Low-Carbohydrate and Very-Low-Carbohydrate (including Ketogenic) Diets – NLA Scientific Statement

Carol Kirkpatrick, PhD, MPH, RDN, CLS, FNLA

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 Taskforce

Disclosures/Conflicts of Interest

- None to disclose

Content of the Scientific Statement

- Describe carbohydrate (CHO)-restricted diets, including ketogenic diets (KDs)
- Nutritional ketosis and energy and lipid metabolism
- CHO-restricted diets and energy balance and body weight
- Evidence for effects – weight loss, body composition, and cardiometabolic risk factors
- Safety concerns and adverse effects
- Points for the clinician-patient discussion
- Key recommendations

ACC/AHA Recommendation System: Applying Class of Recommendation and Level of Evidence to Clinical Strategies, Interventions, Treatments, or Diagnostic Testing in Patient Care (Updated August 2015)

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

*Modified from the 2016 ACC/AHA Clinical Practice Guideline Recommendation Classification System

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 2016 ACC/AHA Clinical Practice Guideline Recommendation Classification System

Halperin JL, Levine GN, Al-Khatib SM, et al. Further evolution of the ACC/AHA clinical practice guideline recommendation classification system: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol.* 2016 Apr 5;67(13):1572-1574. doi: 10.1016/j.jacc.2015.09.001.

Content of the Scientific Statement

- **Describe CHO-restricted diets, including KDs**
- Nutritional ketosis and energy and lipid metabolism
- CHO-restricted diets and energy balance and body weight
- Evidence for effects – weight loss, body composition, and cardiometabolic risk factors
- Safety concerns and adverse effects
- Points for the clinician-patient discussion

Table 1. Diet classification based on amount of total daily energy (TDE) and grams/day from CHO

Diet Description	Ketogenic	Calories/Day	CHO % TDE	Protein % TDE	Fat % TDE
VLCHF/KD	Yes	>1,000	<10* (<20-50 g/day)	~10% TDE (1.2-1.5 g/kg)	70-80% TDE
Low-CHO	No	>1,000	10-25** (38-97 g/day)	10-30% TDE	25-45% TDE
Moderate-CHO	No	>1,000	26-44** (98-168 g/day)	10-30% TDE	25-35% TDE
High-CHO	No	>1,000	45-65** (169-244 g/day)	10-30% TDE	25-35% TDE
Very-high-CHO	No	>1,000	>65** (>244 g/day)	10-30% TDE	25-35% TDE
VLCalD†	Varies	<800	Varies	Varies	Varies
Classic KD	Yes	Varies	3	7	90

*Typically the amount of CHO required to induce ketosis in most people (Feinman et al. Nutrition. 2015 Jan;31(1):1-13. doi: 10.1016/j.nut.2014.06.011).

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

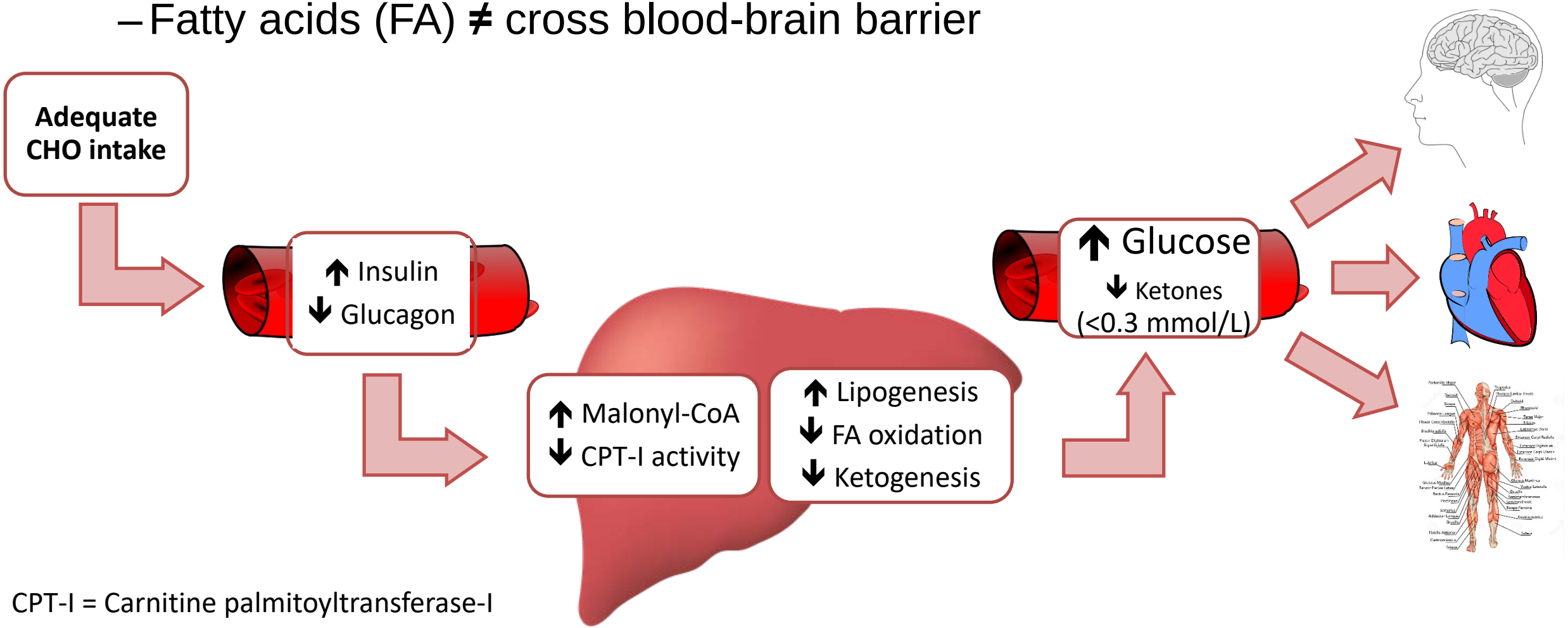
†VLCalDs vary in macronutrient composition – some may be ketogenic if CHO content is low enough; others may not be if CHO content is >50 gm/day.

Content of the Scientific Statement

- Describe CHO-restricted diets, including KDs
- **Nutritional ketosis and energy and lipid metabolism**
- CHO-restricted diets and energy balance and body weight
- Evidence for effects – weight loss, body composition, and cardiometabolic risk factors
- Safety concerns and adverse effects
- Points for the clinician-patient discussion

Impact of Nutritional Ketosis on Energy Metabolism

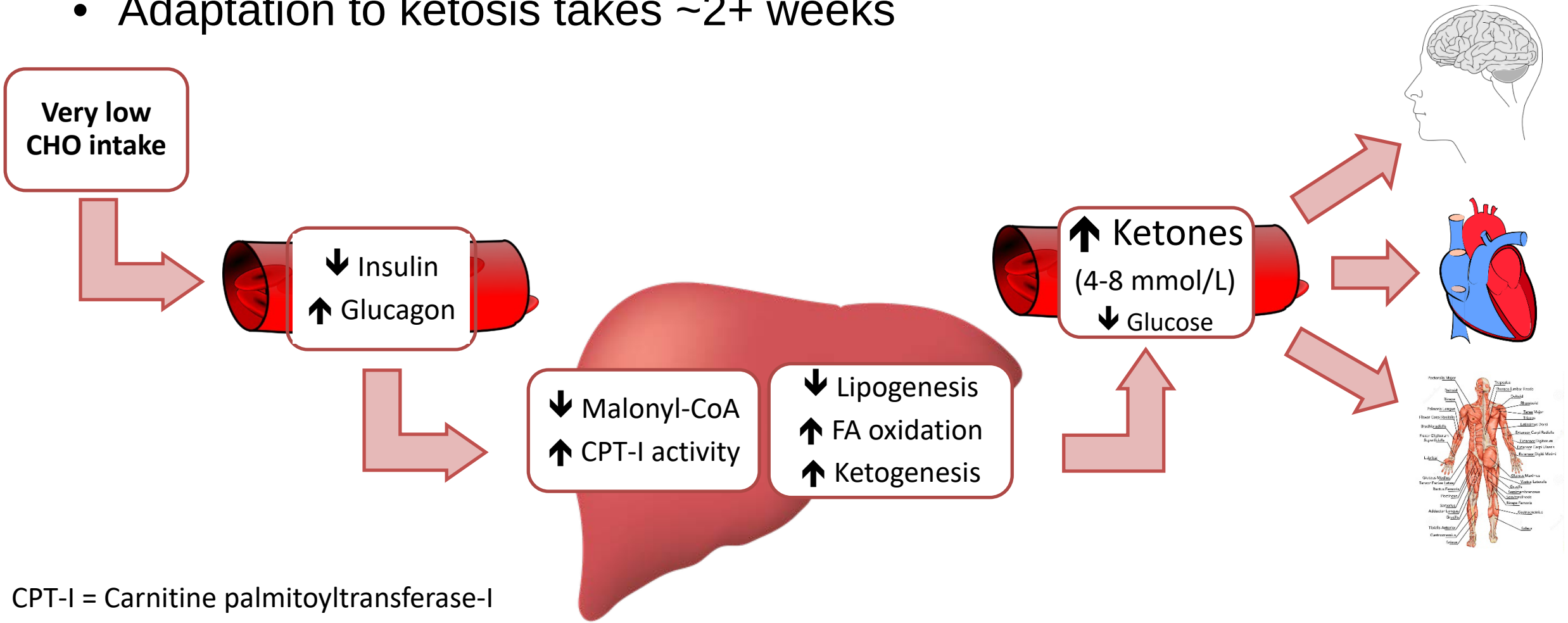
- Glucose preferred energy for central nervous system (CNS)
  - Fatty acids (FA) ≠ cross blood-brain barrier



CPT-I = Carnitine palmitoyltransferase-I

Impact of Nutritional Ketosis on Energy Metabolism

- When glucose ↓, ketones become energy for CNS (at ~4 mmol/L)
- Adaptation to ketosis takes ~2+ weeks



CPT-I = Carnitine palmitoyltransferase-I

Impact of Nutritional Ketosis on Cholesterol Metabolism

- Low-CHO and very-low-CHO/KDs – **variable LDL-C response**
  - Mediated by complex mechanisms
- ↑insulin level – **activates** HMG-CoA reductase
- ↓insulin level – **inhibits** HMG-CoA reductase and **activates** HMG-CoA lyase
- **Theory** – lower CHO diets ↓insulin and ↓cholesterol synthesis
  - **With low saturated fatty acid (SFA) and dietary cholesterol intake**
- **LDL-C levels should be evaluated**

Content of the Scientific Statement

- Describe CHO-restricted diets, including KDs
- Nutritional ketosis and energy and lipid metabolism
- **CHO-restricted diets and energy balance and body weight**
- Evidence for effects – weight loss, body composition, and cardiometabolic risk factors
- Safety concerns and adverse effects
- Points for the clinician-patient discussion

Effects of CHO-restricted Diets on Energy Balance and Body Weight

- RCTs – substitution of **fat for CHO results in ↑ energy expenditure**
  - ? mechanisms
  - ? changes in catecholamines and thyroid hormone levels
- RCTs – **↓ appetite and hunger** reported
  - ? mechanisms
  - ? protein content, changes in gut hormones
- Other
  - Diuretic effects (ketosis and ↓ insulin)
  - ↑ adipose tissue lipolysis
  - ↑ fat oxidation
  - ↑ metabolic costs (gluconeogenesis)
  - Thermic effect of protein

Content of the Scientific Statement

- Describe CHO-restricted diets, including KDs
- Nutritional ketosis and energy and lipid metabolism
- CHO-restricted diets and energy balance and body weight
- **Evidence for effects – weight loss,** body composition, and cardiometabolic risk factors
- Safety concerns and adverse effects
- Points for the clinician-patient discussion

Weight Loss

Author	# of RCTs	Weight (kg) WMD (95% CI)
Naude et al. 2014[57]	14	-0.48 (-1.44 to 0.49)
Bueno et al. 2013[58]	13	**-0.91** (-1.65 to -0.17)
Schwingshackl & Hoffmann 2013[59]	32	0.15 (-0.50 to 0.80); **-0.59*** (-1.04 to -0.15)
Mansoor et al. 2016[60]	11	**-2.17** (-3.36 to -0.99)
Gjuladin-Hellon et al. 2019[78]	5	NR
Sackner-Bernstein et al. 2016[79]	17	**-2.04** (-3.15, -0.93)

Meta-analyses of studies of adults with overweight and/or obesity

*Hypocaloric diet comparisons only

Author	# of RCTs	Weight (kg) WMD (95% CI)
Naude et al. 2014[57]	5	0.91 (-2.08 to 3.89)
Schwingshackl & Hoffmann 2014[61]	14	-0.11 (-1.14 to 0.91)
Meng et al. 2017[62]	9	-0.24 (-2.18 to 1.70)
Snorgaard et al. 2017[63]	10	0.20 (-0.97 to 1.36)
Huntriss et al. 2018[64]	5-7	0.28 (-1.37 to 1.92)
Korsmo-Haugen et al. 2019[65]	7-10	0.14 (-0.29 to 0.57)
Sainsbury et al. 2018[66]	25	-0.43 (-0.93 to 0.07)
van Zuuren et al. 2018[67]	2-3	-0.14 (-1.64 to 1.35)

Meta-analyses of studies of adults with overweight and/or obesity with pre-diabetes and/or type 2 diabetes

Key Points for Evidence for the Effect on Weight Loss

- **Short-term (≤6 months)** hypocaloric low-CHO/very-low-CHO diets **may** >> weight loss vs. hypocaloric high-CHO, low-fat (HCLF diets)
- **Longer-term (>6 months)** – low-CHO/very-low-CHO diets **weight loss equal** to HCLF diets
- Very-low-CHO diets **difficult to maintain**; **not clearly superior** for weight loss in adults with overweight and obesity w/ or w/o T2D
- **Particularly low adherence** to low-CHO and, especially, very-low-CHO diets
- **Personal preference** should be considered when selecting a weight loss diet

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** (i.e., CHO, fat) versus limiting calories from a single energy source (i.e., CHO).	IIa	B-R
A low-CHO diet (50-130 g CHO/day) or very-low-CHO/KD (~20-49 g CHO/day) **is a reasonable option for some patients for a limited period of time (2-6 months) to induce weight loss**.	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/day) is reasonable for longer-term (>6 months) weight loss and maintenance**.	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.

Content of the Scientific Statement

- Describe CHO-restricted diets, including KDs
- Nutritional ketosis and energy and lipid metabolism
- CHO-restricted diets and energy balance and body weight
- **Evidence for effects –** weight loss, **body composition,** and cardiometabolic risk factors
- Safety concerns and adverse effects
- Points for the clinician-patient discussion

Key Points for Evidence for the Effect on Body Composition

- **Ketosis** is associated with **body water loss**
- **Initial weight loss** with low-CHO/very-low-CHO/KDs is **primarily water loss**
- **CHO-restricted diets result in greater loss of lean body mass** (LBM) vs. 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/day) to preserve LBM during weight loss**.	IIa	B-R

Abbreviations: 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.

Content of the Scientific Statement

- Describe CHO-restricted diets, including KDs
- Nutritional ketosis and energy and lipid metabolism
- CHO-restricted diets and energy balance and body weight
- **Evidence for effects –** weight loss, body composition, and **cardiometabolic risk factors**
- Safety concerns and adverse effects
- Points for the clinician-patient discussion

LDL-C

Author	# of RCTs	LDL-C (mg/dL) WMD (95% CI)
Naude et al. 2014[57]	14	2.71 (-0.39 to 6.19)
Bueno et al. 2013[58]	13	**4.64** (1.55 to 7.73)
Schwingshackl & Hoffmann 2013[59]	32	**3.11** (1.71 to 4.51)
Mansoor et al. 2016[60]	11	**6.19** (0.12 to 12.8)
Gjuladin-Hellon et al. 2019[78]	5	1.55 (-1.55 to 4.64)
Sackner-Bernstein et al. 2016[79]	17	**8.6** (3.6 to 13.7)

Meta-analyses of studies of adults with overweight and/or obesity

Author	# of RCTs	LDL-C (mg/dL) WMD (95% CI)
Naude et al. 2014[57]	5	3.87 (-2.32 to 10.44)
Schwingshackl & Hoffmann 2014[61]	14	1.93 (-3.87 to 7.73)
Meng et al. 2017[62]	9	1.55 (-3.09 to 6.19)
Snorgaard et al. 2017[63]	10	-0.39 (-3.87 to 2.71)
Huntriss et al. 2018[64]	5-7	1.93 (-3.87 to 7.35)
Korsmo-Haugen et al. 2019[65]	7-10	1.16 (-3.87 to 6.19)
Sainsbury et al. 2018[66]	25	NR
van Zuuren et al. 2018[67]	2-3	2.32 (-3.09 to 8.12)

Meta-analyses of studies of adults with overweight and/or obesity with pre-diabetes and/or type 2 diabetes

HDL-C

Author	# of RCTs	HDL-C (mg/dL) WMD (95% CI)
Naude et al. 2014[57]	14	**1.55** (0.39 to 3.09)
Bueno et al. 2013[58]	13	**3.48** (2.32 to 4.64)
Schwingshackl & Hoffmann 2013[59]	32	**2.35** (1.29 to 3.42)
Mansoor et al. 2016[60]	11	**5.41** (3.48 to 7.35)
Gjuladin-Hellon et al. 2019[78]	5	**3.48** (0.77 to 5.80)
Sackner-Bernstein et al. 2016[79]	17	**5.1** (3.5 to 6.7)

Meta-analyses of studies of adults with overweight and/or obesity

Author	# of RCTs	HDL-C (mg/dL) WMD (95% CI)
Naude et al. 2014[57]	5	0.00 (-3.48 to 3.09)
Schwingshackl & Hoffmann 2014[61]	14	**1.93** (0.39 to 3.09)
Meng et al. 2017[62]	9	**2.71** (1.16 to 4.25)
Snorgaard et al. 2017[63]	10	NR
Huntriss et al. 2018[64]	5-7	**2.32** (1.55 to 3.48)
Korsmo-Haugen et al. 2019[65]	7-10	2.32 (-0.39 to 5.03)
Sainsbury et al. 2018[66]	25	NR
van Zuuren et al. 2018[67]	2-3	**4.64** (2.71 to 6.57)

Meta-analyses of studies of adults with overweight and/or obesity with pre-diabetes and/or type 2 diabetes

Triglycerides

Author	# of RCTs	TG (mg/dL) WMD (95% CI)
Naude et al. 2014[57]	14	-5.31 (-12.4 to 2.66)
Bueno et al. 2013[58]	13	**-15.9** (-23.9 to -7.09)
Schwingshackl & Hoffmann 2013[59]	32	**-8.38** (-13.5 to -3.25)
Mansoor et al. 2016[60]	11	**-23.0** (-32.8 to -13.3)
Gjuladin-Hellon et al. 2019[78]	5	**-9.74** (-15.9 to -2.66)
Sackner-Bernstein et al. 2016[79]	17	**-28.8** (-39.1 to -18.5)

Meta-analyses of studies of adults with overweight and/or obesity

Author	# of RCTs	TG (mg/dL) WMD (95% CI)
Naude et al. 2014[57]	5	-7.09 (-43.4 to 23.0)
Schwingshackl & Hoffmann 2014[61]	14	**-16.8** (-20.3 to -12.4)
Meng et al. 2017[62]	9	**-29.2** (-39.9 to -18.6)
Snorgaard et al. 2017[63]	10	NR
Huntriss et al. 2018[64]	5-7	**-21.3** (-31.0 to -11.5)
Korsmo-Haugen et al. 2019[65]	7-10	-8.86 (-20.4 to 2.66)
Sainsbury et al. 2018[66]	25	NR
van Zuuren et al. 2018[67]	2-3	**-16.8** (-28.3 to -4.43)

Meta-analyses of studies of adults with overweight and/or obesity with pre-diabetes and/or type 2 diabetes

Key Points for Evidence for the Effects on Blood Lipids/Lipoproteins

- Meta-analyses results: **variable total-C and LDL-C response** to low-CHO and very-low-CHO diets
- A **high SFA content key factor** for ↑ LDL-C
- **Genetic factors play a role** in the individual variability of LDL-C levels (e.g., apoE)
- **Baseline and follow-up lipid/lipoprotein assessment** are essential to identify extreme responses

Key Points for Evidence for the Effects on Blood Lipids/Lipoproteins

- Compared to HCLF diets, low-CHO diets
  - **Generally ↓ TG** levels
  - **Generally ↑ HDL-C** levels (short-term)
- **Improved TG and HDL-C** levels achieved at **low- and moderate-CHO intakes** vs. very-low-CHO
  - May improve long-term adherence

HbA1c

Author	# of RCTs	HbA1c (%) WMD (95% CI)
Naude et al. 2014[57]	14	NR
Bueno et al. 2013[58]	13	-0.24 (-0.55 to 0.06)
Schwingshackl & Hoffmann 2013[59]	32	NR
Mansoor et al. 2016[60]	11	NR
Gjuladin-Hellon et al. 2019[78]	5	NR
Sackner-Bernstein et al. 2016[79]	17	NR

Meta-analyses of studies of adults with overweight and/or obesity

Author	# of RCTs	HbA1c (%) WMD (95% CI)
Naude et al. 2014[57]	5	0.01 (-0.28 to 0.30)
Schwingshackl & Hoffmann 2014[61]	14	-0.17 (-0.39 to 0.06)
Meng et al. 2017[62]	9	**-0.44** (-0.61 to -0.26)
Snorgaard et al. 2017[63]	10	0.04 (-0.04 to 0.13)
Huntriss et al. 2018[64]	5-7	**-0.28** (-0.53 to -0.02)
Korsmo-Haugen et al. 2019[65]	7-10	0.00 (-0.10 to 0.09)
Sainsbury et al. 2018[66]	25	-0.09 (-0.21 to 0.03)
van Zuuren et al. 2018[67]	2-3	-0.02 (-0.37 to 0.41)

Meta-analyses of studies of adults with overweight and/or obesity with pre-diabetes and/or type 2 diabetes

Key Points for the Effects on Glucose, HbA1C, Insulin and Insulin Sensitivity, and Hypoglycemic Medication Use

- Compared to HCLF diets, low-CHO diets
  - **Did not reduce FBG or insulin levels more** in clinical trials
  - Greater **short-term reduction in HbA1c** – less difference >1 year
  - **Reduced the use of diabetes medications**
    - Achieved at CHO intake levels that did not induce ketosis
- In T2D, **Mediterranean dietary pattern** vs. low-CHO diets
  - ↓ TG and HbA1c
  - ↑ HDL-C

Systolic BP

Author	# of RCTs	SBP (mmHg) WMD (95% CI)
Naude et al. 2014[57]	14	-2.00 (-5.00 to 1.00)
Bueno et al. 2013[58]	13	-1.47 (-3.44 to 0.50)
Schwingshackl & Hoffmann 2013[59]	32	NR
Mansoor et al. 2016[60]	11	-1.02 (-2.98 to 0.94)
Gjuladin-Hellon et al. 2019[78]	5	NR
Sackner-Bernstein et al. 2016[79]	17	-1.7 (-3.5 to 0.2)

Meta-analyses of studies of adults with overweight and/or obesity

Author	# of RCTs	SBP (mmHg) WMD (95% CI)
Naude et al. 2014[57]	5	0.31 (-3.1 to 3.72)
Schwingshackl & Hoffmann 2014[61]	14	0.59 (-2.18 to 3.36)
Meng et al. 2017[62]	9	NR
Snorgaard et al. 2017[63]	10	NR
Huntriss et al. 2018[64]	5-7	**-2.74** (-5.27 to -0.20)
Korsmo-Haugen et al. 2019[65]	7-10	-1.39 (-3.20 to 0.43)
Sainsbury et al. 2018[66]	25	NR
van Zuuren et al. 2018[67]	2-3	1.60 (-1.50 to 4.70)

Meta-analyses of studies of adults with overweight and/or obesity with pre-diabetes and/or type 2 diabetes

Diastolic BP

Author	# of RCTs	DBP (mmHg) WMD (95% CI)
Naude et al. 2014[57]	14	-0.03 (-1.68 to 1.62)
Bueno et al. 2013[58]	13	**-1.43** (-2.49 to -0.37)
Schwingshackl & Hoffmann 2013[59]	32	NR
Mansoor et al. 2016[60]	11	-1.01 (-2.75 to 0.74)
Gjuladin-Hellon et al. 2019[78]	5	NR
Sackner-Bernstein et al. 2016[79]	17	NR

Meta-analyses of studies of adults with overweight and/or obesity

Author	# of RCTs	DBP (mmHg) WMD (95% CI)
Naude et al. 2014[57]	5	0.09 (-1.95 to 2.13)
Schwingshackl & Hoffmann 2014[61]	14	**-1.30** (-1.73 to -0.87)
Meng et al. 2017[62]	9	NR
Snorgaard et al. 2017[63]	10	NR
Huntriss et al. 2018[64]	5-7	-0.99 (-2.24 to 0.25)
Korsmo-Haugen et al. 2019[65]	7-10	-0.55 (-2.17 to 1.06)
Sainsbury et al. 2018[66]	25	NR
van Zuuren et al. 2018[67]	2-3	0.88 (-1.25 to 3.02)

Meta-analyses of studies of adults with overweight and/or obesity with pre-diabetes and/or type 2 diabetes

Key Point for the Effects on Blood Pressures

Low-CHO/very-low-CHO diets vs. HCLF diets

- Produced **inconsistent effects on blood pressures** – adults with overweight/obesity with and without pre-diabetes or T2D

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**.	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**.	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 a HCLF diet.	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**.	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**.	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**.	IIb	B-R

*The NLA grading system adopted the methodology and classification system used in the 2015 ACC/AHA Clinical Practice Guideline Recommendation Classification System.

Key Points for the Effects of Low-CHO and Very-low-CHO Diets on Emerging Risk Factors

- Weight loss ↓ C-reactive protein (CRP)
  - Current evidence: **no difference** between low-CHO/very-low-CHO diets vs. HCLF diets
- **Potentially unfavorable gut microbiota changes** and fecal metabolite shifts with low-CHO/very-low-CHO diets
  - Clinical significance is unknown
- **Short-term exposure to a low-CHO, high-fat diet** vs. a very-low-fat plant-based diet – associated with ↑**TMAO**
  - Clinical significance is unknown

Content of the Scientific Statement

- Describe CHO-restricted diets, including KDs
- Nutritional ketosis and energy and lipid metabolism
- CHO-restricted diets and energy balance and body weight
- Evidence for effects – weight loss, body composition, and cardiometabolic risk factors
- **Safety concerns and adverse effects**
- Points for the clinician-patient discussion

Key Points for Safety Concerns Associated with Low-CHO and Very-low-CHO Diets, Including Ketogenic Diets

- **Close medical supervision is essential for some patients**
  - ASCVD
  - History of atrial fibrillation
  - Presence or history of heart failure, kidney disease, or liver disease
  - T2D – risk of hypoglycemia, potential for medication adjustment
  - Hypertension – risk of hypotension, potential for medication adjustment
  - Vitamin K-dependent anticoagulation therapy – more frequent monitoring may be required due to the potential change in vitamin K bioavailability and its effect on anticoagulation therapy.

Key Points for Safety Concerns Associated with Low-CHO and Very-low-CHO Diets, Including Ketogenic Diets

- **VLCHF/KDs are contraindicated in some patients**
  - History of hypertriglyceridemia-associated pancreatitis
  - Severe hypertriglyceridemia
  - Inherited causes of severe hypercholesterolemia
  - Rx sodium-glucose cotransporter 2 (SGLT2) inhibitors – increased risk of SGLT2 inhibitor-associated ketoacidosis
- Both low- and high-CHO intake associated with ↑ risk of mortality
  - Moderate-CHO intake associated with the lowest risk of mortality

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**.	III: Potential Harm	C-EO
Because VLCHF/KDs **are contraindicated** in patients with a **history of acute pancreatitis, severe hypertriglyceridemia, or inherited severe hypercholesterolemia**, they are **not recommended** for these patients.	III: Potential Harm	C-EO
Because low-CHO and very-low-CHO/KDs can **increase the risk of hypoglycemia** it **is reasonable** to **monitor glycemic control and make adjustments in diabetes medication**.	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**.	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.	III: Potential Harm	C-EO
Long-term consumption of extreme CHO intakes (low and high) have been associated with all-cause, cardiovascular, and cancer mortality in the general population.	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.

Content of the Scientific Statement

- Describe CHO-restricted diets, including KDs
- Nutritional ketosis and energy and lipid metabolism
- CHO-restricted diets and energy balance and body weight
- Evidence for effects – weight loss, body composition, and cardiometabolic risk factors
- Safety concerns and adverse effects
- **Points for the clinician-patient discussion**

Key Points for the Clinician-patient Discussion on Low-CHO and Very-low-CHO Diets, Including Ketogenic Diets

- **Clinician-patient discussion** before initiation
- May be an option for **short-term (2-6 months)** initial weight loss
- **Long-term** weight maintenance and cardiovascular health – **gradually ↑ CHO intake**
  - Emphasis on CHO foods associated with ↓ cardiometabolic risk
    - **Unprocessed foods; vegetables, fruits, whole grains, nuts/seeds, and legumes**
- Comprehensive multi-disciplinary lifestyle intervention programs facilitate weight loss and maintenance
  - ↓ calorie intake
  - ↑ physical activity
  - Behavior change therapy

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.	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.	IIa	B-R
A **moderate-CHO intake (>130-225 g/day) 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.	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/week, and strength/resistance activities.	I	A
To **maintain long-term (>1 year) 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/week**.	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.

Gaps in the Evidence

- **Factors that influence** energy expenditure and appetite
- **Effects of different levels of CHO** intake on cardiometabolic indices and disease outcomes
  - Need RCTs of longer duration
  - Need RCTs with CHO intake goal adherence through end of study
- **Possible threshold** where CHO intake does not have to be severely restricted and still achieve benefit
- **Long-term effects** of low-CHO diet or very-low-CHO/KDs
  - Body weight changes and weight loss maintenance
  - Microbiome, TMAO production, inflammatory markers
  - ASCVD risk and other chronic illnesses (e.g., cancer, neurological)

Conclusions/Summary Statement

- There is **not one macronutrient distribution that is superior** for weight loss or for the management of T2D
- There is a **physiological basis for potential metabolic benefits** of CHO-restriction vs. higher CHO in some individuals (↓appetite, ↑energy expenditure)
- Low-CHO/very-low-CHO diets **may improve**
  - TG and HDL-C levels
  - Glycemic control and reductions in diabetes medications
- Low-CHO/very-low-CHO diets have **variable effects on LDL-C**
- **No differences for most cardiometabolic risk markers by ~2 years**

Conclusions/Summary Statement

- **Adherence** to the severe CHO restriction of very-low-CHO diets is **challenging**
  - Potential to cause adverse side effects – “keto flu,” GI complaints, nutrient inadequacies
- Very-low-CHO, high-fat diets **differ from nutrition recommendations** of various professional organizations
  - Severely restrict or eliminate foods associated with cardioprotective benefits
  - Often encourage high intake of foods known to increase ASCVD risk (e.g., processed meats, foods rich in SFAs)
- **Long-term studies** on potential impact of ASCVD outcomes are **lacking**

Conclusions/Summary Statement

- **Decision** about following a low-CHO/very-low-CHO diet should be made **after a clinician-patient discussion**
  - Risks and benefits and consideration of patient preference
- If a very-low-CHO diet is adopted, **ideally** individuals receive
  - Medical supervision
  - Baseline and regular assessment of lipid/lipoproteins
  - Referral to a comprehensive multidisciplinary lifestyle intervention
- **Promotion of overall health and decreased ASCVD risk**
  - Achieving a healthy body weight and long-term weight maintenance
  - A cardioprotective dietary pattern
  - Increased physical activity

Thank You!

Special thanks to the writing group team

- Julie P. Bolick, MS, RDN, CD, CLS, FNLA
- Penny M. Kris-Etherton, PhD, RDN, CLS, FNLA
- Geeta Sikand, MA, RDN, CLS, FNLA
- Karen E. Aspry, MD, MS, FNLA
- Daniel E. Soffer, MD, FNLA
- Kaye-Eileen Willard, MD, FNLA
- Kevin C. Maki, PhD, CLS, FNLA, FTOS, FACN

Special thanks to

- Terry A. Jacobson, MD, FNLA, NLA Scientific Statements Committee Chair
- Vivian Grifantini, NLA Projects & Group Manager