Ketogenic Diet for Dyslipidemia & Metabolic Syndrome

Conference on Nutritional Ketosis & Metabolic Therapeutics
Tampa, FL, Jan 29, 2016

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Saturated Fat & the Diet Heart Hypothesis

↑ SFA Intake ➔ ↑ Plasma LDL ➔ ↑ Heart Disease

(?)

METABOLIC THERAPEUTICS

Slides by Jeff Volek
Obesity Trends in the U.S.

“Only a relatively small subset of adults has maintained a healthy weight in the context of current low fat guidelines.”

Prevalence of and Trends in Diabetes Among Adults in the United States, 1988-2012

Andy Menke, PhD; Sarah Casagrande, PhD; Linda Geiss, MA; Catherine C. Cowie, PhD


All while we are eating less saturated fat!
The majority of Americans are consuming too many sugars & starches relative to their tolerance.
Saturated Fat & the Diet Heart Hypothesis

<table>
<thead>
<tr>
<th>Upward Arrow</th>
<th>Text</th>
<th>Downward Arrow</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑ SFA Intake</td>
<td></td>
<td>↓ SFA Intake</td>
</tr>
<tr>
<td>↑ Plasma LDL</td>
<td></td>
<td>← ?</td>
</tr>
<tr>
<td>↑ Heart Disease</td>
<td></td>
<td>↑ Metabolic Syndrome</td>
</tr>
<tr>
<td>↑ Carb Intake</td>
<td></td>
<td>→ Diabetes</td>
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</table>

Metabolic Syndrome

Diabetes
Conclusions Over a mean of 8.1 years, a dietary intervention that reduced total fat intake and increased intakes of vegetables, fruits, and grains did not significantly reduce the risk of CHD, stroke, or CVD in postmenopausal women and achieved only modest effects on CVD risk factors, suggesting that more focused diet and lifestyle interventions may be needed to improve risk factors and reduce CVD risk.
Diseases associated with insulin resistance and its secondary manifestations (T2D, metabolic syndrome, obesity) are epidemic.
Ingest Carbohydrate

Blood Glucose
(\approx 1-2\, \text{teaspoons})

Path to Health

Glycogen
(\approx 300-400\, \text{g})

Path to Metabolism

Metabolic Syndrome

Lipogenesis (fat synthesis)

Excess carb intake drives up blood SFA levels

Glycogen (\approx 100\, \text{g})

\uparrow 16:0
\uparrow 16:1

DAMAGE
The Insulin Resistance Continuum

Carbohydrate Intolerant

Insulin Resistant
  Type-2 Diabetes
  Metabolic Syndrome
  Obesity
  Expanding Waistline

Insulin Sensitivity
  Athletes
  Normal BMI

Carbohydrate Tolerant
Keto-adaptation
Better Health/Performance/Recovery

T2D…Metabolic Syndrome…Obese…Normal-Weight…Active…World-Class Athletes
Well-formulated ketogenic diets counteract insulin resistance and its secondary manifestations

- **Ornish diet**
- **SAD (Standard American Diet)**
- **Mediterranean diet**
- **Paleo (Paleolithic diet)**

**Note:**

- **Carbs (%)** = Percent of dietary carbs relative to daily energy expenditure
- **Protein (%)** = Percent of dietary protein relative to daily energy expenditure
- **Protein (g/kg RW)** = Grams of dietary protein relative to reference body weight

**Generally accepted upper threshold of ‘Low Carb’**

- **WFKD** (Well formulated ketogenic diet)
- **Ornish diet**
- **SAD (Standard American Diet)**
- **Mediterranean diet**
- **Paleo (Paleolithic diet)**
Ketogenic diets are palatable & pleasurable

2500 kcal, <50 g Carbohydrate

Breakfast (Scrambled eggs with sides of spinach and sausage)
Scrambled eggs...2 large + 1 Tbsp palm oil
Mozzarella Cheese...1 oz
Pork Sausage...2 links (48 g)
Chopped frozen Spinach, boiled...3/4 cup (142.5 g) + 1.5 Tbsp Butter

Snack
½ Avocado...67 g
Swiss Cheese...2 oz (56 g)

Lunch (Broiled Salmon and a side salad)
Broiled Atlantic Salmon...4 oz + 1 Tbsp Butter
Side Salad: Mixed Baby greens...2,5 cups
Diced Tomatoes...1/4 cup
Chopped Onion...1/8 cup
Feta Cheese...1 oz
Black and Green Olives...4 each
Blue Cheese Dressing...1.5 Tbsp

Snack
Peanuts, oil-roasted...1 oz
Hood Calorie Countdown Milk...1/2 cup

Dinner (Sirloin with sautéed mushrooms and Cauliflower “mashed potatoes”)
Beef Sirloin Tips...3 oz
Olive oil...1.5 Tbsp
Sautéed Mushrooms...1/4 cup
Olive oil cooking spray
Cauliflower “Mashed Potatoes”: Boiled Cauliflower...1 cup +
Shredded Cheddar Cheese...1 oz
Butter...1 Tbsp
Sugar Free jello...1/2 cup (121 g)

“I started noticing that I…
1) had no inclination to snack and
2) wake up not hungry. Please note that I feel great, even euphoric.”
<table>
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<tr>
<th>Condition</th>
<th>Ketones (mmol/L)</th>
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<tr>
<td>Moderate-carbohydrate diet (fed state)</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>Moderate-carbohydrate diet (fasted state)</td>
<td>0.1 to 0.3</td>
</tr>
<tr>
<td>Fasting (weeks)</td>
<td>5 to 7</td>
</tr>
<tr>
<td>Very low-carbohydrate diet (&lt;50 g/day)</td>
<td>0.5 to 3.0</td>
</tr>
<tr>
<td>Very low-carbohydrate diet (post-exercise)</td>
<td>1.0 to 5.0</td>
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<tr>
<td>Keto-acidosis (insulin insufficiency)</td>
<td>10 to 20+</td>
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Notes:
- Moderate-carbohydrate diet
  - Fed state: <0.1 mmol/L
  - Fasted state: 0.1 to 0.3 mmol/L

- Fasting: 5 to 7 weeks
- Very low-carbohydrate diet
  - <50 g/day: 0.5 to 3.0 mmol/L
  - Post-exercise: 1.0 to 5.0 mmol/L
- Keto-acidosis
  - Insulin insufficiency: 10 to 20+ mmol/L

10X magnification factor for values.
Invited Review

β-hydroxybutyrate: Much more than a metabolite

John C. Newman \textsuperscript{a, b}, Eric Verdin \textsuperscript{b, *}

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\textsuperscript{b} Gladstone Institutes, University of California San Francisco, 1650 Owens St., San Francisco, CA 94158, USA

ABSTRACT

The ketone body β-hydroxybutyrate (βOHB) is a convenient carrier of energy from adipocytes to peripheral tissues during fasting or exercise. However, βOHB is more than just a metabolite, having important cellular signaling roles as well. βOHB is an endogenous inhibitor of histone deacetylases (HDACs) and a ligand for at least two cell surface receptors. In addition, the downstream products of βOHB metabolism including acetyl-CoA, succinyl-CoA, and NAD\(^+\) (nicotinamide adenine dinucleotide) themselves have signaling activities. These regulatory functions of βOHB serve to link the outside environment to cellular function and gene expression, and have important implications for the pathogenesis and treatment of metabolic diseases including type 2 diabetes.
The Many Beneficial Effects of Beta-Hydroxybutyrate (BOHB)

- Accelerated free fatty acid release to enable weight loss & endurance exercise
- Ketogenesis
- Ketones as fuel
- BOHB 300-600 kcal/d
- BOHB for colonocytes
- Brain health
- Gut health

- Glycogen sparing/
  ↑ Fat oxidation
- ↓ inflammatory airway disease & asthma
- 26% increased longevity
- ↓ systemic oxidative stress & inflammation

- ↓ glycolytic flux
- ↓ allergic mast cell degranulation
- Modulation of DA-16,5OXO & SKN-1/Nrf1
- Class 1 histone deacetylase inhibition
When we eat too many carbs relative to our tolerance we develop:

- Central obesity
- High blood pressure
- High triglycerides
- Low HDL-cholesterol
- Insulin resistance
- Plasma saturated fat
Low carbohydrate diets far outperform low-fat diets on markers associated with insulin resistance.
Systematic review and meta-analysis of clinical trials of the effects of low carbohydrate diets on cardiovascular risk factors

Dietary Intervention for Overweight and Obese Adults: Comparison of Low-Carbohydrate and Low-Fat Diets. A Meta-Analysis

Jonathan Sackner-Bernstein¹ *, David Kanter², Sanjay Kaul³

Conclusions

This trial-level meta-analysis of randomized controlled trials comparing LoCHO diets with LoFAT diets in strictly adherent populations demonstrates that each diet was associated with significant weight loss and reduction in predicted risk of ASCVD events. However, LoCHO diet was associated with modest but significantly greater improvements in weight loss and predicted ASCVD risk in studies from 8 weeks to 24 months in duration. These results suggest that future evaluations of dietary guidelines should consider low carbohydrate diets as effective and safe intervention for weight management in the overweight and obese, although long-term effects require further investigation.
Ketogenic diets are more likely to effect global improvement in markers of metabolic syndrome.

Results after 3 months in 40 subjects with metabolic syndrome randomized to either a low carbohydrate or low fat diet (Forsythe et al. 2008).
Most reliable response to carbohydrate restriction

Dyslipidemia: Triglycerides

A ketogenic diet improves the postprandial lipemic & vascular response to a high fat meal

Volek et al. Lipids. 44:297-309, 2009

Volek et al. Metabolism. 2009 July 24
More effective than other lifestyle changes (exercise, smoking cessation, weight loss, n-3 PUFA)

Not dependent on starting levels

Stronger effect in women

Dependent on the cholesterol content of diet

Low carbohydrate diets consistently increase LDL particle size.
A CRD improves qualitative features of LDL (increased particle size)

\[ y = -\frac{25.996}{x} \times 1.1777 \times R = 0.95026 \]

\[% \text{ Pattern B} \]
\(% \text{ CHO} \]


Lipoprotein subfractions and cardiovascular disease risk
Ronald M. Krauss

Several recent studies have shown independent relationships of levels of LDL size to risk of coronary artery disease

1) What is the association of **dietary** SFA intake and risk for chronic disease?

2) What is the association of **plasma** SFA level and risk for chronic disease?

3) What is the association between dietary SFA and plasma SFA; and the role of carbohydrate?
<table>
<thead>
<tr>
<th>Study</th>
<th>Pooled Cohort Studies</th>
<th>Baseline Cohort (n)</th>
<th>Follow-Up (yr)</th>
<th>Interpretation</th>
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If you decrease SFA, it matters what you replace it with!

Replacing 5%en of SFA w/ **carbs** ↑ coronary events (HR 1.07)

*CHs for SFAs (per 5 E% increments)*

*P value, test for heterogeneity=0.51; combined hazard ratio (95% CI)=1.07 (1.01, 1.14)*
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<td>Simon et al. Serum Fatty Acids and the Risk of Coronary Heart Disease. Am J Epidemiol. 1995; 142: 469-76</td>
<td>Men who had heart attacks had higher serum palmitic acid (16:0) and a 68% greater risk of heart disease</td>
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<td>Wang et al. Plasma fatty acid composition and incidence of coronary heart disease in middle aged adults: The Atherosclerosis Risk in Communities (ARIC) Study. Nut Metab Cardiovasc Dis 2003; 13:256-66</td>
<td>In 282 out of 3,591 men who had heart attacks over 11 yr, plasma CE &amp; PL SFAs were higher</td>
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<tr>
<td>Yamagishi et al. Plasma fatty acid composition and incident heart failure in middle-aged adults: the Atherosclerosis Risk in Communities (ARIC) Study. Am Heart J. 2008; 156:965-74</td>
<td>In 197 out of 3,592 adults who developed heart failure, plasma CE &amp; PL SFAs were higher</td>
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# Plasma Saturated Fat Predicts Diabetes

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<tr>
<td>Wang et al. Plasma fatty acid composition and incidence of diabetes in middle-aged adults: the Atherosclerosis Risk in Communities (ARIC) Study. AJCN. 2003; 78:91-8</td>
<td>Depending upon whether you are looking at serum CE or PL, the risk of developing <strong>diabetes</strong> if you start out in the highest 20% is more that 2-to-3 times greater</td>
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<tr>
<td>Warensjo et al. Fatty acid composition of serum lipids predicts the development of the metabolic syndrome in men. Diabetologia. 2005; 48:1999-2005</td>
<td>↑ SFA was associated with development of <strong>metabolic syndrome</strong> 20 yr later</td>
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<tr>
<td>Hodge et al. Plasma phospholipid and dietary fatty acids as predictors of type 2 diabetes: interpreting the role of linoleic acid. AJCN. 2007; 86:189-97</td>
<td>In 3737 adults followed for 4 yr, those who developed <strong>diabetes</strong> had significantly greater plasma PL SFAs and stearic acid</td>
</tr>
<tr>
<td>Patel et al. Fatty acids measured in plasma and erythrocyte-membrane phospholipids and derived by food-frequency questionnaire and the risk of new-onset type 2 diabetes. AJCN. 2010; 92:1214-22</td>
<td>Both plasma and RBC palmitic acid correlate w/ risk of developing <strong>diabetes</strong>: top third &gt;2x more likely to get diabetes than bottom third</td>
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Saturated Fats

1) What is the association of dietary SFA intake and risk for chronic disease?

2) What is the association of plasma SFA level and risk for chronic disease?

3) What is the association between dietary SFA and plasma SFA; and the role of carbohydrate?
Overweight Men and Women with Atherogenic Dyslipidemia (n=40)

Low Fat Diet
~1500 kcal/day

Low Carb Diet
~1500 kcal/day

Saturated Fat = 12 g (208 g CHO)

Saturated Fat = 36 g (45 g CHO)
Despite being higher in saturated fat, a CRD decreases circulating levels of SFA.

RESEARCH ARTICLE

Effects of Step-Wise Increases in Dietary Carbohydrate on Circulating Saturated Fatty Acids and Palmitoleic Acid in Adults with Metabolic Syndrome

Brittanie M. Volk¹, Laura J. Kunces¹, Daniel J. Freidenreich¹, Brian R. Kupchak¹, Catherine Saenz¹, Juan C. Artistizabal¹,², Maria Luz Fernandez², Richard S. Bruno³, Carl M. Maresh¹, William J. Kraemer¹, Stephen D. Phinney⁴, Jeff S. Volek¹,³*

Six Feeding Phases

- Run-In
  - <50 g CHO/d
  - 84 g SFA/d

- C1
  - 47 g CHO/d
  - 76 g SFA/d

- C2
  - 83 g CHO/d
  - 71 g SFA/d

- C3
  - 131 g CHO/d
  - 61 g SFA/d

- C4
  - 179 g CHO/d
  - 49 g SFA/d

- C5
  - 251 g CHO/d
  - 32 g SFA/d

- C6
  - 346 g CHO/d

Week: 1 3 6 9 12 15 18 21
Testing: ↑ ↑ ↑ ↑ ↑ ↑ ↑ ↑
No significant change in serum SFA despite a near 3-fold decrease in intake.
MUFA, Desaturation of palmitic acid by delta 9 desaturase (SCD1)

Minimal dietary intake

Major product human lipogenesis

Higher proportions consistently associated with:

- Obesity
- Hypertriglyceridemia
- Hyperglycemia
- Inflammation
- Metabolic syndrome
- Type-2 diabetes
- Coronary disease
- Heart failure
- Incidence & aggressiveness of prostate cancer
You are what you save from what you eat!

Dietary Matrix

You are what you save from what you eat!

- Plasma SFA; ↓ 16:1
- Insulin Sensitivity
- Normolipidemia

Path Dependence on Dietary Carbs

- Low Dietary CHO
  - ↑ SFA Oxidation
  - ↓ SFA Synthesis

- High Dietary CHO
  - ↑ SFA Storage
  - ↑ SFA Synthesis

Metabolic Health Continuum

- ↓ Plasma SFA; ↓ 16:1
- Insulin Resistance
- Dyslipidemia
Consumption of carbs at levels that exceed a person’s ability to directly oxidize them contributes to increased dyslipidemia, circulating SFA & other cardio-metabolic problems.

Instead of emphasizing low SFA intake, a more rational & effective strategy would be to encourage the vast majority of people to find their ‘right’ level of carbs…then they can enjoy the pleasurable & health-promoting attributes of nutrient-dense foods containing SFA.
Thank You!