The Evidence for a Ketogenic Diet

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History and origin

- 1920’s Hugh Conklin DO + Faith Healer
  - Epilepsy caused by intoxication of brain from the intestines
  - Fasting/Water Treatment up to 25 days
- Lead to studying of metabolic changes in fasting
- 1921 Mayo Clinic
  - High fat low carbohydrate diet + adequate protein for growth
- 1938 Rise of phenytoin, ketogenic diet fell out of favor
- 1990’s Ketogenic diet resurgence
  - Jim Abrahams “First Do No Harm”
What is A Ketogenic Diet?

- Very low carbohydrate: <20g of carbs/day
- High fat: 70-90% of fat in kcal
  - Variability; tailored to patient response and need
- Adequate protein (0.8g/kg/day) 20% of kcal
  - Variability; tailored to patient response and needs
- Natural calorie restriction due to satiety
- Intermittent fasting
The Ketogenic Diet

- **Fasting / Starvation**
  - Limited carbohydrate stores
  - De novo synthesis, from amino acids and proteins
  - Glycerol from Fatty Acids

- **Study demonstrating β-Hydroxybutyrate and acetoacetic acid adequate energy sources for CNS**
  - No decrease in psychometric testing or EEG changes
The Ketogenic Diet

- Consider effects of β-Hydroxybutyrate
  - As an energy source and as a substrate

- Consider effects of a reduction in carbohydrates in diet
  - Carbohydrates as an energy source and as a substrate

- Consider effects of a subsequent reduction in endogenous insulin use
The Ketogenic Diet

- **Mitochondria**
  - Mitochondrial health and its ties to healthy aging
  - ATP: fundamental energy source, majority produced in mitochondria, ETC

- **Most mtROS occurring due to the mtETC**
  - Near proximity to the mtDNA, leading to higher chances of dysfunction
  - Moderate mtROS will cause adaptive changes to accommodate oxidative stress, however an excess needs to be avoided
The Ketogenic Diet

- Ketosis
  - Indirectly promotes Mitohormesis and adaptive changes
  - Increases Reverse Electron Transport
  - Source of Acetylene CoA shifts from Glycolysis to Ketosis and production of β-Hydroxybutyrate
  - FADH2/NADH ratio doubles
  - mtROS increases, promoting Mitohormesis and adaptive changes for increased oxidative stress
The Ketogenic Diet

- **Ketosis**
  - Directly promotes antioxidant effects
  - Ketone bodies utilized as an energy source for the CNS
  - β-Hydroxybutyrate as a substrate
    - Class I and II Histone Deacetylases inhibit FOXO3α and Metallothionein II → results in increased oxidation of proteins and lipids
    - This is inhibited with β-Hydroxybutyrate, decreased measure of protein carbonyls and lipid peroxidases in studies[^1]
The Ketogenic Diet

- Ketosis
  - Increased fat diet, fatty acid availability
  - F. acids upregulate mitochondrial Uncoupling Proteins
  - Function of UCPs includes dissipation of protons in the mtETC independent of ATP synthase (decreased Reverse Electron Transport)
  - Results in lowering excessive mtROS
The Ketogenic Diet

Carbohydrates

- Decreased amounts result in decreased insulin release and utilization
- Reduction of carbohydrate intake results in shift towards fatty acid oxidation
- Lower carbohydrate availability decreases glycogen stores \(\rightarrow\) stimulates AMPK
- AMPK promotes glucose uptake
- Glut 4 receptors downregulate
The Ketogenic Diet

- **Insulin**
  - Utilization is decreased
  - Downregulating SREBP and ChREBP, lipogenic genes
  - Decreased hepatic lipogenesis
  - Inhibits AMPK: decreases Malonyl-CoA

- **Malonyl-CoA**
  - Inhibits the rate limiting step in F.A. oxidation
  - Prevents carnitine acyl transferase in mitochondria
  - This is decreased with decreased insulin demand

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<th>Insulin Activity</th>
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<td>Promotes</td>
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<td>- GLUT 4 upregulation</td>
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<tr>
<td>- Anabolism</td>
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<tr>
<td>- Glycogen storage</td>
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<tr>
<td>- Protein synthesis</td>
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<td>- SREBP1c*</td>
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<th>Inhibits</th>
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<td>- Lipolysis</td>
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<td>- Gluconeogenesis</td>
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Metabolic Syndrome

- NCEP ATP III definition:
  - ≥130/85 mmHg or drug treatment for hypertension
  - Waist ≥102 cm (men) or ≥88 cm (women)
  - ≥1.7 mmol/L (150 mg/dL) or drug treatment for elevated triglycerides
  - <1.0 mmol/L (40 mg/dL) (men); <1.3 mmol/L (50 mg/dL) (women) or drug treatment for low HDL-C
  - ≥5.6 mmol/L (100 mg/dL) or drug treatment for elevated blood glucose
Metabolic Syndrome

- Increased weight is a major risk factor:
  - 60% of those with Metabolic Syndrome were obese
  - 22% overweight

- Insulin resistance, abdominal obesity, elevated BP, elevated Triglycerides, decreased HDL

- Primary treatment goal: weight loss
Metabolic Syndrome

- Metabolic syndrome correlated with high levels of SFAs when looking at plasma fatty acid composition.

- Production of an inflammatory response
  - Increased TNF-α, IL-1β, IL-6 expression in the hypothalamus → leptin and insulin resistance
  - Higher SFA results in higher CVD incidence.

- Carbohydrate restricted diets reduce demand for insulin, decreasing lipogenesis and improving lipid profiles
  - Substitution for SFAs
  - Less inflammatory
  - More monounsaturated fatty acids / polyunsaturated fatty acid in the lipid profile
  - Increased levels of arachidonate, improved insulin sensitivity, reduction in pro-inflammatory responses.
Metabolic Syndrome

- A portion of the Ketogenic Diet includes reduction of carbohydrate intake
  - Reduces Insulin utilization and Glucose availability for storage
  - Promotes F.A. oxidation

- Reduction in carbohydrates without noticeable effect until reduction to 26% of diet
  - Decrease in triglycerides, ApoB, LDL molecules
  - At this level, comparable to weight loss alone
Metabolic Syndrome

- Carb restricted diets compared to Low fat diets⁹
  - CRB with x2 amount of weight loss, decreased abdominal fat mass
  - Improved glycemic control, FBG decreased by 10% on average
  - Presence of serum ketones indicating lipolysis
  - Reduction of atherogenic dyslipidemia (Triglycerides decreased by 51% and increase in HDL 13%)
Metabolic Syndrome

- Long term effects of the Ketogenic Diet in obese population
- Factors measured: weight, BMI, Total Cholesterol, LDL, HDL, Triglycerides, FBG, Urea, Creatinine measured at 8, 16, 24 weeks
- Gradual decrease in weight, sustained HDL elevation, LDL decrease
- No significant long term side-effects up to 2 years noted with dietary implementation
Neurologic Benefits
How the brain benefits

- Acetoacetate $\rightarrow$ preferred for synthesis of neural lipids
- Increased energy stores, mitochondrial biogenesis, metabolic efficiency by bypassing complex I
- Increased GABA
- Decrease of ROS by inducing glutathione peroxidase activity and increase mitochondrial uncoupling proteins
- Anti-inflammatory effects
  - Peroxisome proliferator-activated receptor α inhibits proinflammatory transcription of nuclear factor –κB and activation protein-1
  - Intermittent fasting $\rightarrow$ ↑ cytokine interferon-γ protects against excitotoxic cell death
  - Autophagy
How the brain benefits

- Slows aging
  - Mitochondrial density increased
  - Reduces oxidative stress
- Prevents Apoptosis
  - Intracellular calcium buffer, calbindin is increased; prevention of prodeath signal (clusterin)
- Carbohydrate restriction benefits
  - Protective against glutamate-induced and oxidative stress-induced neuronal death in cell culture
  - Induces stress proteins that suppress ROS production
  - Stabilize intracellular calcium
  - Maintain mitochondrial function
Epilepsy

- Antiepileptic effect associated with increase acetone + acetoacetate
  - Mechanism unknown
- Glucose/calorie restriction + ↑ FFA activates $K_{ATP}$ channels → protective against metabolic stressors (i.e. hypoxia, ischemia, hypoglycemia) & regulate seizure threshold
- Polyunsaturated Fatty Acids reduce neuronal hyperexcitability, decrease ROS
- Metabolic efficiency: up to 46% increase in mitochondria = Mitochondrial Biogenesis
Epilepsy

- **Adult:**
  - Two small case series of adult patients, ketogenic diet and a modified Atkins diet reduced seizure frequency by 50% or more in half of patients with drug resistant epilepsy.

- **Children**
  - If on ketogenic diet >1 year at 3-6 year follow up >90% resolution of intractable epilepsy
  - If on ketogenic diet for 6 months or less, 32% had >90% decrease in seizures and 22% were seizure free
  - No controls in the study
Ischemic & Traumatic Brain Injury

- Ketogenic diet had up to 58% reduction in cortical contusion volume at 7 days (rat study)
- 48 hr fast in a 4 vessel occlusion for 30 min was protective against neuronal loss in striatum, neocortex, hippocampus (rat)
- Cortical neuron loss prevention in ketogenic diet with insulin-induced hypoglycemia
- Exogenous β-hydroxybuterate reduces brain damage and improve neuronal function in models of brain hypoxia, anoxia, and ischemia
Ischemic & Traumatic Brain Injury

- Glutamate-mediated excitotoxicity $\rightarrow$ ROS $\rightarrow$ apoptosis $\rightarrow$ necrosis
  - Acetoacetate attenuation of ROS prevents apoptosis
- Intracellular calcium overload $\rightarrow$ apoptosis
  - Calbindin increased in ketogenic diet which buffers intracellular calcium
- Mitochondrial dysfunction
- Increased intake of $\beta$-hydroxybuterate
Parkinson’s Disease

- Uncontrolled clinical study showed 43% mean reduction in Unified Parkinson’s Disease Rating Scale (42q on function) after 28 days on ketogenic diet.
- Subjective perception of “moderate to very good” improvement from symptoms
- Increased consumption of essential fatty acids associated with lower risk of developing Parkinson’s disease
- Improved oxidative phosphorylation → enhanced ATP production
- Bypassed complex I derangements
Amyotrophic Lateral Sclerosis

- Mitochondrial dysfunction leads to neuronal cell death
  - Ketogenic diet promotes ATP synthesis
  - Bypass inhibition of complex I in mitochondrial respiratory chain
- Transgenic mice on ketogenic diet
  - Lost motor function later than controls
  - Weighed more
  - More motor neurons at end of study
  - No extension in survival time
Alzheimer’s Disease

- 43 day ketogenic diet resulted in 25% reduction in soluble amyloid β(1-40) & (1-42) but no cognitive improvement in rats
  - Protects against amyloid toxicity
- Improved motor function in transgenic mice with Alzheimer's
- Exogenous ketone (AC-1202) for 90 days administration show improvement in ADAS- Cognitive Behavior scores in mild to moderate Alzheimer’s disease patients without APOE4 allele
  - Provides alternative, possibly superior fuel source, in the setting of decreased brain glucose metabolism
Cancer

- Warburg effect - aerobic glycolysis; Deplete tumor’s metabolic energy source to fuel activity
- Ketogenic diet markedly decrease tumor growth rates (calorie restriction)
- Reduction of ROS production in malignant glioma cells
- Reduction of genes encoding signal transduction pathways and growth factors in glioma growth
- Case studies
  - Medium Chain Triglyceride diet showed benefit in pediatric patients with advanced malignant astrocytoma
  - Elderly female with glioblastoma multiforme concomitantly treated w/ radiotherapy, temozolomide, and a ketogenic diet resulted in undetectable tumor after 2 months
- Improved emotional functioning, less insomnia
- Does not apply to all cancers
Other considerations

- Autoimmune Disorders
- Gastrointestinal Pathologies
- Migraine
- Psychiatric disorders
- Autism
- Mitochondrial disorders (peds)
- Athletic Applications
Advice you can trust

Are you interested in keto or low carb to revolutionize your health? We'll make your journey simple and inspiring. We show no ads, take no industry money and sell no products. Instead we’re funded by the people. Welcome to Diet Doctor. More
2. What to eat on a keto diet

Here are typical foods to enjoy on a ketogenic diet. The numbers are net carbs per 100 grams. To remain in ketosis, lower is generally better:


Dietdoctor.com