Ketogenic Diet and Epilepsy

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What are ketones and the ketone diet?
Back to the basics: Ketones

Blood sugar, which comes from carbohydrates, is the body’s main source of energy. An absence of insulin circulating the blood causes us to start breaking down stored fat into molecules, aka ketones. The liver plays an important role in this process called ketosis.

Once reaching ketosis, most cells will use ketone bodies to generate energy until the next time you eat carbohydrates again.
3 Types of Ketones

**ACETOACETATE**

\[ CH_3C(OH)C(=O)CH_2COOH \]
- technically, a ketone -

**BETA-HYDROXYBUTYRIC ACID**

\[ CH_3CH(OH)CH_2CO_2H \]
- technically, not a ketone -

**ACETONE**

\[ (CH_3)_2CO \]
- technically, a ketone -
- **Acetoacetate (AcAc)**
  - Created from the breakdown of fatty acids
  - Either converted into BHB or turned into acetone
- **Beta-Hydroxybutyric acid (BHB)**
  - Formed from acetoacetate
    - Technically not a ketone because of its structure, but is considered as one within the keto diet
- **Acetone**
  - Created as a side product of acetoacetate
  - Breaks down quickly
  - Is removed from the body through the waste or the breath
Ketosis - The Production of Ketone

- Uses body fat instead, an alternative source of fuel
- Ketones are made in the liver to create energy from body fat
When does this process of Ketosis occur?

- Ketosis
  - Fasting
  - After prolonged exercise
  - During starvation
  - Eating a low-carb ketogenic diet
Ketogenic Diet: A Fat-Fueled Brain
**BRAIN FUEL**

**GLUCOSE**

Your brain is designed to metabolize glucose 99% of your life.

**KETONE BODIES**

- **Acetone**
- **Acetoacetate**
- **2-Hydroxybutyric acid**

Your brain resorts to ketone body metabolism as an emergency backup fuel when carbohydrates are limited.
To carb or not to carb...

Cutting back on or completely eliminating most carb sources in the ketogenic diet, including:

- Whole and processed grains
- Candies and baked goods
- Fruit juices and sugary soft drinks
- Refined sugars
- Fruits
- Starches like potatoes and pastas
- Beans and legumes

Also, eating moderate amounts of protein and, most importantly, high amounts of fats to rev up fat burning
A brief picture summary to recap...

The Ketogenic Diet

Follow a strict low-carb diet → Liver processes fat into ketones → Ketones fuel your cells

(It's more complex than that, but you get the idea)
Seizures and the Ketogenic Diet
Can the ketogenic diet help mediate epilepsy?

- Mechanisms of KD (the ketogenic diet) and ketones are not clearly understood because no single mechanism can explain how it works
  - However, new data supports ketones having anti-seizing actions
Anti-seizure & neuroprotective properties of ketone bodies

- Keith (1933, 1935)
  - 1st documented testing
  - Acetone and acetoacetate, but not β-hydroxybutyrate, protected rabbits against seizures induced by thujone, a constituent of wormwood oil and a known antagonist of γ-aminobutyric acid, type A (GABAA) receptors
Rho et al. (2002)

- Tested the effects of the ketones (not β-hydroxybutyrate) and found the ketones, Acetone and Acetoacetate, and both stereoisomers, d-(-)- and l-(+) of BHB (β-hydroxybutyrate) protected against sound-induced seizures in the Frings audiogenic seizure-susceptible mouse model.
- With the exception of the d-(-)-isomer of BHB, Acetonate and ACA were anticonvulsant and confirmed that the activity of l-(+) BHB was due to dibenzylamine, a chemical contaminant.
- The study indicate that the anticonvulsant efficacy of the ketogenic diet may be due in part to the direct actions of ACA and acetone.
Evidence of inhibitory properties of ketone bodies in vitro
Inconsistent Results

- Acute hippocampal slices from mice and rats
- Juge et al. (2010): high concentration of acetoacetate reduced miniature excitatory synaptic currents (mEPSC) in CA1 neurons
- Other groups: physiologically relevant concentrations of acetoacetate and β-hydroxybutyrate had no effect on field potentials, population spikes or long-term potentiation
  - No reduction of seizure-like events (SLEs) induced by pentylenetetrazole or low-magnesium when exposed to acetoacetate or β-hydroxybutyrate
- Pretreatment with β-hydroxybutyrate and acetoacetate prevented synaptic dysfunction of all ages
- β-hydroxybutyrate restored synaptic function during glucose deprivation, but only in rats 30 days old or younger
- Inconsistencies may be due to in vivo problems (eg. exposure to ketone bodies was too short)
Studies Using Organotypic Hippocampal Slice Cultures

- **Samoilova et al. (2010) Study**
  - Provoked SLEs using 5 different conditions
    - 4-aminopyridine
    - Low-magnesium
    - Bicuculline
    - High frequency stimulation
    - Oxygen-Glucose deficiency (OGD)
  - Application of β-hydroxybutyrate for 3 days had no effect on any conditions except OGD

- **Kim et al. (2015) Study**
  - Hippocampal slices from epileptic Kcna1-null mice that developed spontaneous SLEs
  - 2 week incubation of a mixture of acetoacetate and β-hydroxybutyrate
    - Reduced the frequency, duration, and intensity of SLEs
Molecular Targets

- Neurotransmitter Systems
- Mitochondria
- ATP-sensitive potassium (KATP) channels
- Histones
- Anti-inflammatory
GABA and the Neurotransmitter Systems

- Ketone bodies have shown to increase GABA levels in rats injected with β-hydroxybutyrate
- Ketone body metabolism decreases aspartate, increasing GABA synthesis
- Acetoacetate inhibits SLC17 vesicular neurotransmitter transporters
  - Acetoacetate was found to be as efficacious and potent an inhibitor of other SLC17 transporters, VNUT (vesicular nucleotide transporter) and VEAT (vesicular excitatory amino acid transporter)
    - VNUT, which loads ATP into vesicles, this action seems paradoxical because it would lower synaptic inhibition. However, this loss of inhibition may be outweighed by the release of glutamate and GABA synthesis

Glutamate Decarboxylase

\[ \text{HOOC} - \text{NH}_2 - \text{COOH} \rightarrow \text{HOOC} - \text{NH}_2 \]

\[ \text{unc-25} \]

\[ \text{γ-Aminobutyric Acid (GABA)} \]
Mitochondria

- “Powerhouse of the cell”
- Regulates synaptic transmission via 3 mechanisms
  1. Production of ATP
  2. Generation of reactive oxygen species (ROS) signaling and regulation of cellular functions
  3. Sequestration of cytosolic calcium
     a. Taking calcium from the fluid within the cell
- Any issues can cause a dysregulation across synaptic, neuronal, and network activities
Krebs Cycle/Citric Acid Cycle/ Tricarboxylic Acid (TCA) Cycle

- Ketone bodies in KD are a more efficient fuel source than glucose
- Ketone bodies outcompete glucose for neuronal acetyl-CoA by inhibiting glycolytic flux upstream of pyruvate kinase, which catalyzes the final steps of glycolysis
- Ketone body metabolism maximizes the redox difference between the mitochondrial NAD⁺/NADH couple of Complex I and the coenzyme Q/QH₂ couple of Complex II, resulting in an increased proton gradient, enhanced potential for ATP synthesis and increases in the free energy of ATP hydrolysis
- Essentially, ketone bodies modulate mitochondrial respiration and ATP synthesis under stressful conditions
Membrane Permeability Transition Pore (mPTP)

- Regulate the homeostatic status of the mitochondria
- Too much calcium or reactive oxygen species (ROS) can leave the mPTP open
  - Inhibition of ATP production, mitochondrial swelling, and the release of calcium, ROS, and cytochrome c into the cytosol triggering cell death
- Acetoacetate and β-hydroxybutyrate can inhibit mPTP opening indirectly via decreased ROS levels as well as facilitate enhanced mitochondrial respiration, NADH oxidation and ATP production
ATP-sensitive potassium (KATP) channels

- Inward rectifying Katp channels are inhibited by ATP and open when ATP levels are low
  - Represent a direct link between membrane excitability and the metabolic state of the cell
  - Indirectly activated by acetoacetate and β-hydroxybutyrate and decreases neuronal excitability
- β-hydroxybutyrate-induced increased ATP production has been proposed as a form of metabolic autocrine regulation that ultimately reduces neuronal and network excitability and nothing gets fired out
Histone (Lysine) Deacetylases and Gene Regulation

- β-hydroxybutyrate inhibits histone deacetylases (HDAC)
  - HDAC-enzymes that remove acetyl groups from lysine residues on histones and other proteins such as transcription factors and other enzymes
    - Deacetylation of histones loosens the tight wrapping of DNA, thus enabling gene transcription, whereas deacetylation of transcription factors or enzymes can increase or decrease their activity
  - β-hydroxybutyrate-induced HDAC inhibition resulted in up-regulation of genes in the FOXO3A transcription factor network, including the anti-oxidants catalase, mitochondrial superoxide dismutase (SOD2) and metallothionein 2, collectively leading to reduced oxidative stress in kidney cells
  - Co-application of acetoacetate and β-hydroxybutyrate were earlier found to increase catalase activity in hippocampal slices during oxidative stress

- HDAC part of corepressor complex that inhibits peroxisome proliferator-activated receptor (PPAR)γ, a transcription factor that also regulates many antioxidant genes.
  - Acetoacetate increased PPAR γ expression and in in vivo experiments, genetic or pharmacologic loss of PPAR γ reduced the anti-seizure effects of the KD
Anti-inflammatory Effects

- Seizures induce inflammation and increase levels of cytokines and chemokines
  - secreted from both activated glia and neurons in many experimental models of acute and chronic seizures and increase neuronal and network hyperexcitability

- β-hydroxybutyrate regulates 2 inflammatory mechanisms
  - Hydroxy-carboxylic acid receptor 2 (HCA2) = G protein-coupled receptor activated by β-hydroxybutyrate
    - Induced strokes in mice and found that mice fed a KD or was give β-hydroxybutyrate developed smaller infarcts than the control
  - The innate immune sensor NOD-like receptor protein 3 (NLRP3) inflammasome is a multi-protein complex that controls the activation of caspase-1 and the release of the pro-inflammatory cytokines IL-1β and IL-18 in macrophages
    - When damage associated molecular patterns occur, macrophages lose cytoplasmic K+ and causes the assembly of the inflammasome
  - β-hydroxybutyrate stops NLRP3 inflammasomes from coming together by preventing K+ efflux
Ketogenic Diet Treatment in Adults with Refractory Epilepsy

Klein et al. (2010)
Introduction

- Seizures in ~35% of patients with epilepsy fail to respond to antiepileptic drug (AED) treatment
- The Ketogenic Diet has been shown to be effective in children with refractory epilepsy
  - Study with KD children
    - 7-15% → seizure free
    - 25-40% → 90% seizure reduction
    - 55% → +50% seizure reduction
- Although the diet is relatively safe and comes with very little risk, it has not been extensively clinically tested in adults
  - Assumptions that adults would not be as compliant as children in regards to the complex dietary restrictions
Methods

● Subjects: 12 men and women (aged 25-65) with failed treatment of 3+ AED, with seizures occurring more than once every two months
  ○ Excluded participants if they had renal, liver, cardiovascular/cerebrovascular, mitochondrial or fatty acid metabolism disease

● Completed pre-treatment evaluations with an epileptologist, a nutritionist and a nurse
  ○ Subjects were given meal plans that included 3 set meals and 2 snacks

● The ketogenic diet was initiated during a 45 day hospitalization
  ○ 24-48 hours of fasting
  ○ Slow increase in calories over a three day period

● Subjects were taught to measure ketone levels in their urine using Ketostix
Methods: Ketogenic Diet

- 3:1 ratio diet
  - \([\text{fat}] : [\text{carbohydrate + protein}]\)
  - Chosen instead of the 4:1 diet usually tested in children based on palatability
- An average of 1600 kcals per day
  - Supplemented with vitamins, calcium and phosphorus
- Subjects were seen by an epileptologist and a nutritionist 1 week, 3 weeks, 5 weeks, and 2 months after discharge
  - After this, they saw an epileptologist every month and a nutritionist every 3 months
- If seizures did not improve by 2 months, subjects were switched to a 4:1 ratio diet
Evaluation Methods

- Seizure frequency was measured at 4 months
  - During each visit, seizure frequency, treatment compliance and use of antiepileptic drugs was evaluated
- Physical examinations, BMI measurements
- Patients used Ketostix to check ketone concentration in urine 1-3 times per day
- Quality of life and alertness measured
  - Patient-Weighted Quality of Life in Epilepsy Inventory (QOLIE31-P)
  - Epworth Sleepiness Scale (ESS)
- Laboratory evaluations included: complete blood count (CBC), comprehensive metabolic panel (CMP), beta-hydroxybutyrate (BOHB - ketone), fasting lipid levels, glucose and insulin levels, glycosylated hemoglobin, leptin levels, AED levels and urine calcium levels
Results - Subject Disposition

- 12 subjects enrolled; 23 subjects screened but declined participation due to reluctance to give up regular diet

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>Sex</th>
<th>Age</th>
<th>Epilepsy type</th>
<th>Age at epilepsy onset</th>
<th>Seizure type</th>
<th>No. of past AEDs</th>
<th>Current AEDs (mg/day)</th>
<th>Comorbidity</th>
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<td>7</td>
<td>GTC, Abs, Myo</td>
<td>8</td>
<td>TPM 1000</td>
<td>Obesity, depression, (T_4)</td>
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<td>F</td>
<td>40</td>
<td>PGE</td>
<td>3</td>
<td>GTC, Abs, Myo</td>
<td>7</td>
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<td>Obesity, OSA, hypertension, peptic ulcerative disease, (T_4)</td>
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<td>3</td>
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<td>PGE</td>
<td>23</td>
<td>GTC</td>
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<td>TPM 350</td>
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<td>10</td>
<td>GTC, Abs, Myo</td>
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<td>LEV 5000, LTG 600</td>
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<td>2</td>
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<td>OXC 1800, LTG 425, TGB 10</td>
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<td>CPS/GTC</td>
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<td>OXC 600</td>
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* PGE, primary generalized epilepsy; LRE, localization-related epilepsy; Ab, absence seizures; Myo, myoclonic seizures; GTC, generalized tonic–clonic; CPS, complex partial seizures; SPS, simple partial seizures; CBZ, carbamazepine; LEV, levetiracetam; LTG, lamotrigine; OXC, oxcarbazepine; PGB, pregabalin; TGB, tiagabine; TPM, topiramate; VPA, valproate; \(T_4\), hypothyroidism; OSA, obstructive sleep apnea; VNS, vagus nerve stimulation.
Results - Subject Disposition

- Discontinued treatment during first 4 months (psychosocial reasons or lack of efficacy)
- 3 subjects stopped after 8, 24, and 25 months (wanted regular food)
- 9 subjects elected to continue past 4 months
- Stopped at 7 months (pregnant)
- Still in treatment
## Results - Seizure Control

### Table 2

Monthly frequency of only generalized tonic-clonic and complex partial seizures for 4-month baseline, KD treatment months 1–4, and whole treatment duration.

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>Treatment duration (months)</th>
<th>Seizure frequency/month</th>
<th>% Change</th>
<th>AED change on KD</th>
<th>Compliance*</th>
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<td>Baseline</td>
<td>KD months 1–4</td>
<td>Whole treatment</td>
<td>KD months 1–4</td>
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<td>100</td>
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<td>0.75</td>
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<tr>
<td>Mean (SD)</td>
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<td>2.07</td>
<td>0.99</td>
<td>0.91</td>
<td>38.44</td>
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</table>

* Compliance grading: 0 = none; 1 = mild, 2 = moderate, 3 = complete.
* Subject dropped out after 4 days and is not included in data analysis.
* P = 0.05.
* P = 0.04.
Results - Seizure Control

75% Seizure reduction within the first month of treatment in 25% of patients

10 subjects saw improvement in seizures

- 25% of subjects (3) saw a 75% reduction in seizures
- 42% of subjects (5) saw +50% reduction in seizures in the first four months of treatment
- 50% of subjects (6) saw +50% reduction in seizures over the entire experiment
Results

- **Antiepileptic Drugs**: held constant in 9 of 11 subjects who were taking them
  - Two subjects significantly reduced AED consumption
  - One subject discontinued all AED consumption and continued on the ketogenic diet alone

- **Weight**: 
  - Mean weight declined by 38.7lb (212.8lb → 171.1lb)
  - Mean BMI reduced from 33.6 to 27.5 kg/m² (18.3% reduction)
  - Weight loss associated with reduction in mean leptin levels in all participants whose leptin was measured (10/10)

- **Quality of Life**: both QOLIE-31-P and ESS scores rose non significantly
Discussion

- This study of KD in adults with refractory epilepsy resulted in an overall improvement in seizure frequency, with 25% of participants seeing a 75% reduction in 4 months.
- The treatment was well tolerated with good compliance.
- Demonstrated that a ketogenic diet in adults is feasible.

Limitations: small sample size (n=12), uncontrolled selection of subjects and the open-label, non-randomized design.
Ketogenic Diets and Alzheimer’s Disease

Lange et al. (2016)
Rationale for the use of ketogenic diets in AD

- The switch to a keto deficient, high carbohydrate diet during the development of agriculture may play a role in the development of AD
  - See “High carbohydrate diets and Alzheimer’s disease,” (Henderson 2003)
  - Height and lifespans were severely shortened during much of the agricultural revolution (Mehta 2001)
    - Ancient Indian literature chronicles the agricultural revolution to be an “abomination”
    - Was a consequence of necessity from overhunting, not ingenuity
  - ApoE4 is much lower in historically agricultural societies
Rationale for the use of ketogenic diets in AD

- Both high carb diets and the E4 allele suppress lipid metabolism and when combined, greatly increase the occurrence of heart disease and AD (Henderson 2003)
  - Glucose hypometabolism is an early sign of AD (Chen et al, 2011)
  - The brain is only 2% of our body weight but uses 20% of our energy

- Almost entirely glucose
  - Fatty acids cannot cross the Blood-Brain Barrier
- Why would we want to reduce the amount of glucose further with a ketogenic diet??
“Ketone bodies when present at sufficient concentrations to saturate metabolism can support most, if not all, basal (non-signaling) neuronal energy needs and up to approximately half of the activity-dependent oxidative needs of neurons”

- Ketone bodies - hydroxybutyrate and acetoacetate can act as glucose replacements
  - Ketone bodies produce more energy than glucose (more ATP)
  - This bypasses the impaired insulin function that reduces glycolysis
  - Ketone metabolism appears unaffected by early ad (Castellano et al., 2015)
- Ketones also “improve mitochondrial function, reduce the expression of apoptotic and inflammatory mediators[,] increase the activity of neurotrophic factors … protect neurons against multiple types of neuronal injury and to have mitochondrial effects similar to those following calorie restriction”
Ketone bodies in a cell culture model of AD

- 1-methyl-4-phenylpyridinium (aka MPP), a heroin analogue is toxic to dopaminergic neurons in the substantia nigra (Kashiwaya et al. 2000)
  - inhibiting the mitochondrial NADH dehydrogenase multienzyme complex
  - Indistinguishable from Parkinson's disease
- Amyloid protein fragment Aβ_{1–42} kills hippocampal cells, producing AD like effects
- D-β-hydroxybutyrate, a ketone body, protects neurons from both the above.
- A - anti-TH-stained mesencephalic neuronal cell control
- B – cells with 5 μM MPP added
- C – cells with 5 μM MPP and 4 mM ketone bodies
- D – cells with 4 mM ketone bodies

- A - 18-day embryonic rat hippocampal tissue (control)
- – after 14 h exposure to 5 μM Aβ₁₋₄₂
- C – after 14 h exposure to 5 μM Aβ₁₋₄₂ and 4 mM ketone bodies
- D – cells with 4 mM ketone bodies
Ketogenic diets in animal models of AD

- Van der Auwera et al. 2005 rodent study
- Transgenic mice ("London" APP mutation) which have high soluble Aβ at 3 months and extensive plaques at 12-14 months were fed *ad libitum* either a high carb diet or ketone diet (79% fat, 0.76% carbs)
  - Ketone diet mice immediately lost weight (didn’t like the food)
    - Gained it back with mixed diet but lost weight again when transitioned to ketone only
    - Weekly blood samples showed greatly increased BHB levels (ketogenic state)
Ketogenic diets in animal models of AD

- No behavioral effects between mice
- Aβ levels much lower in ketone diet mice
- Unexpected that a brief ketone diet reduced Aβ levels
- Other studies which showed high fat/cholesterol increase AD effects were not low carb
  - Carbs stimulate insulin promoting fat storage
Ketogenic diets in animal models of AD

- Brownlow et al 2013 rodent study
- Looked at 5 month old APP/PS1 mice (amyloid deposition) and Tg4510 mice (tau deposition) with standard and ketogenic diet
  - KD increased ketosis and reduced glucose levels (as expected)
  - No diet induced weight difference (only genotype mediated)
  - KD significantly increased motor performance but not reverse memory deficits
    - Could be due to better metabolic efficiency in muscles
  - No changes in amyloid or tau
Ketogenic diets in animal models of AD

- Other studies have shown the fasting can mimic ketogenic diet benefits
  - Produces a ketogenic response
- Medium chain triglycerides doses showed increased mitochondrial function in aged dogs
  - These are easily converted to ketone bodies
  - Showed a decrease in Aβ, especially in the parietal lobe
- In a female triple-transgenic AD (3xTgAD) mouse model, mitochondrial bioenergetic deficits preceded AD pathology
  - 2-deoxy-D-glucose caused a ketogenic effect by blocking the glucose metabolism, showing a reduction this deficit, and reduced Aβ pathology.
Ketogenic diets in animal models of AD

- Ketone ester based diets in male 3xTgAD mice showed reduced A and hyperphosphorylated tau deposition in the hippocampus, amygdala and cortex
  - After 4 and 7 months, they showed significant improvements in learning and memory (Morris water maze)
- Ketone bodies can limit the anabolic capacity of the cell, since they cannot provide intermediates for the citric acid cycle
  - Supplementation with anaplerotic compounds (triheptanoin) showed a reduced astroglial response and less proinflammatory cytokines
- Future studies are needed to see how translational these animal studies are.
Citations


Alzheimer’s cont: clinical trials
A few ways to induce ketosis in humans

1. Administration of a high-fat, low-carb, low protein diet
2. Administration of medium chain triglycerides
3. Administration of ketone bodies
Medium chain triglycerides

In contrast to ketogenic diet, medium chain trig. are broken down regardless of availability of other nutrients, so no need to restrict carb intake.

Amount exceeds capacity of citric acid cycle and leads to production of ketone bodies in liver mitochondria.

When fatty acids oxidized at high rates, large amounts of AcoA are produced.

Do not undergo regulation imposed on long chain fatty acids but undergo obligatory oxidation.
1. Increase in ketone body levels on older adults with memory disorders

Used oral administration of medium chain triglycerides

20 subjects with AD or mild cognitive impairment either took treatment or placebo (RCT)

Significant increase in BHB was observed 90 min later

- This increase moderated by ApoE genotype:
  - In ApoE4+ patients, BHB levels continued to rise from 90-120 min period
  - Levels in ApoE- patients remained constant
  - Administration facilitated performance in ApoE-, not ApoE+

Overall, higher ketone levels in plasma= higher paragraph recall performance compared to placebo (future studies needed to consider effects of ApoE gene status)
2. Increased ketone levels in adults with *probable* AD (via medium chain trig)

Oral ketogenic compound (AC-1202, medium chain triglycerides) administered to individuals with *probable* AD to see if chronic induction of ketosis could improve memory performance

152 patients over 90 days in a randomized, placebo-controlled, double-blind, parallel group study

Participants had diagnosis of mild to moderate AD and continued taking AD medications as well as continued their normal (not necessarily ketogenic) diets—results stratified by ApoE status

Increased levels of ketone bodies 2 hrs after administration

After 45 and 90 days, both population groups (- and +) showed improvement on a cognitive capacity measure compared to placebo

Fractionated coconut oil (med. chain trig. used) got FDA approval for AD treatment in US
3. Ketogenic diet effects on cognitively impaired adults

23 adults with mild cognitive impairment randomly assigned to either high-carb or low-carb diet

After 6 week testing period, verbal memory scores were improved in those taking low carb diet

For entire sample, changes in weight, insulin level, calorie intake, and performance was not correlated with entire sample; but, there was a moderate trend toward changes in insulin levels and memory with the low carb group

Ketone levels positively correlated with memory performance

Low carb diet can improve memory function in adults at risk for AD

(Mechanism of action yet to be determined)
4. New way to induce hyperketonemia?

63 y/o patient with younger onset AD for 12 years given a potent ketogenic agent ((R)(R)-3-hydroxybutyl (R)-3-hydroxybutyrate (ketone monoester)

Ketone monoester has been shown to boost learning and memory performance in mouse models of AD

Administered as a food supplement without changes in diet

Over 20 month trial period, BHB levels significantly increased which improved mood, affect, behavior, cognitive performance. Overall, an increase in patients self-sufficiency and reduced need for supervision also noted

Patients function improved when presence of ketone bodies increased in plasma; declined as they returned to baseline

More routine studies needed to establish correlation
Possible problems with ketogenic diets in AD

Physicians afraid of ketosis because it can be a life threatening condition called ketoacidosis in patients with Type-1 diabetes- this appears as severe kyperketonemia due to insulin deficiency
KETOSIS VS KETOACIDOSIS

They are not the same!

KETOSIS

- Low level of ketones in the blood
- Normal process of the body
- Safe function of a low-carb, ketogenic diet

KETOACIDOSIS

- Extremely high level of ketones in blood
- Can turn the blood acidic, deadly if untreated
- Occurs in diabetics who don’t take enough insulin or aren’t well, people who are starving, or alcoholics
KETOSIS VS. KETOACIDOSIS

KETOSIS
- Ketosis is used to treat a range of health conditions, including:
  - Type 2 diabetes
  - Heart disease
  - Metabolic syndrome
  - Alzheimer’s disease
  - Parkinson’s disease
  - Cancer
  - Aids
  - Obesity
  - Epilepsy

HEALTHY SAFE STATE

DANGEROUS STATE
Ketosis can have the following symptoms:
- Nausea, thirst
- Frequent urination
- Vomiting
- Fatigue
- Confusion
- Weakness or dizziness
- Shortness of breath
- Pulse-slowed rate
- Coma
- Low blood pressure

KETOACIDOSIS
- Ketoacidosis is not recommended due to insufficient insulin from pancreas
- Produces ketone bodies
- Produces ketone bodies

ACIDIC STATE
- High lactic acid in blood
- Low body pH

HEALTHY SAFE STATE

DANGEROUS STATE
Ketoacidosis can lead to coma and even death.
Other problems

- relatively small number of clinical trials, so hard to assess side effects of ketogenic diet in patients with AD

  - (Mostly was just gastrointestinal effects AKA patients had a very upset stomach)- my personal question is possible conjunction with probiotics?

- AD patients tend to gravitate toward high-carb diet, so ketogenic diet may be hard to maintain (med chain trig. may be preferable)
Conclusion and Future Directions

- More than 50% of all dementia caused by AD, and the global and regional glucose hypometabolism is a target for therapeutic intervention.

- Toxic effects on hippocampal neurons reversed by BHB presence suggesting a neuroprotective effect (*also potential for depression?*)

- Animal studies on high fat diets need to be re-evaluated in light of carb intake.
Because of differences in ApoE (+) populations, there would have to be routined genetic testing to predict efficacy of possible ketogenic therapeutic intervention.
Preclinical or early symptomatic treatment may benefit from administration of ketone bodies or ketogenic diet; however, more studies would need to be done on people with limited neuropathological alterations, because it is unclear as of now whether a ketogenic diet can systematically help cognitive decline due to AD in the preclinical stage.
I feel like a Roman Warrior on cocaine. That's what keotosis does for me.

DrFumbles88 27/M/188cm | SW: 145 Kg | CW 125 Kg | GW >90 Kg  267d
For real. Sometimes I'll wake up zooming already.

Backaboo  F/5'6/SW215/CW182  267d
Ketosis had reduced my rheumatoid arthritis inflammation to almost nothing. This reduces my pain. RA is an autoimmune I think I'm killing it with being in ketosis. I'm off my meds - I barely ever take ibuprofen anymore.

cantithat 27F/5'6" ISW: 188CW: 133GW: 125  267d
+1 for significant reduction in RA pain/inflammation with keto. Literally the only reason I vehemently adhere to this WOE.

Becksboo  F/5'6/SW215/CW182  267d
RA is the reason why I keto

aberadale  M/69/5'4" HW 207 | keto@199 | CW:152 | GW:155  267d
I'm the same way and I only have minimal arthritis. Ibuprofen works to reduce pain for me better than most of the over the counter NSAIDs but it caused an imbalance in your gut flora. I have not been taking ibuprofen for the past 6 months. I've often commented that my little finger joint is still not flexible but it no longer has pain. Carbs appear to cause inflammation in my body so I'll be avoiding them for the rest of my days. Weight loss is only part of this wonderful new life I've found via ketosis.

Isolatedwoods19  267d
Same! I've been able to reduce my immune suppressing show to once every 3 weeks instead of weekly. I have ankylosing spondylitis and fibro, and some other immune related stuff.
It's also really helped my depression, which is heavily related to the inflammation.

Captain Midnight M38 5'7" S210(?) 12161 G150  267d