Effects of Dietary Glycemic Load on Energy Expenditure: Results from the Framingham State Food Study

Cara B. Ebbeling, PhD
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Disclosure
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FINANCIAL DISCLOSURE
No relevant financial relationship exists

Background
- Biological factors strongly influence body weight
  - With weight loss, hunger increases and energy expenditure decreases
  - Physiological adaptations defend against long term weight change
- Genetic factors are known to affect body weight
  - Explain some of the variance in BMI
  - Cannot explain why the average person today, compared with 40 years ago, seems to be “defending” a much higher body weight
A Call for an End to the Diet Debates

As the obesity epidemic persists, the time has come to end the pursuit of the "ideal" diet for weight loss and disease prevention.

- The only consistent finding among the trials is that adherence... was most strongly associated with weight loss and improvement in disease-related outcomes.

- The pursuit of the ideal macronutrient content diet is unidimensional, ignoring 2 of the 3 major components of standard lifestyle interventions: behavioral modification and exercise. To consider lifestyle interventions as diets ignores their complexity, with behavioral modification as the piece that specifically addresses adherence.

- To evaluate dietary composition in the context of lifestyle interventions ignores the importance of conducting trials with high internal validity before aiming to test external validity.

- Feeding studies provide the best approach for maximizing internal validity when evaluating the effects of diets varying in macronutrient composition.

Diverse Audience

Practitioners – Public Health Professionals – Researchers
Faculty – Staff – Students – Media
Study Participants – Patients – People Interested in Healthful Nutrition

Balance
- Technical scientific "language"
- "Lay terms"

Linkages
- Data collection protocols
- Reported data

Reported Data
- Numbers
- Bottom line

Partnerships

Research team
- Boston Children’s Hospital
- Framingham State University

Food service team
- Sodexo

Assabet Valley Regional Technical High School

Framingham State Food Study: (FS)2 Specific Aim

To evaluate the effect of three diets varying widely in carbohydrate-to-fat ratio (high-carbohydrate, moderate-carbohydrate, low-carbohydrate) on energy expenditure during weight-loss maintenance, using a controlled feeding protocol.

Lay Terms
- Energy Expenditure → Calories Burned – "Burn Rate"

Hypothesis
- Total energy expenditure during weight-loss maintenance will differ among test diets through 20 weeks.

Primary Outcome
- TEE, assessed by doubly-labeled water methodology

ClinicalTrials.gov Identifier: NCT02068885

Published Manuscripts • (FS)2 • 2018


Practically speaking, what was the research question?

This suggests that calorie content of a diet is more important than composition.

“A calorie is a calorie!”

Does it really matter whether calories come from carbohydrate or fat?

**Methods**

**Study Design and Dietary Interventions**

**Primary Outcome**
- Total Energy Expenditure

**Secondary Outcomes**
- Resting Energy Expenditure
- Physical Activity and Sedentary Time
- Skeletal Muscle Work Efficiency
- Fasting Blood Draw: 1,5-Anhydroglucitol, Ghrelin

**Effect Modifier**
- Insulin Secretion

**Macronutrient Composition of Test Diets**

What proportion of calories came from carbohydrate vs. fat?

<table>
<thead>
<tr>
<th>Carbohydrate (% energy)</th>
<th>Hi Carb</th>
<th>MOD Carb</th>
<th>LO Carb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consistency and Differentiation</td>
<td>60</td>
<td>40</td>
<td>20</td>
</tr>
<tr>
<td>Added Sugar (% total carbohydrate)</td>
<td>15</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Fat (% energy)</td>
<td>20</td>
<td>40</td>
<td>60</td>
</tr>
<tr>
<td>Saturated Fat (% total fat)</td>
<td>35</td>
<td>35</td>
<td>35</td>
</tr>
<tr>
<td>Protein (% energy)</td>
<td>20</td>
<td>20</td>
<td>20</td>
</tr>
</tbody>
</table>

**Dinner Example**

**Hi Carb**
- Herb Grilled Salmon, 55 g
- Leaf Spinach, 100 g
- Long Grain & Wild Rice, 115 g
- Greek Yogurt, non-fat, 160g
- Dried cranberries, 20 g
- Whole Wheat Bread, 27 g
- Orange Sections, 180 g
- Milk, skim, 85 g
- Salt, 0.3 g

**MOD Carb**
- Herb Grilled Salmon, 90 g
- Leaf Spinach, 100 g
- Long Grain & Wild Rice, 100 g
- Cheddar Cheese, 10 g
- --
- Peanut, 6 g
- Orange Sections, 165 g
- Milk, 2%, 120 g
- --

**LO Carb**
- Herb Grilled Salmon, 80 g
- Leaf Spinach, 100 g
- --
- Cheddar Cheese, 15 g
- --
- Peanut, 33 g
- Orange Sections, 95 g
- Milk, 2.25%, 100 g
- Salt, 0.3 g
(FS)2 Kitchen

>160,000 meals!

Intervention Integrity

How well did we implement the intervention?

- Food service staff completed:
  - 95% of the intended spot weight checks
  - 97% of the intended packaged menu item checks

- For completed spot weight checks, comparing actual weights with target weights:
  - 67% of the menu items within narrow tolerance limits
  - ±0.1 g of target for items ≤10 g and ±0.5 g for items >10 g
  - 98% were within ±5 g deviation that would not compromise macronutrient differentiation

- For the packaged menu item checks:
  - 99% of the take-out meals contained all intended menu items

Methods

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Effect Modifier

- Insulin Secretion

Research Center

“The (FS)2 House”
**Isotope Enrichment**

**Back to Basic Chemistry!**

<table>
<thead>
<tr>
<th>Element</th>
<th>Mass Number</th>
<th>% Natural Abundance</th>
<th>Doubly-Labeled Water</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>1</td>
<td>99.965</td>
<td>2H₂¹⁺⁸O</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0.015</td>
<td></td>
</tr>
<tr>
<td>O</td>
<td>16</td>
<td>99.76</td>
<td></td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>0.204</td>
<td></td>
</tr>
</tbody>
</table>

Mass number: protons + neutrons in an atom
Isotopes: chemically identical, different number of neutrons (different mass)

**Isotopic Label Elimination**

*How do the isotopes leave the body?*

- **Carbonic anhydrase reaction**

  \[ \text{CO}_2 + \text{H}_2\text{O} \leftrightarrow \text{H}_2\text{CO}_3 \leftrightarrow \text{H}^+ + \text{HCO}_3^- \]

  Equilibrium between oxygen atoms in exhaled carbon dioxide and body water provides a biochemical basis for doubly-labeled water methodology.

- **Label elimination**

  \[ 2\text{H}_2^{18}\text{O} \rightarrow \text{C}^{18}\text{O}_2 \text{ and } \text{H}_2^{18}\text{O} \]

  \[ 2\text{H}_2\text{O} \]

**Methods**

**Study Design and Dietary Interventions**

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**Effect Modifier**

- Insulin Secretion

**Secondary Outcomes**

- Resting Energy Expenditure: Calories burned at rest

- Physical Activity and Sedentary Time
• Skeletal Muscle Work Efficiency
  Power generated per increase in energy expenditure above resting
  More calories burned at a given workload \(\rightarrow\) Lower efficiency (a good thing)

• Ghrelin
  Hormone produced primarily in the stomach
  Reported to lower energy expenditure and promote fat deposition
  Lower is better

• 1,5-Anhydroglucitol
  Biomeasure of compliance
  Marker of carbohydrate intake for people who do not have diabetes

Effect Modification

- Occurs when the effect of the exposure on an outcome differs depending on the level of a third variable, the effect modifier.

Effect Modifier | Outcome
--- | ---
Insulin Secretion | Total Energy Expenditure

Dietary Composition | Total Energy Expenditure

Significant effect modification would lend support to the Carbohydrate-Insulin Model.

• Oral Glucose Tolerance Test \(\rightarrow\) Insulin Secretion

75-gram oral glucose load

<table>
<thead>
<tr>
<th>Time (minutes)</th>
<th>Insulin-30</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>40</td>
<td>20</td>
</tr>
<tr>
<td>60</td>
<td>30</td>
</tr>
<tr>
<td>80</td>
<td>40</td>
</tr>
<tr>
<td>100</td>
<td>50</td>
</tr>
<tr>
<td>120</td>
<td>60</td>
</tr>
</tbody>
</table>

Median Insulin-30 at PRE: 114.6 \(\mu\)IU/mL

Participants

Flow of Participants Through the Trial
Participants Included in Statistical Analyses
PRE-Weight-Loss Participant Characteristics
Average weight loss, relative to PRE body weight, for participants randomly assigned to a diet arm

N=164
10.5 ± 1.7%

Intention-to-Treat Analysis
Excluded two participants
1) Developed a disqualifying medical condition, hypothyroidism
2) Provided unreliable doubly-labeled water data at START

N=162

Per Protocol Analysis
Included only participants achieving weight-loss maintenance (≤ 2 kg of START anchor weight)

N=120

Results Consistent for Other Biomeasures of Compliance

Serum 1,5-Anhydroglucitol

A) Intention-to-treat: n=162
B) Per protocol: n=120

Total Energy Expenditure

Doubly-Labeled Water Methodology
Total and Resting Energy Expenditure

Resting energy expenditure did not differ by diet group. Total energy expenditure was significantly higher with LO.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Dietary Intervention Group</th>
<th>N</th>
<th>Pre-Randomization START Mean (SE)</th>
<th>Change: AYHBD END - START</th>
<th>Trend Estimate (95% CI)</th>
<th>P between groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total energy expenditure kcal/day</td>
<td>HE</td>
<td>38</td>
<td>271 (17)</td>
<td>-182 (-380 to 17)</td>
<td>-0.001</td>
<td>0.69 (0.36 to 1.0)</td>
</tr>
<tr>
<td></td>
<td>MOD</td>
<td>39</td>
<td>277 (12)</td>
<td>26 (-44 to 96)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>LO</td>
<td>44</td>
<td>275 (26)</td>
<td>-38 (-170 to 13)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per Protocol</td>
<td>HE</td>
<td>38</td>
<td>146 (28)</td>
<td>29 (-4 to 86)</td>
<td>0.18</td>
<td>8.3 (-13 to 28)</td>
</tr>
<tr>
<td></td>
<td>MOD</td>
<td>38</td>
<td>197 (27)</td>
<td>28 (-2 to 35)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>LO</td>
<td>42</td>
<td>146 (26)</td>
<td>-53 (-28 to 28)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Physical Activity and Sedentary Time

MVPA was marginally higher with LO. Total physical activity and sedentary time did not differ by diet group.

Skeletal Muscle Work Efficiency

Skeletal muscle work efficiency did not differ by diet group.

Plasma Ghrelin

Ghrelin showed a steeper decline with LO compared to HI. (possible explanation for change in total energy expenditure)

Effect Modification by Insulin-30

Total Energy Expenditure

Power to achieve a relatively precise effect estimate for the primary outcome

Biomeasures indicating substantial and sustained differentiation between diets

 Doubly-labeled water methodology to assess total energy expenditure

Control for dietary protein and body weight

Design of diets to reflect realistic and healthful examples of different macronutrient compositions

Strengths

- One of the largest and longest controlled feeding studies
- Sufficient intervention duration to avoid confounding by transient metabolic adaptations
- Power to achieve a relatively precise effect estimate for the primary outcome
- Biomeasures indicating substantial and sustained differentiation between diets
- Doubly-labeled water methodology to assess total energy expenditure
- Control for dietary protein and body weight
- Design of diets to reflect realistic and healthful examples of different macronutrient compositions
Limitations

• Some non-compliance (free-living participants)
• Generalizability: Translation to public health (self-prepared meals)

Conclusions

• Dietary composition seems to affect energy expenditure independently of body weight.
• A low glycemic load high fat diet might facilitate weight loss maintenance beyond the conventional focus on restricting energy intake and encouraging physical activity.
• If metabolic benefits of reduced glycemic load diets are confirmed, development of appropriate behavioral and environmental interventions would be necessary for optimal translation to public health (generalizability, external validity).

Directions for Additional Research

• Examine the effects of glycemic load on body weight, with control of energy intake
• Compare diets aiming to reduce glycemic index at prevailing carbohydrate levels compared with restricting total carbohydrate
• Explore subgroup susceptibility based on insulin secretion and other biological factors
• Determine whether extreme carbohydrate restriction (ketogenic diet) confers unique advantages for obesity or specific conditions such as diabetes
• Explore the mechanisms relating dietary composition to energy expenditure

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Study Participants

Leadership

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SetPoint Health: David Blackburn
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Thank You!