Cardiovascular Safety of Ketogenic Therapy

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Medical Director, The Coalition for Metabolic Health
Medical consultation services: lowcarbcardiologist.com

WHY ARE WE TALKING ABOUT KETOGENIC THERAPY?

More Than a Diet—Changes Our Body's Metabolism

Change from glucose as the primary fuel to fatty acids.

BY THE END OF THIS SESSION

Learning Objectives

1. Recognize that ketogenic metabolic therapy is different from simply "eating keto."
2. Explain how ketogenic therapy improves metabolic health, improving the vast majority of measurable cardiovascular risk factors.
3. Describe the ways in which the cardiovascular risks of eating low carb/high fat are often misrepresented and incorrectly portrayed in the scientific and mainstream press.
4. Recognize that concerns about elevated LDL-cholesterol and ketogenic therapy are relevant only to a minority of individuals.

WHY ARE WE TALKING ABOUT KETOGENIC THERAPY?

More Than a Diet—Changes Our Body's Metabolism

Change from glucose as the primary fuel to fatty acids.

Most of the body uses fatty acids to create energy, and part of the process also creates ketones.

WHY ARE WE TALKING ABOUT KETOGENIC THERAPY?

More Than a Diet—Changes Our Body's Metabolism

WHY ARE WE TALKING ABOUT KETOGENIC THERAPY?

More Than a Diet—Changes Our Body's Metabolism

Change from glucose as the primary fuel to fatty acids.
No dietary requirement for carbs

Most of the body uses fatty acids to create energy.

The brain doesn't use fatty acids, but can easily and efficiently use ketones.

WHY ARE WE TALKING ABOUT KETOGENIC THERAPY?

More Than a Diet

REFRACTORY SEIZURES

Treatment

in kids and adults

Meira et al, Front Neurosci. 2019

WHY ARE WE TALKING ABOUT KETOGENIC THERAPY?

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Meira et al, Front Neurosci. 2019

TYPE 2 DIABETES · UP TO

55–70%

remission

Goldenberg et al, BMJ. 2021 · Athinarayanan et al, Front Endocrinol (Lausanne). 2019

SERIOUS MENTAL ILLNESS

Improved

symptoms

Psychiatry Research, Volume 335, 2024 · Campbell et al, BJPsych Open. 2019

More than just eating bacon!

WHY ARE WE TALKING ABOUT KETOGENIC THERAPY?

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Meira et al, Front Neurosci. 2019

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COMMON WORRIES

Concerns Surrounding Ketosis

01 **Ketoacidosis**

02 **Fat**

03 **Meat**

04 **Heart Disease**

WHY ARE WE TALKING ABOUT KETOGENIC THERAPY?

More Than a Diet

REFRACTORY SEIZURES

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KETOSIS IS A STATE, NOT A MENU

Almost Any Diet Can Be Keto



Steak with herb butter



Scrambled eggs with asparagus



Salmon, avocado, nuts and olive oil

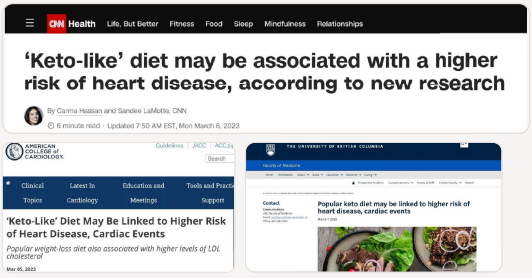
What defines ketosis is how few carbohydrates are eaten, not which foods fill the plate.

PART 2

Is There Increased Cardiac Risk With Ketosis?

THE HEADLINES

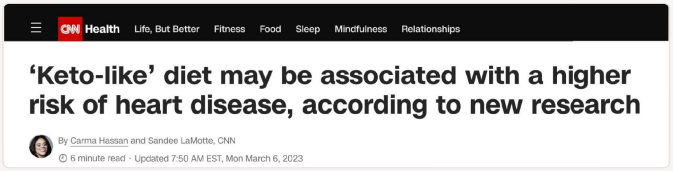
What the Public Read



Sources: CNN Health, March 6, 2023 · American College of Cardiology, March 2023 · University of British Columbia

THE HEADLINES

What the Public Read



Source: CNN Health, March 6, 2023

READING PAST THE HEADLINE

Not Keto At All

THE HEADLINES

Based on unpublished data

"Low carb" was defined as 25% of calories from carbohydrate.

THE MATH

125 g

2,000 kcal × 0.25 = 500 kcal from carbs; 500 ÷ 4 = 125 grams of carbohydrate.

A USUAL KETOGENIC DIET

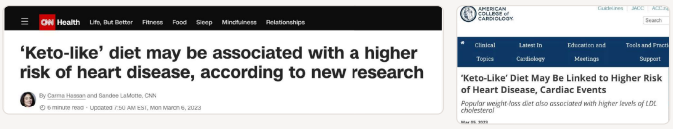
20–30 g

of carbohydrate per day.

Source: CNN Health, March 6, 2023 (reporting on unpublished data); calculation shown for a 2,000 kcal diet

THE HEADLINES

What the Public Read



Sources: CNN Health, March 6, 2023 · American College of Cardiology, March 2023

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A USUAL KETOGENIC DIET

20–30 g

of carbohydrate per day.

There is nothing “keto-like” about this diet!

Source: CNN Health, March 6, 2023 (reporting on unpublished data); calculation shown for a 2,000 kcal diet

Is there increased cardiac risk with ketosis?

Most likely, no.

Evidence reviewed in the slides that follow

SEIDELMANN ET AL · LIMITATIONS

Lower-Quality Evidence

FOOD-FREQUENCY QUESTIONNAIRE

2 times

in 25 years

Very low hazard ratio: HR 1.20

THE LOW-CARB GROUP WAS MORE LIKELY TO BE MALE AND TO:

- Smoke
- Drink alcohol
- Have diabetes
- Less physical activity
- Lower education

Source: Seidelmann et al, Lancet Public Health. 2018

THE STUDY BEHIND THE CLAIM

Seidelmann et al.

LANCET PUBLIC HEALTH · VOLUME 3, ISSUE 9 · SEPTEMBER 2018

Dietary carbohydrate intake and mortality: a prospective cohort study and meta-analysis

Sara B Seidelmann, Brian Claggett, Susan Cheng, Mir Henglin, Amil Shah, Lyn M Steffen, et al.

Source: Seidelmann et al, Lancet Public Health. 2018 · DOI: 10.1016/S2468-2667(18)30135-X

SAME INGREDIENT, DIFFERENT MEAL

Risk of Dietary Fat / Red Meat



LOW CARB

Steak salad



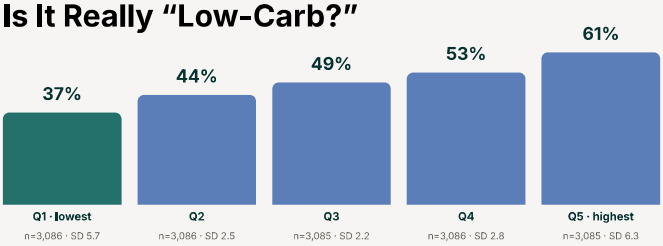
HIGHER CARB

Spaghetti with meat sauce

Illustrative examples; red meat appears in both low-carb and higher-carb eating patterns

SEIDELMANN ET AL · CARBOHYDRATE QUINTILES

Is It Really "Low-Carb?"



Median % of energy from carbohydrate. The "low-carb" group still ate more than a third of calories as carbs.

Source: Seidelmann et al, Lancet Public Health. 2018

CONTEXT MATTERS

Which "Fat?"



WHOLE FOOD

Sliced steak



PROCESSED COMBINATION

Cheesesteak sandwich

Illustrative examples

PART 3

Do Very Low Carb Diets Increase LDL-C and CV Risk?

SYSTEMATIC REVIEW AND META-ANALYSIS

Falkenhain et al.

AMERICAN JOURNAL OF CLINICAL NUTRITION · 2021

Effect of carbohydrate-restricted dietary interventions on LDL particle size and number in adults in the context of weight loss or weight maintenance

Kaja Falkenhain, Lauren A Roach, Sara McCreary, Eric McArthur, Ethan J Weiss, Monique E Francois, Jonathan P Little

Source: Falkenhain et al, AJCN. 2021 · DOI: 10.1093/ajcn/nqab212

SYSTEMATIC REVIEW AND META-ANALYSIS

Gjuladin-Hellon et al.

NUTR REV · 2019 MAR 1;77(3):161–180

Effects of carbohydrate-restricted diets on low-density lipoprotein cholesterol levels in overweight and obese adults

Gjuladin-Hellon T, Davies IG, Penson P, Amiri Baghbadorani R

RANDOMIZED CONTROLLED TRIALS

8

n = 1,633; 818 carbohydrate-restricted, 815 low-fat

Source: Gjuladin-Hellon et al, Nutr Rev. 2019

FALKENHAIN ET AL · RESULTS

Bigger LDL Particles, Fewer of Them

RANDOMIZED TRIALS

38

1,785 participants

LDL PEAK PARTICLE SIZE

Increased

SMD = 0.50; 95% CI 0.15, 0.86; P < 0.01

LDL PARTICLE NUMBER (LDL-P)

Reduced

With carbohydrate-restricted diets

Source: Falkenhain et al, AJCN. 2021

GJULADIN-HELLON ET AL · RESULTS

No Significant Difference in LDL-C

AT 6 MONTHS

No difference

AT 12 MONTHS

No difference

AT 24 MONTHS

No difference

> Large randomized controlled trials of at least 6 months with carbohydrate restriction appear superior in improving lipid markers compared with low-fat diets. Guidelines should consider carbohydrate restriction as an alternative strategy for dyslipidemia in populations with cardiometabolic risk.

Source: Gjuladin-Hellon et al, Nutr Rev. 2019 (abstract, paraphrased)

RANDOMIZED CLINICAL TRIAL

Petersen et al.

CELL METABOLISM · CLINICAL AND TRANSLATIONAL REPORT · OPEN ACCESS

Effect of diet macronutrient content on the cardiometabolic response to weight loss: A randomized clinical trial

Max C Petersen, Gordon I Smith, Sarah S Farabi, ... Marc K Hellerstein, Bruce W Patterson, Samuel Klein

Source: Petersen et al, Cell Metabolism · ClinicalTrials.gov NCT02706262

CARDIOMETABOLIC EFFECTS OF 10% WEIGHT LOSS · KETOGENIC VS MEDITERRANEAN VS VERY-LOW-FAT

Three Findings

01

Superior hepatic insulin sensitivity

Muscle insulin sensitivity rose ~50% in all groups; keto produced a 2–3-fold greater rise in hepatic insulin sensitivity ($p < 0.001$).

02

Greatest reduction in liver fat and glycemia

Intrahepatic triglyceride, hepatic de novo lipogenesis, HbA1c and 24-h glucose and insulin fell most with very-low-carbohydrate.

03

Neutral impact on lipids

No differences among groups in LDL-C, apoB or 24-h plasma triglycerides.

Source: Petersen et al, Cell Metabolism · population: people with metabolically unhealthy obesity (prediabetes, hepatic steatosis) · NCT02706262

BHANPURI ET AL · TYPE 2 DIABETES CARE MODEL WITH NUTRITIONAL KETOSIS · 1 YEAR

LDL-C Rose, but Risk Did Not

LDL-C

+10%

Source: Bhanpuri et al, Cardiovasc Diabetol. 2018

PETERSEN ET AL · LDL-C AT 4 MONTHS

No Change in LDL at 4 Months

KETO DIET

23%

of calories from saturated fat

No difference in LDL change versus a Mediterranean diet or a very-low-fat, plant-forward diet.

Diets were adjusted for an equal 10% weight loss.

Source: Petersen et al, Cell Metabolism · NCT02706262

BHANPURI ET AL · TYPE 2 DIABETES CARE MODEL WITH NUTRITIONAL KETOSIS · 1 YEAR

LDL-C Rose, but Risk Did Not

LDL-C

+10%

10-YEAR ASCVD RISK SCORE

−12%

Source: Bhanpuri et al, Cardiovasc Diabetol. 2018

OPEN-LABEL, NON-RANDOMIZED, CONTROLLED STUDY

Bhanpuri et al.

CARDIOVASCULAR DIABETOLOGY · 2018

Cardiovascular disease risk factor responses to a type 2 diabetes care model including nutritional ketosis induced by sustained carbohydrate restriction at 1 year

Nasir H Bhanpuri, Sarah J Hallberg, Paul T Williams, Amy L McKenzie, Kevin D Ballard, Wayne W Campbell, James P McCarter, Stephen D Phinney, Jeff S Volek

Source: Bhanpuri et al, Cardiovasc Diabetol. 2018

BHANPURI ET AL · TYPE 2 DIABETES CARE MODEL WITH NUTRITIONAL KETOSIS · 1 YEAR

LDL-C Rose, but Risk Did Not

LDL-C

+10%

10-YR ASCVD RISK SCORE

−12%

APO B

No change

SMALL LDL-P

−20%

APO B / APO A1

−9%

TG / HDL RATIO

−29%

LARGE VLDL

−39%

Source: Bhanpuri et al, Cardiovasc Diabetol. 2018

SETHI ET AL · 4 MONTHS OF KETOGENIC THERAPY FOR SERIOUS MENTAL ILLNESS WITH METABOLIC DYSFUNCTION

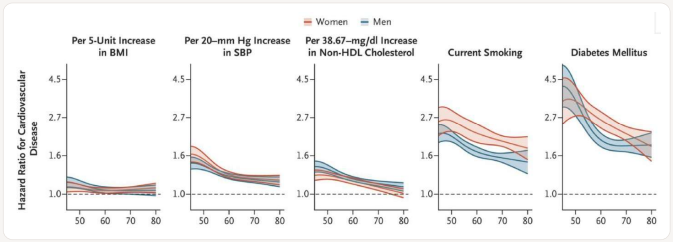
LDL vs Cardiac Risk

LDL	CALCULATED CARDIAC RISK
+21%	−7%

Source: Sethi et al, Psychiatry Research. 2024

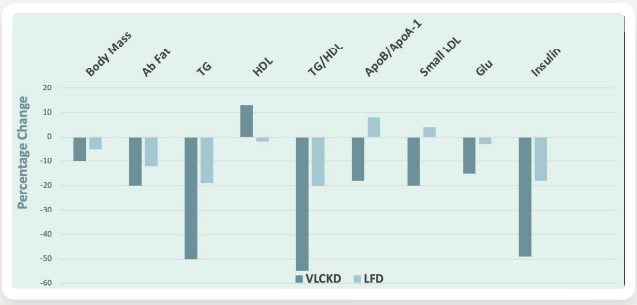
HAZARD RATIO FOR CARDIOVASCULAR DISEASE BY AGE

Diabetes Increases Risk More Than LDL



Source: Magnussen et al, N Engl J Med. 2023

PERCENTAGE CHANGE · VERY-LOW-CARBOHYDRATE KETOGENIC DIET VS LOW-FAT DIET



Source: Hite et al, Nutr Clin Pract. 2011 · values approximate, read from the published figure (VLCKD / LFD)

SHORT REPORT

Calkins et al.

AMERICAN JOURNAL OF PREVENTIVE CARDIOLOGY

One-year change in PREVENT-estimated cardiovascular risk during telehealth metabolic care centered on a therapeutic ketogenic diet

Matthew Calkins, Laura Buchanan, Kelly Curtis, Tro Kalayjian, Camden Richardson, Erin M Saner, Adrian Soto-Mota

Source: Calkins et al, Am J Prev Cardiol

WOMEN'S HEART STUDY · 21.4-YEAR FOLLOW-UP · HAZARD RATIO FOR CORONARY HEART DISEASE

Metabolic Risk Outweighs LDL-C

RISK FACTORS		BIOCHEMICAL MARKERS	
Type 2 diabetes mellitus	10.71	Lipoprotein insulin resistance	6.40
Metabolic syndrome	6.09	Triglycerides	2.14
Hypertension	4.58	Apolipoprotein	1.89
Obesity	4.33	Non-HDL cholesterol	1.67
Smoking	3.92	LDL cholesterol	1.38
Family history of premature CHD	1.50–2.00	Inflammatory biomarkers	1.20–1.80

Source: Dugani et al, JAMA Cardiol. 2021 · bars share one scale; a hazard ratio of 1.0 means no added risk

CALKINS ET AL · HOW THE STUDY WORKED

Study Design

EMPLOYEES OF ONE MANUFACTURER

120

Retrospective single-arm cohort across seven TOWARD cohorts (2022–2023); all BMI ≥ 25 kg/m²

THE PROGRAM

Messaging, virtual visits, coaching and remote patient monitoring with connected home devices.

An individualized whole-food diet limiting carbohydrates to ≤ 30 g/day, with no prescribed saturated fat restriction.

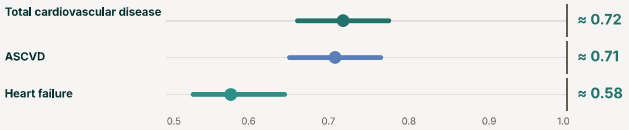
Medications adjusted as clinically indicated, including deprescription.

Fasting panels at baseline and 12 months.

Source: Calkins et al, Am J Prev Cardiol

PREVENT 10-YEAR RISK AT ONE YEAR (N = 90) · YEAR-1 / BASELINE RATIO, 95% CI

Estimated 10-Year Risk Fell



A ratio of 1.0 (dark line) means no change from baseline; all three estimates sit below it.

Source: Calkins et al, Am J Prev Cardiol · primary estimate; values approximate, read from the published figure

ROBERTS ET AL · HOW THE STUDY WORKED

Study Design

WHO WAS COMPARED

Adults with type 2 diabetes or obesity receiving individualized nutritional therapy (INT) between January 1, 2016 and June 1, 2025, compared with propensity score-matched controls.

PRIMARY OUTCOME 1

MACE-3

Nonfatal myocardial infarction, nonfatal stroke, or death from any cause

PRIMARY OUTCOME 2

MACE-6

MACE-3 plus percutaneous coronary intervention, hospitalization for heart failure, or unstable angina

PRIMARY OUTCOME 3

New CVD

All new-onset cardiovascular disease events

PRIMARY OUTCOME 4

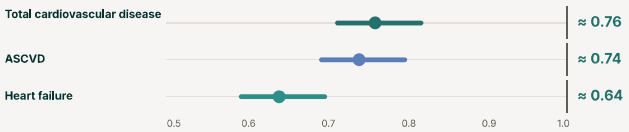
Hypertension

New-onset hypertension

Source: Roberts et al, Cardiology and Therapy. 2026

PREVENT 30-YEAR RISK AT ONE YEAR (N = 73) · YEAR-1 / BASELINE RATIO, 95% CI

Estimated 30-Year Risk Fell Too



A ratio of 1.0 (dark line) means no change from baseline; all three estimates sit below it.

Source: Calkins et al, Am J Prev Cardiol · primary estimate; values approximate, read from the published figure

ROBERTS ET AL · EVENTS PER 1,000 PERSON-YEARS

Lower MACE with Ketogenic Intervention

MACE-3

95% CI 0.29–0.65 · P < 0.001

INT 4.1

Controls 9.3

HAZARD RATIO **0.44**

MACE-6

Adds PCI, heart failure hospitalization or unstable angina

INT 5.7

Controls 10.8

HAZARD RATIO **0.52**

INT = individualized nutritional therapy. MACE-3 findings span 18,957 person-years of follow-up.

Source: Roberts et al, Cardiology and Therapy. 2026 · incidence rates as reported in the abstract

RETROSPECTIVE CLAIMS-BASED COHORT STUDY

Roberts et al.

CARDIOLOGY AND THERAPY · PUBLISHED OCTOBER 2, 2026

Cardiovascular Outcomes Among Adults with Type 2 Diabetes or Obesity Receiving Carbohydrate-Reduced Nutrition via Telemedicine: A Retrospective Claims-Based Cohort Study

Caroline G. P. Roberts, Priya V. Shanmugam, Shaminie J. Athinarayanan, Adam J. Wolfberg, Stephen Raskin, Francisco Lopez-Jimenez

INDIVIDUALIZED NUTRITIONAL THERAPY, ENROLLED

2016–2025

Compared with propensity score-matched controls

Source: Roberts et al, Cardiology and Therapy. 2026

WITH WEIGHT LOSS OR IN A TYPE 2 DIABETES POPULATION

Keto Impact on LDL and CV Risk

- No net increase in LDL
- Reduction in calculated cardiovascular risk
- Dramatically improved metabolic-health lipid markers
- No impact despite a higher saturated fat level
- Appears to reduce claims based CV outcomes

Caveat: no long term RCT data

Summary of: Gjuladin-Hellon 2019 · Falkenhain 2021 · Petersen (Cell Metabolism) · Bhanpuri 2018 · Sethi 2024

PART 4

Lean-Mass Hyper Responder (LMHR)

WHY IT MAY HAPPEN

Proposed Mechanisms of LMHR

01

Energy delivery

02

Weight stable and metabolically healthy

03

Not saturated fat mediated

Source: Norwitz et al, Curr Dev Nutr. 2021

DESCRIBING THE PHENOTYPE

Norwitz et al.

CURRENT DEVELOPMENTS IN NUTRITION · 2021 NOV 30;6(1):NZAB144

Elevated LDL cholesterol with a carbohydrate-restricted diet: evidence for a "Lean Mass Hyper-Responder" phenotype

Nicholas G Norwitz, David Feldman, Adrian Soto-Mota, Tro Kalayjian, David S Ludwig

Source: Norwitz et al, Curr Dev Nutr. 2021 · DOI: 10.1093/cdn/nzab144 · PMID: 35106434

KETO CTA

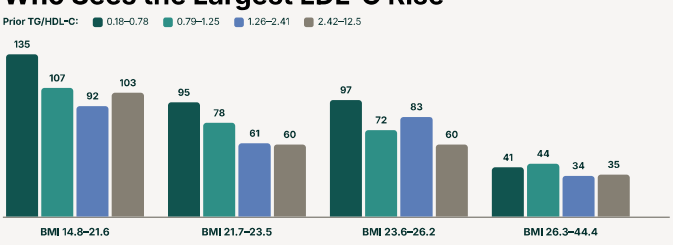
Published KETO CTA Data

[Add the published KETO CTA data and citation here]

Source: [add citation]

CHANGE IN LDL-C (MEDIAN, MG/DL) BY BMI AND PRIOR TG/HDL-C QUARTILE

Who Sees the Largest LDL-C Rise



Source: Norwitz et al, Curr Dev Nutr. 2021 (Figure 2) · values transcribed from figure labels; BMI in kg/m²

KETO CTA

Lessons from the Keto CTA Study

1 **More attention to CTA with plaque analysis than ever before**

Lessons drawn from the Keto CTA study

KETO CTA

Lessons from the Keto CTA Study

1. More attention to CTA with plaque analysis than ever before
2. LMHR are not one homogenous group

Lessons drawn from the Keto CTA study

KETO CTA

Lessons from the Keto CTA Study

1. More attention to CTA with plaque analysis than ever before
2. LMHR are not one homogenous group
3. Presence of plaque is likely the biggest determining factor
4. Cross-study comparisons are not accurate
5. Starting a new field of study is challenging

Lessons drawn from the Keto CTA study

KETO CTA

Lessons from the Keto CTA Study

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KETO CTA

Lessons from the Keto CTA Study

1. More attention to CTA with plaque analysis than ever before
2. LMHR are not one homogenous group
3. Presence of plaque is likely the biggest determining factor
4. Cross-study comparisons are not accurate
5. Starting a new field of study is challenging
6. Hopefully lots of attention is a good thing in the end

Lessons drawn from the Keto CTA study

KETO CTA

Lessons from the Keto CTA Study

1. More attention to CTA with plaque analysis than ever before
2. LMHR are not one homogenous group
3. Presence of plaque is likely the biggest determining factor
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Lessons drawn from the Keto CTA study

PART 5

What to Do About Increased LDL?

1. Weigh risk vs benefits

Source: Norwitz et al, Curr Dev Nutr. 2021

PART 5

What to Do About Increased LDL?

1. Weigh risk vs benefits
2. Cycle carbs

Source: Norwitz et al, Curr Dev Nutr. 2021

PART 5

What to Do About Increased LDL?

1. Weigh risk vs benefits
2. Cycle carbs
3. Swap saturated for mono- and polyunsaturated fat
4. Statins, ezetimibe, PCSK9 inhibitors, others
5. Use imaging to monitor the real disease

Options discussed by the presenter

PART 5

What to Do About Increased LDL?

1. Weigh risk vs benefits
2. Cycle carbs
3. Swap saturated for mono- and polyunsaturated fat

Options discussed by the presenter

IN SUMMARY

Ketogenic Therapy Takeaways

1. Ketosis is a metabolic and physiologic state, not one diet.
2. Effective treatment for metabolic dysfunction and brain and psychiatric disorders.
3. Cardiac risk is misunderstood and misrepresented.
4. LDL increase is often offset by overall cardiac risk reduction.
5. LMHR are the exception, not the rule.
6. Many options exist for lowering LDL while continuing ketogenic therapy.

PART 5

What to Do About Increased LDL?

1. Weigh risk vs benefits
2. Cycle carbs
3. Swap saturated for mono- and polyunsaturated fat
4. Statins, ezetimibe, PCSK9 inhibitors, others

Options discussed by the presenter

Thank You