The Case for, and against the Ketogenic diet

Sangeeta Pradhan, RD, LDN, CDE

Copyright 2019, Sangeeta Pradhan, RD, LDN, CDE. All rights reserved.

Disclaimer: The material presented here is based upon the available research at this point in time. It is understood that there may be changes in the evidence that occur over time.

Objectives

• Describe the pathophysiology of nutritional ketosis and how this differs from normal metabolism
• Describe the carb-insulin theory of obesity
• Compare and contrast the epidemiological data and that from RCTs that support or refute a ketogenic diet (KD)
• Discuss the evidence supporting the metabolic and neurological benefits of KD
• Describe screening and monitoring criteria for a KD
• Describe the safety and efficacy of KDs
• Review the adverse effects of KDs
• Analyze the available evidence to draw appropriate conclusions

Richard Feynman quote:

• “The first principle is that you must not fool yourself and you are the easiest person to fool. After you’ve not fooled yourself, it’s easy not to fool other scientists.”

Carb trends 70s-late 90's

Did we just turn yet another theory on its head?

The old (now obsolete) pyramid
What is the Carbohydrate-insulin model of obesity?

- Increased carbs
  - Proportionately higher insulin levels
  - Sequesters fat in adipose tissue and prevents body from accessing it
  - Decreased availability of FFA = cellular internal starvation
  - Adaptive decrease in energy expenditure, increased food intake

Ketogenesis, gluconeogenesis in the liver

- Gluconeogenesis
- Glucose undergoes glycolysis
- Pyruvate
- Fatty acids
- Acetyl CoA
- TCA cycle
- Acetoacetate
- Acetone
- Beta-hydroxybutyrate
- Amino acids
- Oxaloacetate
  - Decreased with low CHO
  - Diverted to produce glucose for extra hepatic tissue esp. brain
  - Acetyl CoA builds up, triggers ketogenesis

Normal metabolism: Adequate CHO, adequate insulin

- Adequate glucose
- Pyruvate
- Acetyl CoA
- Fatty acids
- Ketones
  - < 0.3 mMol/L

What is Nutritional Ketosis? (Fats burn in the flame of carbs)

- Induced by low carb diet (20-50 grams per day)
- Ketones >0.5 mmol, ~0.5-3 mmol seen
- May take few days to weeks to get into adaptive phase
- During DKA, Ketones could be upwards of 10 mmol
- NK is not dangerous and ketones will not cross about 5 mmol
- pH remains normal at ~ 7.4
- BG remains within physiological levels (why?)

Formation of ketone bodies

- Normally ketones < 0.3 mMol/L
Brain switches to ketones for fuel during starvation.

Ketone bodies as a fuel for the brain during starvation

Source: Oliver E. Owen

Biochemistry and Molecular Biology Education, Volume 33, Issue 4
First published: 03 November 2006

Contrasting BG, ketone levels w/normal diet, KD and DKA

<table>
<thead>
<tr>
<th>Blood Levels</th>
<th>Normal Diet</th>
<th>Ketogenic Diet</th>
<th>Diabetic Ketosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose (mg/dL)</td>
<td>80–120</td>
<td>60–80</td>
<td>&gt;300</td>
</tr>
<tr>
<td>Insulin (µU/L)</td>
<td>6–23</td>
<td>6.6–9.4</td>
<td>≈0</td>
</tr>
<tr>
<td>KB conc (mmol/L)</td>
<td>0.1</td>
<td>7/8</td>
<td>&gt;25</td>
</tr>
<tr>
<td>pH</td>
<td>7.4</td>
<td>7.4</td>
<td>&lt;7.3</td>
</tr>
</tbody>
</table>

Source: Ketogenic Diet for Obesity: Friend or Foe?

Progressive rise in ketone levels

Fasting state
- Ketone (mEq/L): 0.1
- Ketone (mmol/L): 0.1–0.3

Fasting (weeks)
- Ketone (mEq/L): 5–7
- Ketone (mmol/L): 0.5–3.0

Very low carb diet (post-exercise)
- Ketone (mEq/L): 10–20+
- Ketone (mmol/L): 1.0–5.0

Insulin resistance along a continuum= Carb intolerance?

Carb intolerant
- Prediabetes
- Type 2 DM
- Metabolic syndrome
- Obesity

Carb tolerant
- Insulin sensitivity
- Athletes
- BMI wnl

The fate of glucose depends upon whether you are insulin sensitive or insulin resistant

Skullmen's glycogen: 300–400 gms. Carbs gets oxidized in muscle or stored as glycogen in insulin sensitive subjects

Carbohydrates converted to liver glycogen, ~300 gms; (Dietary glucose)
**Keto-adaptation occurs after sustained nutritional ketosis over consecutive weeks**

- **Ketones:** Water soluble compounds made from beta fatty acid oxidation
- **Ketosis:** A metabolic state with blood levels >0.5 mmol/L
- **Nutritional ketosis:** Ketosis produced from excessive restriction of carbs, forcing the body to use ketones vs glucose as fuel. Some experts argue that calorie restriction is also necessary.
- **Ketoacidosis:** Excessive production of ketone bodies, with blood levels > 10 mmol/L, seen in uncontrolled Type 1 DM
- **Keto-adaptation:** Shift in metabolism from using glucose to fatty acids and ketones as a fuel source—may take several weeks of sustained ketosis

---

**Dietfits RCT: The Case against**

The DIETFITS RCT assigned 609 participants to either a healthy, whole foods low fat or healthy, low carb diet for 12 months with 22 counseling sessions with a dietitian. No significant weight-loss differences were seen between the low-fat and low-carb groups. Neither genetics nor insulin production could predict weight-loss success on either diet. No significant differences between groups for most other health markers. For isocaloric, isoprotein diets, neither low-fat nor low-carb is superior when it comes to weight loss.

---

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

- **ARIC study**
- **Sweet spot is 50-55% carbs**
- **U shaped curve, < 40% carbs, >70% conferred mortality risk**
- **Low carb dietary patterns w/animal derived protein associated with higher mortality**
- **Low carb dietary patterns w/plant derived protein associated with lower mortality**
- **The food source modulates mortality rate!**

---

**Link between protein type and all cause mortality, cause-specific mortality, NHANES III**

- **2 large prospective US studies**
- **Higher animal protein intake associated with higher mortality**
- **Plant protein inversely associated with mortality**
- **Substitution of plant protein for animal protein, especially from processed red meat, was associated with lower mortality**
- **Does not prove cause-effect, co-relational study**
- **Another meta-analysis supported long-term harm and no CV protection w/LCD, but the observational studies were limited.**
Case against: Health benefits of eating carbs, the right ones

- Artificial intestine or human gut simulator
- Fecal samples from donors to recreate this bacterial environment
- A balanced Western diet, vs a no-carb, no-protein diet made exclusively of fats
- Gut bacteria metabolize undigestible polysaccharides
- Decreased production of short-chain fatty acids and antioxidants
- Changing to a fat-only diet, led to a substantial decrease in the production of SCFA and antioxidants

Case against: High fat diet induces endotoxemia that originates from the gut

The type of fat matters in animal studies

- High Fat markedly and rapidly alters the gut microbiota.
- The types of lipids mice consume affect the composition of their gut microbiota.
- This influences whether the animals develop obesity-related inflammation.
- Mice fed a high-lard diet developed signs of metabolic disease, while mice fed fish oil remained healthy.

Effect of high fat diet, restored with Oligo fructose in mice

Are fiber famished bacteria linked to poor health? Does a KD support adequate fiber intake?

Long term research in rats: the case against
Short-term impact of a classical ketogenic diet on gut microbiota in GLUT1-Deficiency syndrome

A pilot study on 6 patients on KD compared microbiota composition before and after 3 months on diet. There were no statistically significant differences at 3 months in Firmicutes and Bacteroidetes. Statistically significant increase in Desulfovibrio, associated with gut mucosa inflammation linked with animal fat consumption. Warrants more studies.

Case for: Low-carbohydrate diets v. low-fat diets on weight and CVD risk factors: meta-analysis of RCTs

- 11 Studies (1369 participants) met the inclusion criteria:
  - The LC diet had a carbohydrate intake of 20-40 gm/day <20% of kcals
  - Previously healthy subjects
  - LC group had a greater reduction in weight loss compared to LF group
  - However, LDL increased by .16 mmol as well
  - The beneficial changes of LC diets must be weighed against the possible detrimental effects of increased LDL-cholesterol.

Is saturated fat really bad? Where do we stand? Pooling some studies

- The total matrix of the food is more important than just its fatty acid profile in predicting CHD risk
- Overall dietary patterns emphasizing whole grains, vegetables, fruits, and nuts trump over a focus on specific macros and macro-nutrient composition
- Evidence from "adequately controlled" RCTs: SFA and n-6, CHD
- Meta-analysis of prospective, epidemiological studies shows no significant evidence that saturated fat is associated with an increased risk of CHD.
- To reduce atherogenic dyslipidemia, it is suggested that we avoid refined carbs, and reduce excess adiposity.

12 week study comparing 2 hypocaloric diets (Case for)

- 12 week study comparing 2 hypocaloric diets in 40 folks with atherogenic dyslipidemia
  - CRD (%C:F:P = 12:59:28) and LFD (56:24:20)
- CRD: glucose: (-12%), Insulin (-50%), HDL (13%), Tchol/HDL ratio (-14%)
- Favorable response to LDL particle size, post prandial lipemia
- Despite 3x saturated fat intake, SFA intake in TG decreased and levels + significant decrease in palmitoleic acid.

24 week trial How does LCD stack up against LCKD? (case for)

- LCD vs VLCKD
- LCD: VLCKD
- 102 w/diabetes
- Weight, BMI, WC, BG, A1C, lipids, uric acid measured before and periodically during the 24 weeks
- Both diets had beneficial effects that were more significant for folks on the LCKD.
Combination Biphasic Ketogenic Mediterranean Diet and Mediterranean Diet Maintenance for long term weight loss success.

- Study showed that:
  - Brief periods of ketogenic diet separated by longer periods of maintenance w/Mediterranean diet, led to successful long-term weight loss and improvements in health risk factors

Efficaciousness of keto diets

- Weight loss
- Appetite reduction set to increased satiety
- Decreased fat storage and increased fat mobilization
- Increased metabolic efficiency, decreased RQ
- Improved glucose tolerance via reduced insulin levels in IR folks

Ketones as metabolites

- SCFA such as butyrate from fiber fermentation by gut bacteria are HDAC inhibitors, help in the expression of pro-survival genes in neurological disorders
- May inhibit tumor growth
- Prevent neuronal injury and death caused by free radicals
- Shift from excitatory to inhibitory neurotransmitters thus reducing seizure activity?
- Upregulates transcription of anti-oxidant genes epigenetic modulators or “switches”.
- Caveat: limited, shorter duration studies in human beings, studies are in vitro or in animal models

Ketones as super fuels

- Burning fat produces less CO2, so decreased respiratory quotient
- Ketones are considered a “clean burn” as they produce fewer free radicals
- They are considered a “super fuel” because they produce more ATP than glucose oxidation
Defining characteristics of ketones

- Water soluble
- Cross the blood brain barrier, unlike the fatty acids they are made from
- Important fuel source for the brain during starvation
- Glycogen stores have to be depleted before they are produced
- High intensity exercise
- Synthesized in the liver, not oxidized in the liver
- Act like hormones with favorable effects in other organs: epigenetics modulators
- Easily metabolized by heart and skeletal muscle
- Beneficial under conditions when normal glucose metabolism is disrupted such as AD, cancer

Preliminary research in various disease states

Patient selection: The Pre-KD assessment requires:

- Detailed history and physical examination,
- Specific laboratory tests*, nutritional assessment, and counseling of the patient and family members.
- Some therapeutic meds have high carb content

Monitoring

Labs should be evaluated at pre-diet baseline and after initiation at intervals determined by a healthcare team (often q 3 months)

- CMP
- Fasting lipid panel
- CBC with platelets
- Liver profile
- Ionized calcium, magnesium, phosphate, selenium, zinc.
- Vitamins A, E, B12 and D, copper, folate, free and total carnitine, pre-albumin, β-hydroxybutyrate, urinalysis and urine organic acids.

Absolute contraindications and Risk factors

Contraindications
- Pancreatitis
- Liver failure
- Disorders of fat metabolism
- Primary carnitine deficiency
- Porphyrias
- Pyruvate kinase deficiency

Complicating risk factors
- Renal stones
- Severe dyslipidemia
- Severe GERD
- Poor oral intake
- CMPY
- Chronic metabolic acidosis

Diet initiation

- There isn’t one specific keto diet
- Patients can enter ketosis with varying levels of dietary carbohydrates
- Finger stick testing w/glucometer is the best strategy
- Well formulated diets generally have 5-10% carbs, 15-20% protein and 75-80% fats.
- KD “experts” discourage calorie counting and suggest eating fat to satiety which often means people “under-eat” and lose weight.
- Most clinical studies have included MVI and mineral supplements along with K and Na supplements.
Getting into NK

Generally ~50 grams or less of digestible, and absorbable carbs.

Some could be in NK at 70 grams, IR folks may need < 30 - 40 grams.

Measuring ketones rather than counting grams of carbs.

The appropriate carb level may be a moving target.

On a 2000 kcal KD, relative macro %, compare against AMDR

- Protein 1.2 - 1.5 g/kg
- Fat: consumed to "satiety"
- Not encouraged to count calories

Carbs, 5-10% < 50 gm
- 5-15 gm proteins based foods
- 10-15 gm veggies
- 5-10 gm fruits
- 5-10 gm miscellaneous

Monitoring

Monitoring urine ketones to ensure diet is being managed correctly.

After a few weeks in ketosis, blood ketones should be monitored.

Precision Keto or Keto Mojo strips are ~99 cents each.

BG, albumin, total protein, cholesterol, triglycerides, serum creatinine q 3 months.

Monitoring, annually

Tests
- Renal Ultrasound
- Bone density
- Carnitine
- Selenium levels
- ECG

Prevention of:
- Nephrolithiasis
- Osteoporosis
- Hyperlipidemia
- Carnitine deficiency
- CMPY

Adverse effects

- Only one of the clinical trials has assessed symptomatic side effects of an LCKD.
- Study showed subjects following an LCKD were more likely to experience side effects than those following a LF diet.
- The change to an LCD in patients on meds with diabetes or HTN should be made by clinicians familiar with the effects of the diet.
- Medication reduction may be required to avoid hypoglycemia or hypotension.

Short and long term effects

Short-term effects:
- Nausea/vomiting
- Constipation
- Dehydration
- Anorexia
- Lethargy
- Hypoglycemia

Long-term effects:
- Disruptions in lipid metabolism
- Severe hepatic steatosis
- Hypoproteinemia
- Mineral deficiencies
- Increased redox imbalance
- Cardiomyopathy
- Nephrolithiasis
Side effects

- Upon starting KD, 4-10 days of the “keto flu” resulting from decreased circulating volume from decreased insulin and electrolyte shifts
- Insulin levels decline as carbs decrease
- Anti-natriuretic effect of insulin causes Na loss (next slide)
- As glycogen reserves deplete, you lose water
- Dehydration w/loss of water and Mg, Ca, K along with risk of kidney stones
- Lethargy, depressed mood and irritability, constipation, diarrhea, headache and muscle cramps

Insulin drops, Na gets excreted

Nutrient deficiencies

- Fewer whole grains, legumes, fruits and starches
- Deficient in Ca, Vitamin D, Se, Mg, Phosphorus, Fe
- Prebiotics from resistant starches, root vegetables
- Lack of fiber: constipation and adverse effects on gut microbiome (most concerning)
- Small risk of kidney damage with excess Nitrogen excretion if excess protein is mistakenly consumed (if mistaken for “Atkins”)

Post-ketogenic diet assessment

Safety

- Couple of studies* have raised safety concerns
- Concerns raised about impact of high fat diets on lipids
- Increased HDL, decreased TGs
- Increased LDL remains a concern, some studies show larger LDL particles
- Inhibition of cholesterol synthesis through HMG-CoA reductase, activated by insulin
- High levels of acidifying AA may raise BP
- Dyslipidemia, fatty liver, GIT, reduction in beta cells and inflammation in mice
- Very long term KD in children with intractable epilepsy may lead to a progressive reduction of bone mineral content

Unanswered questions??

- Lack of fiber, excess fat and potential dysbiosis
- Nature of the carbs, % fat in some studies
- Long term effects, safety issues
- Do the health benefits extend to higher risk folks?
- For which disease conditions do the benefits outweigh risks?
- Safe for diseases with impaired fat and protein metabolism?
Some short term metabolic benefits

Available long-term research still very limited, most studies have spanned 8-24 weeks, some without control groups, what happens 10, 20 years later?

Nutrient deficiencies, lacking food groups

Relative lack of fiber, SCFA impact on microbiome is concerning

Very rigid not realistic, keto-flu

In or out of ketosis, palatability and acceptance

Should be reserved as a (short-term) option only for those w/refractory weight gain* (patients should be encouraged to follow a whole foods meal plan first esp. if they have been strict diets with poor nutrient quality at all/*)

Transition to Mediterranean diet is advised

Careful monitoring and patient selection required (not a “do it yourself” diet)

Robust, long term studies in human subjects required

Harvard’s Chan school of Public Health

To Keto or Veto??

Appendix: Case against: How does a HFHC stack up against high fiber, isocaloric AHA?

Two groups (n=10 each), of normal, healthy, lean subjects (BMI < 25 kg, comparable mean age, BMI, sex

Group 1: HFHC diet for group 1 (carbs 41%, 17% protein, 42% fat)

Group 2: AHA diet, isocaloric rich in fruit and fiber (58% CHO, 15% protein, 27% fat)

Overnight fast

Increase in inflammatory cytokines, ROS, LPS seen with HFHC meal, not seen with the AHA meal

Triggers an inflammatory cascade leading to inflammatory cytokines, IL-6 and IL-8

Limitation of study: very small, one post prandial response

Appendix: 70/20/10 macros

1 egg + 2 tsp olive oil + ½ cup cooked veggies

1/3 avocado or 1/3 cup nuts

2 oz protein + 1 tbsp olive oil + 1 cup salad + ½ cup cooked veggies

1/3 cup nuts + Greek yogurt 8oz

2 oz protein + 1 T Olive oil + 1 cup salad + ½ cup zoodles

1/3 cup nuts

1500 calories with 10% =150 calories from carbs, 20% protein = 75 grams and 116 grams of fat

Conclusion

Bibliography