycemic control and potential need for medication adjustment; thus, individuals following a very-low-CHO diet for T2D management should be medically supervised.[100] OHAs and/or insulin may need to be reduced or discontinued after initiation of a very-low-CHO or KD.[22,45,100,108] Patients should be instructed to monitor their blood glucose levels before taking OHAs or insulin to prevent hypoglycemia.[100] Patients taking sodium-glucose cotransporter 2 (SGLT2) inhibitors should avoid VLCHF/KDs because of an increased risk of SGLT2 inhibitor–associated ketoacidosis.[109,110] Westman et al.[100] recommended discontinuing SGLT2 inhibitors before initiating a very-low-CHO KD because of the risk of normoglycemic ketoacidosis. Murdoch et al.[111] recently published a practical guide for adapting diabetes medication for patients with T2D following low-CHO diets.

A reduction in blood pressure frequently occurs in patients with hypertension who follow low-CHO or very-low CHO diets. Patients should monitor blood pressure at home or in clinic, and antihypertensive medications may need to be tapered or discontinued, especially if symptoms of orthostatic hypotension occur with a low-CHO or very-low-CHO diet.[45,100] Diuretics may need to be tapered or discontinued to prevent dehydration and/or hypotension.[100] In patients with T2D and microalbuminuria, Westman et al.[100] recommended continuing a low dose of a renal-protective antihypertensive medication if a patient does not become hypotensive.

Patients taking a vitamin K antagonist for anticoagulation should be instructed on consistent vitamin K intake and the potential for increased vitamin K intake from nonstarchy and green leafy vegetables. More frequent monitoring of anticoagulation therapy may be required because of the potential change in vitamin K intake and its effect on anticoagulation therapy.[45,100]

Carbohydrate intake and mortality

The evidence related to CHO intake and mortality is from observational studies. Noto et al.[112] conducted a quantitative meta-analysis of cohort studies that examined the association between low-CHO diets and all-cause mortality and CVD incidence. Their meta-analysis of 4 cohort studies (n = 272,216) found an association between adhering to a low-CHO diet (relative risk [RR] 1.31; 95% CI: 1.07, 1.59; P = .007) or low-CHO, high-protein diet (RR 1.30; 95% CI: 1.01, 1.68; P = .04) and a significantly increased risk for all-cause mortality. Meta-analyses examining the association between a low-CHO diet or a low-CHO, high-protein diet and CVD incidence in 7 cohort studies (a total of 469,963 participants) did not find a significant increase

in the risk of CVD incidence.[112] Most recently, Mazidi et al.[113] examined the association between low-CHO diets and overall or cause-specific mortality from NHANES study data (n = 24,825) and found that participants with the lowest CHO intake (<39% TDE) based on 24-hour recall assessment had the highest risk of overall (hazard ratio [HR] 1.32; 95% CI: 1.14, 2.01, $P < .001$), CVD (HR 1.51; 95% CI: 1.19, 1.91, $P < .001$), cerebrovascular (HR 1.50; 95% CI: 1.12, 2.31, $P < .001$), and cancer (HR 1.36; 95% CI: 1.09, 1.83, $P < .001$) mortality. In addition, analysis of pooled data from 9 prospective cohort studies (n = 462,934 participants) found that participants with the lowest CHO intake had the highest risk of overall (RR 1.22; 95% CI: 1.06, 1.39; $P < .001$; n = 8 studies), CVD (RR 1.13; 95% CI: 1.02, 1.24, $P < .001$; n = 6 studies), and cancer mortality (RR 1.08; 95% CI: 1.01, 1.14, $P = .02$; n = 3 studies).[113] Seidelmann et al.[114] examined the association between CHO intake and all-cause mortality in the ARIC study (n = 15,428), as well as a meta-analysis with data from ARIC plus 7 multinational prospective studies (n = 432,179). Their analyses demonstrated that both low (<40% TDE) and high CHO (>70% TDE) intake was associated with a higher risk of mortality (20% and 23%, respectively) with 50–55% TDE CHO associated with the lowest risk of mortality. Results indicated that, when animal-based protein or fat was substituted for CHO, the associated risk of mortality increased by 18% whereas mortality decreased by 18% when CHO was replaced by plant-based protein or fat.[114] The reasons for the association between CHO restriction and increased mortality are not well understood. Possible explanations include a reduced intake of vegetables, fruits, and grains, and an increased intake of animal-based protein, which results in varying levels of dietary bioactive components (ie, free fatty acids, protein, fiber, minerals, vitamins, and phytochemicals) with CHO restriction. Higher CHO intakes may be associated with lower economic status and lower quality CHO foods (ie, refined and higher GI).[113,114] Based on the results of these observational studies, severe CHO restriction for weight loss, if followed, should be limited to short periods (2–6 months) followed by a transition to a healthy dietary pattern for the long-term with adequate intake of fiber-rich CHO foods and inclusion of plant-based proteins and unsaturated fats to ensure nutritional adequacy and promote overall and CV health.

Key points

- Close medical supervision is essential for individuals with ASCVD, risk of atrial fibrillation, or the presence or history of heart failure, kidney disease, or liver disease who choose to follow a very-low-CHO diet or KD.
- VLCHF/KDs are contraindicated in patients with a history of hypertriglyceridemia-associated acute pancreatitis, severe hypertriglyceridemia, or inherited causes of severe hypercholesterolemia.
- Individuals with T2D should receive medical supervision and cardiometabolic monitoring while on very-low-CHO diets or KDs.
- Low-CHO and very-low-CHO diets can lead to hypoglycemia or hypotension and may require adjustment in diabetes or hypertension medications.
- Patients taking SGLT2 inhibitors should avoid very-low-CHO KDs because of an increased risk of SGLT2 inhibitor–associated ketoacidosis.
- More frequent monitoring of vitamin K–dependent anticoagulation therapy may be required with very-low-CHO diets due to the potential change in vitamin K bioavailability and its effect on anticoagulation therapy.

Key recommendations—safety concerns*	COR	LOE
For individuals with ASCVD, risk of atrial fibrillation, the presence or history of heart failure, kidney disease, or liver disease who choose to follow a low-CHO or very-low-CHO diet, **close medical supervision is recommended.**[106,107]	III: Potential Harm	C-EO
Because VLCHF/KDs are **contraindicated** in patients with a history of hypertriglyceridemia-associated acute pancreatitis, severe hypertriglyceridemia, or inherited severe hypercholesterolemia, they are **not recommended** for these patients.[101–105]	III: Potential Harm	C-EO
Because low-CHO diets and very-low-CHO/KDs can increase the risk of hypoglycemia, it **is reasonable** to monitor glycemic control and make adjustments in diabetes medication.[100,108]	III: Potential Harm	B-R
SGLT2 inhibitors **should not be used** in patients choosing to follow very-low-CHO/KDs due to an increased risk of SGLT2 inhibitor–associated ketoacidosis.[100,109,110]	III: Harm	B-NR
More frequent monitoring of vitamin K–dependent anticoagulation therapy **may be reasonable** with a very-low-CHO/KD due to the potential change in vitamin K intake and its effect on anticoagulation therapy.[45,100]	III: Potential Harm	C-EO
Long-term consumption of extreme CHO intakes (low and high) **has been associated with all-cause, CV, and cancer mortality** in the general population.[112–114]	III: Potential Harm	B-NR

*The NLA grading system adopted the methodology and classification system used in the 2015 ACC/AHA Clinical Practice Guideline Recommendation Classification System[73] (Table 3). All recommendations were graded by the Class of the Recommendation (COR) and by the Levels of the Evidence (LOE) supporting the Recommendation.

- Both low- and high-CHO intake has been associated with a higher risk of mortality in the general population; moderate-CHO intake has been associated with the lowest risk of mortality in the general population.

Points for the clinician-patient discussion regarding low-CHO and very-low-CHO diets, including ketogenic diets

Health professionals are a trusted source of nutrition information.[15] In a systematic literature review (9 studies with 9564 subjects) that evaluated the effectiveness of nutrition care provided by primary care physicians, 5 studies reported an observed improvement in nutrition behavior and 7 reported improvements in cardiometabolic risk factors.[115] Health professionals are uniquely positioned to use their expertise to help patients seeking guidance about effective diets for weight loss and cardiometabolic health. Based on current treatment guidelines and recommendations for weight loss, there are a variety of dietary approaches that can produce weight loss in adults with overweight or obesity.[34] The treatment objective is to achieve ideal CV health and, thus, target not only weight loss, but also other health behaviors (nonsmoking, body mass index <25 kg/m^2, physical activity at goal levels, and a dietary pattern that is consistent with current evidence-based recommendations) and ideal health factors (untreated total cholesterol <200 mg/dL, untreated blood pressure $<120/<80$ mm Hg, and FBG <100 mg/dL).[116] A systematic review of the prevalence and outcomes of ideal CV health in both US and other populations reported an inverse association between increasing number of ideal CV health metrics and all-cause and CVD-related mortality risk.[117] Moreover, for each increase in ideal CV health metrics, there is a decreased risk of all-cause and CV mortality by 11% and 19%, respectively.[118] The importance of lifestyle factors was emphasized by a study (n = 55,685) that found a healthy lifestyle was associated with a substantially lower risk of coronary events compared with an unhealthy lifestyle, regardless of the genetic risk for coronary artery disease.[119]

As noted in the ACC/AHA Guideline on the Primary Prevention of CVD,[17] the most important way to prevent ASCVD is to promote a healthy lifestyle throughout the life span. An essential component of this is to meet current food-based dietary recommendations and decrease SFA and *trans* fat, sodium, and added sugars.[17,120] An overall cardioprotective dietary pattern for adults emphasizes the intake of vegetables, fruits, nuts, whole grains, lean vegetable or animal protein, and fish, and minimizes the intake of foods rich in SFA, *trans* fats, and cholesterol, processed meats, refined CHO foods and foods with added sugars, and sweetened beverages.[17–19,120] The dietary recommendations for CVD prevention should be implemented in a way that accommodates cultural, ethnic, or economic influences that shape individual food preferences.[17–20,120]

For adults with overweight and obesity, of the myriad of weight loss diets evaluated, there is no evidence that one is superior or ideal,[121] and counseling and caloric restriction in conjunction with a comprehensive lifestyle intervention are recommended for achieving and maintaining weight loss.[17,34,122] Based on the results of clinical studies, patients with overweight or obesity who receive high-intensity lifestyle interventions, including referral to a nutrition professional (ie, RDN) for multiple nutrition counseling sessions, and participation in $\geq$14 weight loss intervention visits over 6 months with a trained interventionist have improved outcomes compared with those who do not.[34] Guidelines for the treatment of patients with overweight or obesity recommend that a structured lifestyle intervention program with a multidisciplinary team is available to patients and based on the phases of disease prevention (ie, primary, secondary, tertiary).[122] In addition, referral to an RDN, when feasible, for multiple face-to-face visits, can improve results for biomarkers of cardiometabolic risk, including weight loss, lipids, and glycemic control.[123] Information on referral to an RDN and reimbursement is available on the NLA "5-minute Nutrition Tool" tear sheet for providers (www.lipid.org, follow link to "Practice Tools," then "Patient and Clinician Tear Sheets," then "Clinician's Lifestyle Modification Toolbox–Tools for Clinicians").

A comprehensive lifestyle intervention program includes reduced calorie intake, increased physical activity, and behavior change therapy to facilitate weight loss or maintenance of reduced body weight. The behavior change program typically includes regular self-monitoring of weight, food intake, and physical activity.[34,122] Physical activity recommended for weight loss includes increased aerobic activity, such as brisk walking, for $\geq$150 min/wk. To maintain lost weight or minimize weight regain in the long term ($>$1 year), higher levels of physical activity, approximately 200 to 300 min/wk, are recommended.[17,19,34,122,124] As noted by Kahan and Manson,[125] helping patients manage weight loss expectations is important. It may be unrealistic for many patients to achieve a "normal" weight. Nonetheless, a sustained weight loss of 5–10% is often achievable and improves health. Additional weight loss can be pursued over time.

Although a low-CHO diet (initially <20 g/d and transitioning to <30 g/d) can be used in practice with medical supervision, if this is the preferred weight loss strategy chosen by a patient, it is strongly recommended that the patient transition to a healthier dietary pattern that meets current dietary recommendations for ideal cardiometabolic and CV health. As discussed previously, studies have shown that long-term adherence to a very-low-CHO/KD is challenging and, noted by Brouns,[2] over time many individuals appear to shift to higher CHO intakes (130–160 g/d). Professional guidance, preferably from an RDN whenever feasible, increases the likelihood that individuals will transition to a healthy dietary pattern that is sustained and promotes maintenance of a reduced body weight.[17,19,34,108,122]

Important to this NLA Scientific Statement, the 2019 *Nutrition Therapy for Adults with Diabetes or Prediabetes:*

Consensus Report[108] and the American Diabetes Association (ADA) *Lifestyle Management: Standards of Medical Care in Diabetes*[109] reviewed the current evidence for individualized nutrition therapy for adults with prediabetes or diabetes and recognized that there is convincing evidence from several meta-analyses that a reduction in overall CHO intake improves glycemia and cardiometabolic risk factors in persons with T2D. Moreover, for select adults with T2D who do not meet glycemic targets or when reducing antiglycemic medications is a priority, a reduction in CHO intake with a low-CHO[108,109] or very-low-CHO eating plan[108] is considered a viable approach. Although the *Consensus Report*[108] did not include a discussion of RCTs that varied the SFA content of low- and very-low-CHO diets, a study by Tay et al.[126–128] did show a very-low-CHO (14% TDE; <50 g/d), high-unsaturated/low-saturated fat diet (<10% TDE SFA) and high in dietary fiber (25 g/d) vs an HCLF diet (53% TDE CHO; <10% TDE SFA) elicited similar weight loss, LDL-C, and HbA1c reductions. However, the VLCHF (low SFA) diet achieved greater reduction in diabetes medications, better improvements in diurnal blood glucose stability, greater reductions in TGs, and maintenance of HDL-C levels. Thus, if implemented appropriately with lower SFA intake, there are benefits of CHO-restricted diets, principally on glycemic control, but also on other cardiometabolic risk factors, in persons with T2D. It was recognized by the *Consensus Report*[108] and as illustrated in this NLA Scientific Statement that, to date, the evidence for benefits of low-CHO and very-low-CHO diets for diabetes control are based largely on short-term studies; hence, further research (especially longer term) is needed on low-CHO diets that meet all of the nutrition recommendations of the *Consensus Report*[108] and ADA *Lifestyle Management Standards*,[109] including adequate dietary fiber (14 g/1000 calories) and <2300 mg/d sodium. Weight loss is recommended, if indicated, and an eating pattern should be individualized to achieve long-term adherence. Despite emerging benefits for lower CHO diets on glycemic control in persons with diabetes, if these diets are implemented in clinical settings, they require close medical supervision.

In summary, because a healthy body weight is a key metric for CV health, weight loss in adults with overweight or obesity improves cardiometabolic risk factors.[129] Thus, an energy-reduced diet that meets all dietary recommendations for heart health will promote healthy weight loss and improve CV health. To promote long-term maintenance of a reduced body weight and decreased ASCVD risk, a healthy dietary pattern coupled with behavior change strategies and increased physical activity are essential.

Key points

- There should be a clinician-patient discussion regarding need for and oversight of low-CHO diets or very-low-CHO/KDs before initiation.
- Low-CHO and very-low-CHO diets may be an option for a short-term initial weight loss period (2–6 months).
- For long-term weight maintenance and CV health, it is recommended to gradually increase CHO intake. An emphasis should be placed on CHO foods associated with reduced cardiometabolic risk, including vegetables, fruits, whole grains, and legumes.
- A comprehensive lifestyle intervention program includes reduced calorie intake, increased physical activity, and behavior change therapy to facilitate weight loss or maintenance of reduced body weight.

Key recommendations for long-term weight loss and maintenance*	COR	LOE
Referral to a comprehensive lifestyle intervention program with a multidisciplinary team (which may include physicians, advanced practice nurses, physician assistants, registered dietitian nutritionists, exercise specialists, and psychologists) **is reasonable** as a way to facilitate weight loss or maintenance of reduced body weight.[17,34,122]	IIa	B-NR
Addressing behavioral, family, cultural, and social dynamics and accommodating ethnic or economic influences that shape individual food preferences and physical activity habits **can be useful** to promote long-term success as part of comprehensive lifestyle intervention programs.[17,34,122]	IIa	B-R
A moderate-CHO intake (>130–225 g/d) with an emphasis on including foods known to be associated with improved cardiometabolic health **may be a reasonable** long-term strategy to manage weight and promote health in general.[19,122]	IIb	B-R
It **is recommended** that all patients receive counseling on reducing sedentary activity and increasing physical activity, including both aerobic physical activity, such as brisk walking, for ≥150 min/wk, and strength/resistance activities.[17–19,122,124]	I	A
To maintain long-term (>1 y) weight loss or minimize weight regain, it **is reasonable** to counsel patients on engaging in higher levels of physical activity of approximately 200 to 300 min/wk[17,19,122,124]	IIa	B-R

*The NLA grading system adopted the methodology and classification system used in the 2015 ACC/AHA Clinical Practice Guideline Recommendation Classification System[73] (Table 3). All recommendations were graded by the Class of the Recommendation (COR) and by the Levels of the Evidence (LOE) supporting the Recommendation.

Gaps in the evidence

Based on the review of the evidence for this NLA Scientific Statement, there are gaps in the knowledge base about the long-term effects of low-CHO and very-low-CHO diets, including KDs, on cardiometabolic health, ASCVD risk, and overall health and mortality. Future research is needed to determine:

- the factors that influence EE and appetite with low-CHO diets and very-low-CHO diets, including KDs;
- the effects of different levels of CHO intake on cardiometabolic indices and disease outcomes with well-designed RCTs of longer duration that compare a range of diets, ideally including a very-low-CHO/KD and low-CHO, moderate-CHO, and high-CHO diets, where strong efforts are made to promote adherence with the CHO intake goal through end of study;
- whether a possible threshold exists where CHO intake does not have to be severely restricted and still achieve benefit as suggested by Gibson et al.,[38] thus, whether a moderate-CHO and moderate-fat diet can achieve similar benefits as a very-low-CHO/KD through improved long-term adherence and inclusion of foods associated with more favorable cardiometabolic outcomes; and
- the long-term effects of following a low-CHO diet or very-low-CHO/KD on body weight changes and maintenance of weight loss; the microbiome, TMAO production, and other inflammatory markers associated with higher ASCVD risk; and finally, atherosclerosis and ASCVD risk, as well as other chronic illness (eg, cancer).

Conclusion/summary statement

As discussed in this NLA Scientific Statement, low-CHO diets and very-low-CHO/KDs are increasing in popularity. Results from meta-analyses and guidelines from professional organizations suggest that there is not one macronutrient distribution that is superior for weight loss or for the management of T2D. Evidence suggests that there is a physiological basis for potential metabolic benefits of CHO-restriction compared with dietary strategies with a higher CHO content in some individuals. Results from meta-analyses indicate that low-CHO and very-low-CHO diets may elicit improvements in TG and HDL-C levels, glycemic control, and reductions in diabetes medications, but have variable effects on LDL-C levels; however, by approximately 2 years, there are no differences for most cardiometabolic risk markers. Moreover, three separate observational studies, including a large prospective cohort study with long-term follow-up, have shown that a very-low-CHO intake is associated with increased all-cause mortality. Evidence also demonstrates that adherence to the severe CHO restriction of very-low-CHO diets is challenging and has the potential to cause adverse side effects. In addition, VLCHF diets challenge the nutrition recommendations of various professional organizations, severely restrict or eliminate foods associated with cardioprotective benefits, and encourage a high intake of foods known to increase ASCVD risk (eg, processed meats, foods rich in SFAs). Long-term studies on the potential impact of ASCVD outcomes are lacking.

The decision about whether a patient should consider following a low-CHO or very-low-CHO diet should be made after a clinician-patient discussion about the risks and benefits of these diets and consideration of patient preference. If a very-low-CHO diet is adopted, individuals with overweight or obesity without T2D should, ideally, receive medical supervision, baseline and regular assessment of lipid/lipoproteins, and, when feasible, multiple sessions with an RDN to facilitate dietary adherence with personalized nutrition counseling and behavior modification, as well as replacement of CHO with unsaturated fatty acids and avoidance of excessive intakes of SFA and cholesterol. Individuals following low-CHO or very-low-CHO diets for T2D management should receive medical supervision for adjustment of diabetes and hypertension medications as needed. In addition, referral to a behavioral change support team, including an RDN, when feasible, is recommended to facilitate dietary adherence along with personalized nutrition counseling and behavior modification. Patients taking SGLT2 inhibitors should avoid very-low-CHO/KDs because of an increased risk of SGLT2 inhibitor–associated ketoacidosis. Clinician oversight is essential for patients with chronic medical conditions who want to follow low-CHO or very-low-CHO diets, including those with ASCVD, heart failure, T2D, kidney disease, and liver disease. Some patients should not follow a VLCHF diet because of the presence or history of hypertriglyceridemia-associated acute pancreatitis, severe hypertriglyceridemia (ie, propensity for hyperchylomicronemia), or inherited severe hypercholesterolemia.

Referral to a comprehensive lifestyle intervention for weight loss can increase the likelihood of weight loss success and long-term weight management. Referral to an RDN, when feasible, for medical nutrition therapy and lifestyle counseling can improve cardiometabolic risk and encourage the consumption of vegetables, fruits, nuts, seeds, legumes, and whole grains within the context of a CHO-restricted diet. Achieving a healthy body weight and long-term weight maintenance using a cardioprotective dietary pattern and increased physical activity can promote overall health and decrease the risk of ASCVD.

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Conflict of interest

The authors have no conflicts of interest to disclose.

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Appendix

Process of the development of the scientific statement

This scientific statement was developed after the NLA Scientific Statements Committee and the NLA Board of Directors approved a proposal for its development to address the recent popularity of using low-carbohydrate and very-low-carbohydrate diets, including ketogenic diets, for the management of cardiometabolic risk factors and type 2 diabetes. Many authors/researchers have completed high-quality reviews and meta-analyses evaluating low-carbohydrate and very-low-carbohydrate diets, including ketogenic diets; thus, this scientific statement was not meant to be a systematic review and meta-analysis. Rather, this scientific statement was meant to provide a balanced review of the current scientific evidence regarding the potential benefits, risks, and evidence gaps regarding low-carbohydrate and very-low-carbohydrate diets, including ketogenic diets. To that end, at the request of the NLA Executive Committee and Scientific Statements Committee, the NLA Nutrition and Lifestyle Workgroup selected a multidisciplinary team to serve on the NLA Nutrition and Lifestyle Task Force—a writing team and a reviewing/editing team—to develop this scientific statement. The writing team was four registered dietitian nutritionists (RDNs) (CFK, JPB, PMKE, GS), and the reviewing/editing team was three physicians (KEA, DES, KEW) and a clinical nutrition scientist/epidemiologist (KCM).

The Task Force members developed an initial outline for the content of the scientific statement that was approved by the NLA Board of Directors. On approval of the outline, the RDN writing team determined writing assignments based on expertise and conducted the primary research and compilation of evidence on the effects of low-carbohydrate and very-low-carbohydrate diets, including ketogenic diets, on cardiometabolic risk factors. The writing team focused the review of evidence mainly on published systematic reviews and meta-analyses of randomized controlled trials (RCTs). For topics where reviews and meta-analyses were not available, the writing team considered basic research and individual RCTs. Both the writing team and reviewing/editing team were responsible for editing and revision of the scientific statement. The Task Force team graded the key recommendations of this scientific statement using the American College of Cardiology/American Heart Association Evidence-Based Grading System (Table 3).[73] In rating the class (or strength) of the key recommendations, consideration was given to the ''net benefit'' after taking into account potential benefits and risks or harms associated with the dietary interventions examined in the evidence. For rating the level (or quality) of the evidence, consideration was given to obtaining the highest quality evidence to support the key recommendations, such as that from meta-analyses.

The chair of the NLA Scientific Statements Committee reviewed the scientific statement, which was then submitted to the NLA Board of Directors for review and approval by majority vote. This scientific statement presents a high-level discussion of the current evidence and key recommendations to provide guidance to clinicians regarding the use of low-carbohydrate and very-low-carbohydrate diets, including ketogenic diets, for the management of cardiometabolic risk factors.