How Low Can You Go? Evidence Update For Low-Carb Eating

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Disclosures

• Consultant for dietdoctor.com
• Consultant for Guideline Central

Learning Objectives

• Describe the low-carbohydrate eating pattern and the rationale behind it
• Summarize weight loss effects of low-carbohydrate eating plans
• Describe potential mechanisms of weight loss during low-carbohydrate eating
• Describe the effects of low-carbohydrate eating on health and risk factors
Outline

• Background on low-carbohydrate eating pattern
• Weight loss effects
• How weight loss occurs
• Health effects

Nutritional Therapy for Obesity
**Low Carbohydrate Ketogenic Diet (LCKD)**

- Initially, < 20 g of carbohydrates per day
  - Unrestricted amounts of meat and eggs
  - Four oz. hard cheese
  - Two cups salad vegetables
  - One cup low-carbohydrate vegetables

- Calories **not restricted**
- Carbohydrate intake slowly increased as weight goal approached
- Daily multivitamin, copious liquids, broth
Low Carb / High Fat Diet Rationale: The Role of Insulin

- Dietary carbohydrate (sugar or starch) raises serum glucose and insulin
- A carbohydrate restricted (high fat) diet reduces the diet contribution to serum glucose, which then lowers insulin levels
- Insulin is a potent stimulator of lipogenesis (fat storage) and a potent inhibitor of lipolysis (fat burning)
- Lowering insulin levels leads to burning of stored body fat, raising serum ketones and lowering body weight

How Low Can You Go? (Or...Are Carbohydrates Essential in Humans?)

What is known:
- Humans can endogenously synthesize carbohydrates
- Humans do not show signs of deficiency in the absence of dietary carbohydrates
- No reports of micronutrient deficiency syndromes in clinical trials of low carbohydrate ketogenic diets
- RDA for carbohydrates is 130g/day to ensure sufficient glucose for the brain
  -- However, when intake is <130g/day, the body meets energy needs of brain with endogenously produced glucose and ketones

Outpatient Low Carb Trials: Weight Loss

<table>
<thead>
<tr>
<th>Reference</th>
<th>Duration (mo)</th>
<th>Low-fat (kg)</th>
<th>Low-carb (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brehm 2003†</td>
<td>6</td>
<td>-3.9</td>
<td>-8.5*</td>
</tr>
<tr>
<td>Yancy 2004‡</td>
<td>6</td>
<td>-6.5</td>
<td>-12.0*</td>
</tr>
<tr>
<td>Samaha 2003†</td>
<td>132</td>
<td>-1.9</td>
<td>-5.8*</td>
</tr>
<tr>
<td>Foster 2003†</td>
<td>63</td>
<td>-5.3</td>
<td>-9.7*</td>
</tr>
<tr>
<td>Foster 2003†</td>
<td>63</td>
<td>-4.5</td>
<td>-7.3</td>
</tr>
<tr>
<td>Stern 2004‡</td>
<td>132</td>
<td>-3.1</td>
<td>-5.1</td>
</tr>
<tr>
<td>Dansinger 2005§</td>
<td>160</td>
<td>-3.0</td>
<td>-2.1</td>
</tr>
<tr>
<td>Gardner 2007†</td>
<td>311</td>
<td>-1.6</td>
<td>-4.7*</td>
</tr>
</tbody>
</table>

* p <0.05 for between-groups comparison.
For Gardner, comparison was the Zone diet.
RCTs ≥12 months: Low Carb vs Low Fat

<table>
<thead>
<tr>
<th>Study</th>
<th>Mean ± SD at baseline</th>
<th>Mean ± SD at end of study</th>
<th>Mean difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bueno NB, Br J Nutr, 2013</td>
<td>-0.9 ± 1.65</td>
<td>1.1 ± 2.00</td>
<td>-0.9 ± 1.65, -0.17</td>
</tr>
</tbody>
</table>

2-Year Low Carbohydrate Diet Studies

Shai I, NEJM, 2008.

How Weight Loss Occurs: Calories, Calories, Calories!

Calories are Reduced b/c Hunger is Less

<table>
<thead>
<tr>
<th>Study</th>
<th>Wt Loss (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fullness/Satiety</td>
<td>2.00 (4.00, 6.00)</td>
</tr>
<tr>
<td>Hunger</td>
<td>6.35 (0.01, 13.65)</td>
</tr>
<tr>
<td>Desire to Eat</td>
<td>-3.05 (0.25, 2.35)</td>
</tr>
</tbody>
</table>

How Weight Loss Occurs: A Little Bit of Water Loss

Mean Total Body Water, kg

Duration of Intervention

How Weight Loss Occurs: What About Metabolism?

Change in total energy expenditure (Kcal/day)

**Health Effects: Symptomatic Effects**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Low fat (n = 60)</th>
<th>Low carb (n = 59)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation</td>
<td>35%</td>
<td>68%</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Headache</td>
<td>40%</td>
<td>60%</td>
<td>.01</td>
</tr>
<tr>
<td>Bad breath</td>
<td>8%</td>
<td>38%</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Muscle cramps</td>
<td>7%</td>
<td>35%</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>7%</td>
<td>23%</td>
<td>.02</td>
</tr>
<tr>
<td>Weakness</td>
<td>8%</td>
<td>25%</td>
<td>.01</td>
</tr>
<tr>
<td>Rash</td>
<td>0%</td>
<td>13%</td>
<td>.006</td>
</tr>
</tbody>
</table>


**Comparison of Participant Completion Rates of Low-Fat vs Low-Carb Diet Studies**

Each point represents a comparison from one of 19 studies.


**Meta-Analysis: Low Carb vs Low Fat**

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of Trials</th>
<th>Net Difference Low Carb – Low Fat</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight, kg</td>
<td>22</td>
<td>-1.0</td>
<td>-2.2, 0.2</td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>18</td>
<td>-1.0</td>
<td>-3.5, 1.5</td>
</tr>
<tr>
<td>Diastolic BP, mmHg</td>
<td>18</td>
<td>-0.7</td>
<td>-1.6, 0.2</td>
</tr>
<tr>
<td>HDL-C, mg/dL</td>
<td>19</td>
<td>3.3*</td>
<td>1.9, 4.7</td>
</tr>
<tr>
<td>LDL-C, mg/dL</td>
<td>19</td>
<td>3.7*</td>
<td>1.0, 6.4</td>
</tr>
<tr>
<td>TG, mg/dL</td>
<td>20</td>
<td>-14.0*</td>
<td>-19.4, -8.7</td>
</tr>
</tbody>
</table>

*p ≤0.05 for net change. *Hu T, Am J Epidemiol, 2012.*
DIRECT (PI-Iris Shai) Study – 6 years


Glucose and Insulin Response to 300 kcal Meal After 10 days on Diet


*Glucose AUC lowest for low-carb diet (p = .001).
*Insulin AUC different for each diet (p = .001)

Network Meta-analysis Comparing Diet Effects on Glycemia in Type 2 DM

- 56 trials enrolling 4937 participants comparing 9 diets:
  - Low-fat, Vegetarian, Mediterranean, high-protein, moderate-carbohydrate, low-carbohydrate, control, low GI/GL, Paleolithic

- "For reducing HbA1c, the low-carbohydrate diet was ranked as the best dietary approach (SUCRA: 84%), followed by the Mediterranean diet (80%) and Paleolithic diet (76%) compared to a control diet."

Other Benefits in Patients with Diabetes

**RCT using group medical visits (GMVs)**
- Low-carbohydrate weight loss program vs medication intensification to improve glycemia
  - Both improved HbA1c by ~1%
  - Additionally, low-carbohydrate program led to:
    - Greater weight loss by 3.7 kg
    - Reduction in diabetes medication vs increase in comparison arm
    - Transient greater improvement (during greatest weight differences) in diabetes-related distress
    - 50% reduction in hypoglycemia events

_Yancy WS Jr, JAMA Intern Med, 2019._

**Client RJT** 64 yo WF with sleep apnea, diabetes, fatty liver, hypertension, mild CAD

<table>
<thead>
<tr>
<th>Year</th>
<th>Weight</th>
<th>BP meds</th>
<th>DM meds</th>
<th>Lipid meds</th>
<th>Hb A1c</th>
<th>ALT</th>
<th>Trig</th>
<th>CRP</th>
</tr>
</thead>
<tbody>
<tr>
<td>2007</td>
<td>200</td>
<td>Atenolol</td>
<td>Metformin</td>
<td>Colesevelam</td>
<td>7.5</td>
<td>91</td>
<td>277</td>
<td>1.34</td>
</tr>
<tr>
<td>2010</td>
<td>199</td>
<td>Clonidine</td>
<td>Metformin</td>
<td>Niacin</td>
<td>7.2</td>
<td>94</td>
<td>198</td>
<td>1.08</td>
</tr>
<tr>
<td>2011</td>
<td>182</td>
<td>Carvedilol</td>
<td>Metformin</td>
<td>Colesevelam</td>
<td>7.2</td>
<td>61</td>
<td>299</td>
<td>1.04</td>
</tr>
<tr>
<td>2013</td>
<td>151</td>
<td>HCTZ</td>
<td>Metformin</td>
<td>Colesevelam</td>
<td>5.6</td>
<td>17</td>
<td>85</td>
<td>0.42</td>
</tr>
<tr>
<td>2016</td>
<td>144</td>
<td>Lisinopril</td>
<td>Metformin</td>
<td>Niacin</td>
<td>5.5</td>
<td>19</td>
<td>89</td>
<td>0.42</td>
</tr>
<tr>
<td>2018</td>
<td>138</td>
<td>Lisinopril</td>
<td>Metformin</td>
<td>Fish oils</td>
<td>5.4</td>
<td>21</td>
<td>84</td>
<td>0.42</td>
</tr>
</tbody>
</table>

**Low Carb Take Home Points**
- Low carbohydrate intake leads to spontaneous reduction in calorie intake and lower insulin levels
- Body fat breaks down into ketones → used for energy
- Early diuresis requires adequate intake of fluid and salt
- Weight loss mildly better on average than comparison
- If carbohydrate is added back, do it gradually
- Blood pressure and triglycerides decrease, HDL increases
- LDL does not typically increase BUT it does at times
- Blood sugar decreases profoundly--reduce medications at diet start!
Compared with low-fat eating patterns, low-carbohydrate eating patterns typically lead to which of the following changes in serum lipid profiles?

A. Lower HDL cholesterol level
B. Higher HDL cholesterol level
C. Lower LDL cholesterol level
D. Higher triglyceride level
E. Higher triglyceride: HDL ratio
Active Learning Question #1

Compared with low-fat eating patterns, low-carbohydrate eating patterns typically lead to which of the following changes in serum lipid profiles?

A. Lower HDL cholesterol level
B. Higher HDL cholesterol level
C. Lower LDL cholesterol level
D. Higher triglyceride level
E. Higher triglyceride: HDL ratio

Rationale: Multiple randomized clinical trials in various populations and meta-analyses of these trials have shown that low-carbohydrate eating patterns lead to higher HDL cholesterol and lower serum triglycerides whereas low-fat eating patterns lead to lower LDL cholesterol.


Active Learning Question #2

There are data to support that weight loss from a low-carbohydrate eating pattern is related to which of the following?

A. Water loss from use of glycogen stores
B. Water loss related to lower insulin levels
C. Reduced calorie intake
D. Increased energy expenditure
E. All of the above

Rationale: Water loss occurs particularly in the early phase of a low-carbohydrate eating pattern and is thought to be due to a combination of water release that occurs as glycogen stores are used and changes that occur in the kidney when insulin levels are lower resulting in greater release of sodium and water. Multiple studies have shown that low-carbohydrate eating leads to reduced appetite and calorie intake. Studies by Ebbeling show increased energy expenditure measured by doubly labelled water occurs on a low-carbohydrate eating plan.

Ebbeling CB et al. BMJ. 2018;363.
Current Treatment Options for Obesity

<table>
<thead>
<tr>
<th>Risk/Cost</th>
<th>Potency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lifestyle</td>
<td>Includes nutrition, physical activity, and behavioral modification</td>
</tr>
<tr>
<td>Lifestyle + Medication</td>
<td>Includes lifestyle, and anti-obesity medications</td>
</tr>
<tr>
<td>Surgery</td>
<td>(In order of lowest risk/cost and potency): LAGB &lt; VSG &lt; RNY</td>
</tr>
</tbody>
</table>

Potency includes many factors, such as the amount, rate, and sustainability of weight loss, and the long-term resolution of adiposopathy and fat mass disease. Potency varies greatly for each individual (i.e., long-term adherence to a lifestyle program can be as potent as gastric bypass surgery).

The Role of Ketones

- Ketone bodies: molecules that deliver energy
- Ketones can be used by all cells except erythrocytes, cornea, lens, retina
- Ketone levels increase when dieting
  - Fed state: 0.1 mmol/L
  - Overnight fast: 0.3 mmol/L
  - Low-carb diet—induction: 1–3 mmol/L
  - > 20 days fasting: 10 mmol/L
  - Diabetic ketoacidosis: 25 mmol/L
- Serum pH did not decrease below 7.37 in a study performing arterial blood gas analyses

Are Carbohydrates Essential in Humans?

Definitions:
- **Physiological essentiality** - substance that is indispensable for life (e.g., cholesterol)
- **Nutritional essentiality** - substance that is indispensable in the diet (e.g., leucine, linoleic acid, vitamin A, calcium, copper)
  - required in the diet for growth, health, and survival
  - inadequate intake results in characteristic signs of a deficiency disease
  - signs of deficiency are prevented only by the nutrient or a specific precursor of it, not by other substances
- Nutrients that can be removed from the diet without causing growth failure or disease are classified as nonessential


Tondt J, Nutr Res Rev, In Press,
RCTs Comparing LC vs LF Diets

Meta-Analysis: Before/After Low Carb Effects

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<tr>
<th>Variable</th>
<th>No. of Reports</th>
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*p ≤0.05 for net change. Santos FL, Obes Rev, 2013.

Variability of Change in Weight

Heart Disease Risk for Types of Fat

Risk for replacement of X% of energy from carbohydrate by fat.

Hu et al. NEJM, 1997. (Nurses’ Health Study)

Meta-analysis: Association of Saturated Fat with Heart Disease and Stroke

Siri-Tarino PW, Amer J Clin Nut 2009

Meta-analyses: Saturated Fat Intake and Heart Disease

Schwingshackl L, BMJ Open, 2014 (RCTs of secondary prevention: 12 trials, N=7150)
• Reduced fat or modified fat diets did not reduce all-cause mortality, CHD mortality, or CV events

Siri-Tarino, Amer J Clin Nut, 2010 (Prospective cohort studies: 16 studies, N=347,747)
• Saturated fat and CHD RR 1.07 (95% CI 0.96 to 1.19)

Schwingshackl L, BMJ Open, 2014 (RCTs of secondary prevention: 12 trials, N=7150)
• Reduced fat or modified fat diets did not reduce all-cause mortality, CHD mortality, or CV events

Siri-Tarino, Amer J Clin Nut, 2010 (Prospective cohort studies: 16 studies, N=347,747)
• Saturated fat and CHD RR 1.07 (95% CI 0.96 to 1.19)

Chowdhury R, Ann Intern Med, 2014 (Prospective cohort studies: 32 studies, N=530,525)
• Saturated fat and CHD RR 1.02 (95% CI 0.97 to 1.07)

de Souza, BMJ, 2015 (Prospective cohort studies: 12 studies, N=230,080)
• Saturated fat and all-cause mortality RR 1.67 (95% CI 0.99 to 1.03)
• Saturated fat and CHD mortality RR 0.97 (95% CI 0.93 to 1.01)
• Saturated fat and incident stroke RR 1.02 (95% CI 0.98 to 1.07)
• Saturated fat and type 2 diabetes RR 1.06 (95% CI 0.96 to 1.16)

Hooper L, Cochrane, 2015 (RCTs of primary or secondary prevention: 12 trials, N=54,000+)
• Saturated fat and all-cause mortality RR 0.97 (95% CI 0.93 to 1.01)
• Saturated fat and CHD mortality RR 0.96 (95% CI 0.93 to 1.00)
• Mean serum total cholesterol lowered
• Total saturated fat and all-cause mortality RR 0.89 (95% CI 0.84 to 0.95)
• Total saturated fat and CHD mortality RR 0.89 (95% CI 0.84 to 0.95)

Harcombe Z, Br J Sports Med, 2017 (Cohorts 7 studies; N=339,090; mean f/u=11.9y)
• Mean serum total cholesterol lowered
• Total saturated fat and all-cause mortality RR 0.99 (95% CI 0.93 to 1.05)
• Total saturated fat and CHD mortality RR 0.98 (95% CI 0.93 to 1.03)

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• Total saturated fat and CHD mortality RR 0.98 (95% CI 0.93 to 1.03)
Predicted Changes in Blood Cholesterol based on Types of Fat Intake

Based on replacement of 5% of energy as carbohydrate with fatty acid.


Systematic Review Of Diabetes

13 trials met criteria:
- <45% carbohydrate
- 2 to 26 week duration


Network Meta-analysis Comparing Diet Effects on Glycemia in Type 2 DM

- Size of nodes: proportional to total N allocated to each diet
- Thickness of lines: proportional to number of studies of each direct comparison