Moving Toward a Personalized Approach to Nutrition

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Department of Kinesiology
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Storrs, CT
Blue-Sky Thinking

Personalized...

to match specific dietary input and exercise strategies that target specific health outcomes within a person

Ground-Breaking Scientific Discovery

Lifestyle throughout the lifespan

Exercise Core  Nutrition Core

Genotype/Phenotype Assessment

Genes (static)  Gene Products (dynamic)  Biomarkers

Translational Discovery

Bio-informatics

Technology Transfer

Public Outreach/Education  Patents/Commercialization
The Status Quo

- Overweight: 68%
- Obese: 34%
- Metabolic Syndrome: 34%
- Impaired Fasting Glucose: 26%
- Diabetes: 11%

(366 million Worldwide)
The Principle of Human Carbohydrate Intolerance

Mal-Adaptation

Less Conserved Trait:
More and more people respond in an undesirable way

Conserved Trait:
Everyone responds in a similar favorable way

Keto-Adaptation

Carbohydrate Intake

High Variability

Low Variability
People vary in their ability to metabolize carbohydrate. Those who manage carbs well have more diet options. Those who don’t, have fewer options. Obese, IFG, MetSyn, T2D.

**Diabetes =** Side effect of consuming too much carbohydrate relative to a person’s tolerance.
But basic biochemistry and metabolism, and results of clinical trials all point to positive health effects of low carbohydrate diets.

Why such resistance to change?

- Scientists don’t like to admit they were wrong
- Common to criticize what we don’t understand
- Scientist view new information with avoidance
- Emotion trumps logic almost every time
- Willful ignorance
- Cognitive dissonance

Theories have four stages of acceptance:

1) This is worthless nonsense.
2) This is an interesting, but perverse, point of view.
3) This is true, but quite unimportant.
4) I always said so.

-J.B.C Haldane
The many facets of keto-adaptation

Health Performance Recovery

Carb-Based Metabolism

Glucose-Based Glycolytic Increased ROS

Diet/Carb-Driven Regulation

Fat-Based Metabolism

Fatty Acid-Based Mitochondrial Decreased ROS

HO

HO

HO
Insulin is the most important physiological inhibitor of lipolysis


Palmitate Flux

Insulin (pmol/L)
When we eat typical meals consisting of multiple foods, the body must process potentially a hundred or more different chemical signals.

- Macronutrients – exert some of the most powerful signals
- Carbohydrate:
  - Monitored more sensitively and acutely than fatty acids
  - Large range of intakes compatible with health
  - Triggers potent metabolic regulatory elements
Carbohydrate restriction improves the features of Metabolic Syndrome. Metabolic Syndrome may be defined by the response to carbohydrate restriction

Jeff S Volek¹ and Richard D Feinman*²

Dietary carbohydrate restriction induces a unique metabolic state positively affecting atherogenic dyslipidemia, fatty acid partitioning, and metabolic syndrome

Jeff S. Volek³, Maria Luz Fernandez⁴, Richard D. Feinman⁵, Stephen D. Phinney⁶
A ketogenic diet improves glucose, insulin & other traditional and emerging CVD risk factors

Percent changes in glucose, insulin, RBP-4, and markers of atherogenic dyslipidemia after 12 wk of a CRD or low fat diet (LFD) (**P<0.01, *P<0.05).
A ketogenic diet improves the postprandial lipemic & vascular response to a high fat meal

Volek et al. Lipids. 44:297-309, 2009
A ketogenic diet has anti-inflammatory effects

<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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</table>
If you decrease SFA, it matters what you replace it with!

Replacing 5% en of SFA with carbs ↑ coronary events

P value, test for heterogeneity = 0.51; combined hazard ratio (95% CI) = 1.07 (1.01, 1.14)
# Plasma Saturated Fat Predicts Heart Disease

<table>
<thead>
<tr>
<th>Study</th>
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<tbody>
<tr>
<td>Simon et al. Serum Fatty Acids and the Risk of Coronary Heart Disease. <em>Am J Epidemiol.</em> 1995; 142: 469-76</td>
<td>Men who had <strong>heart attacks</strong> had higher serum palmitic acid (16:0) and a 68% greater risk of heart disease</td>
</tr>
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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. <em>Nut Metab Cardiovasc Dis</em> 2003; 13:256-66</td>
<td>In 282 out of 3,591 men who had <strong>heart attacks</strong> over 11 yr, plasma CE &amp; PL SFAs were higher</td>
</tr>
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<td>Yamagishi et al. Plasma fatty acid composition and incident heart failure in middle-aged adults: the Atherosclerosis Risk in Communities (ARIC) Study. <em>Am Heart J.</em> 2008; 156:965-74</td>
<td>In 197 out of 3,592 adults who developed <strong>heart failure</strong>, plasma CE &amp; PL SFAs were higher</td>
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<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 diabetes if you start out in the highest 20% is more that 2-to-3 times greater</td>
</tr>
<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 diabetes 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 diabetes; top third &gt;2x more likely to get diabetes than bottom third</td>
</tr>
</tbody>
</table>
Low Fat Diet
~1500 kcal/day

Saturated Fat = 12 g (208 g CHO)

Low Carb Diet
~1500 kcal/day

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

Dietary Matrix

CHO

SFA

↓ Plasma SFA; ↓ 16:1
Insulin Sensitivity
Normolipidemia

↑ Plasma SFA; ↑ 16:1
Insulin Resistance
Dyslipidemia

Metabolic Health Continuum

You are not what you eat...
You are what you save from what you eat!

Path Dependence on Ambient CHO

Low Dietary CHO
↑ SFA Oxidation
↓ SFA Synthesis

High Dietary CHO
↑ SFA Storage
↑ SFA Synthesis
A dietary carb level that keeps ketones in the desirable range.

Typically, an adult eating 50 g/d of complex carbs in foods has serum BOHB of 1 mM (nutritional ketosis).

Some diabetics & insulin resistant individuals find they need to stay as low as 25 g/d carbohydrate to retain good control and weight stability.
The fate of carbohydrate...

Ingest Carbohydrate

Blood Glucose (~1-2 teaspoons)

Path to Health

Glycogen (~300-400 g)

Oxidation

Path to Metabolic Syndrome

Glycogen (~100 g)

Lipogenesis (fat synthesis)

Carbohydrate Intolerance
MUFA, Desaturation of palmitic acid by \( \Delta 9 \) desaturase (SCD1)

Minimal dietary intake

Major product human lipogenesis

Serum and tissue 16:1 levels are associated with adiposity & IR

People without high blood sugar, but increased 16:1 are at high risk of developing T2D (Wang et al. AJCN. 78:91-8, 03; Lindgarde et al. AJCN. 84:1009-13, 06)

Adipose 16:1 predicts ability to maintain weight after weight loss (Kunesova et al. Physiol Rev. 2012)
Cholesteryl Ester 16:1

16:1 drops sharply and uniformly for all individuals as fat is increased.
A highly controlled 21 week feeding study spanning 6 levels of carbohydrate intake

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
- 1/2 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)

Week

<table>
<thead>
<tr>
<th>Week</th>
<th>0-3</th>
<th>3-6</th>
<th>6-9</th>
<th>9-12</th>
<th>12-15</th>
<th>15-18</th>
<th>18-21</th>
</tr>
</thead>
<tbody>
<tr>
<td>FAT (%)</td>
<td>75%</td>
<td>75%</td>
<td>68%</td>
<td>60%</td>
<td>53%</td>
<td>40%</td>
<td>25%</td>
</tr>
<tr>
<td>CHO (%)</td>
<td>5%</td>
<td>5%</td>
<td>12%</td>
<td>20%</td>
<td>27%</td>
<td>40%</td>
<td>55%</td>
</tr>
<tr>
<td>CHO (g/d)</td>
<td>35 g</td>
<td>35 g</td>
<td>75 g</td>
<td>125 g</td>
<td>175 g</td>
<td>250 g</td>
<td>350 g</td>
</tr>
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</table>

2500-2800 kcal/d; Protein 1.8 g x Ref Wt (~20%en)

“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.”
Identification of diet-responsive gut bacterial and fungal communities and their association with metabolic parameters in individuals with metabolic syndrome

**Phenotype Responses**
- Weight loss
- Adiposity
- Inflammation
- Insulin resistance
- Lipoproteins
- Oxidative stress

**Significant variability** between and within individuals across different diet phases despite constant caloric intake

**The absence of linearity in fat loss** may be due to a number of factors, including alterations in **gut microbiota**
Clinical Applications of Low Carbohydrate Ketogenic Diets
Beneficial effects of ketogenic diet in obese diabetic subjects

Hussein M. Dashti · Thazhumpal C. Mathew · Mousa Khadada · Mahdi Al-Mousawi · Husain Talib · Sami K. Asfar · Abdulla I. Behbahani · Naji S. Al-Zaid

- Obese T2D w/ dyslipidemia
- Fed well-formulated low carbohydrate diet (20 and then 40 g/d) for 56 wk
- Meat, poultry, fish, eggs, cheese, vegetables, + 5 T olive oil providing 80-100 g/d protein
- Significant weight loss and metabolic improvements at 12 wk; continued improvement at 56 wk

Mol Cell Biochem 2007;302:249-56
Targeting insulin inhibition as a metabolic therapy in advanced cancer: A pilot safety and feasibility dietary trial in 10 patients


“Building on this well-designed clinical experiment should help us to better understand the impact of dietary changes on cancer growth and guide us to more effective treatment and prevention strategies.”

Andrea P. Myers, M.D. Ph.D.
Department of Medical Oncology, Dana Farber Cancer Institute
Division of Signal Transduction
Beth Israel Deaconess Medical Center, Boston, Massachusetts, USA

Lewis C. Cantley, Ph.D.
Division of Signal Transduction, Beth Israel Deaconess Medical Center, Department of Systems Biology, Harvard Medical School
Boston, Massachusetts, USA
Neuroprotective role of ketones in:
- Epilepsy
- Aging
- Alzheimer's disease
- Parkinson disease
- Mitochondrial disorders
- Brain trauma
- Others...autism, migraine, depression...
## Ketone Terminology

<table>
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<tr>
<th><strong>Ketones</strong></th>
<th>Small energy containing substances derived from fatty acids that provide fuel to the body.</th>
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<td><strong>Ketosis</strong></td>
<td>A metabolic state characterized by an increase in ketone production, usually marked by blood levels greater than 0.5 mmol/L.</td>
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<td><strong>Nutritional Ketosis</strong></td>
<td>The process of accelerating production of ketones through restriction of dietary carbohydrate.</td>
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<td><strong>Keto-acidosis</strong></td>
<td>A dangerous side effect of Type I diabetes where ketone production reaches levels above 10 mmol/L. This does not happen in non-diabetics.</td>
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<tr>
<td><strong>Keto-Adaptation</strong></td>
<td>The process the body goes through when it is exposed to limited carbohydrate and continuous elevated ketone levels. It is characterized by a shift to using predominately fat for fuel, and takes at least several weeks if not months to fully develop.</td>
</tr>
</tbody>
</table>
A natural part of human metabolism

Ketones, (BOHB) and acetoacetate (AcAc), are produced in liver and released into the blood

Archaic molecules

Metabolic program that is largely silenced since the advent of agricultural carbohydrates

BOHB is a preferred substrate for brain
Keto-adaptation dramatically alters the hypoglycemic threshold.

Provocative Effects of Ketones

- “Clean Burning Fuel”
- Less generation of reactive oxygen species (ROS)
- Increased antioxidant defense
- Greater efficiency in providing cellular energy
- Increase in work output, while a decrease in oxygen consumption

Insulin, ketone bodies, and mitochondrial energy transduction

KIYOTAKA SATO,* YOSHIHIRO KASHIWAYA,* CLAUDIA A. KEON,† NAOTAKA TSUCHIYA,* M. TODD KING,* GEORGE K. RADD,* BRITTON CHANCE,† KIERAN CLARKE,† AND RICHARD L. VEECH*†

The therapeutic implications of ketone bodies: the effects of ketone bodies in pathological conditions: ketosis, ketogenic diet, redox states, insulin resistance, and mitochondrial metabolism

Richard L. Veech*
Suppression of Oxidative Stress by β-Hydroxybutyrate, an Endogenous Histone Deacetylase Inhibitor

Tadahiro Shimazu, Matthew D. Hirschey, John Newman, Wenjuan He, Kotaro Shirakawa, Natacha Le Moan, Carrie A. Grueter, Hyungwook Lim, Laura R. Saunders, Robert D. Stevens, Christopher B. Newgard, Robert V. Farese Jr., Rafael de Cabo, Scott Ulrich, Katerina Akassoglou, Eric Verdin

6 December 2012 / Page 1/ 10.1126/science.1227166
BOHB, at millimolar levels, is an inhibitor of histone deacetylases.
There is a strong basis for tailoring diets to individuals

We can make a huge dent in the prevalence of obesity and related complications by providing credible science-driven personalize dietary guidance (using genetic and non genetic biomarkers)

Carbohydrate is a good place to start
Collaborators
William Kraemer, PhD
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Brian Kupchak, PhD
Linda Straussbaugh, PhD
Richard Feinman, PhD
Richard Bruno, PhD, RD
Maria Luz Fernandez, PhD
Rick Seip, PhD
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Richard Wood, PhD
Doug Bibus, PhD

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Mike Puglusi, PhD
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Catherine Saenz, MS
Laura Kunces, MS, RD
Dina Lajoie, RD

Thank you