P2-651

Personalized Nutritional Ketosis Through a Whole-Food Low-Carb Diet, Medium-Chain Triglycerides, and Other Ketogenic Strategies for People with Alzheimer's Disease and Mild Cognitive Impairment

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Key Points:

Ketones are an alternative fuel to glucose in the brain.

1. Glucose hypometabolism predates AD symptoms by at least 1 to 2 decades.

2. Ketones are taken up normally in affected regions of the Alzheimer's brain.

3. Insulin resistance, a "brain-energy gap", & neuroinflammation are factors in AD.

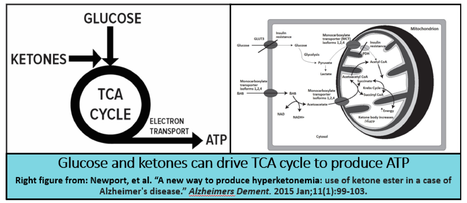
4. Mild to moderate ketosis from a low-carb ketogenic diet and other ketogenic strategies could reverse insulin resistance, fill in the brain-energy gap, and reduce inflammation.

Background:

No existing FDA-approved drug for Alzheimer's disease leads to meaningful improvement in cognition or functionality beyond slowing the disease progress for up to six months. Modifiable lifestyle risk factors are reported to account for at least 30-40% of dementias, with poor diet at the top of the list. Diabetes carries a 6-fold increased risk of developing dementia. Consumption of sugar has increased by about 300 kcal/day over the past 50 years. There has been a parallel rise in rates of obesity, extreme obesity, diabetes, and dementia. Numerous studies report reduced risk or slowing of cognitive decline with a whole-food Mediterranean diet and recent promising studies have combined a Mediterranean-style diet with a low-carbohydrate/higher-healthy fat ketogenic ratio (Neth 2020) or modification of a ketogenic diet (KD) to include MCT oil (Taylor 2017), or coconut oil in keto program recipes (Phillips 2021), or MCT oil with habitual diet (Fortier 2021). Look for details in third column. Larger studies of Mediterranean Keto Diet, KD with/without MCT oil and/or ketone salts are in progress. An NIH/NIA funded trial of a betahydroxybutyrate/butanediol monoester in older people with metabolic syndrome to study biomarkers of brain aging and cognitive performance is currently in progress (NCT04421014), as well as a trial of a novel ketone ester for aging (NCT05585762). More than 50 clinical trials are currently underway for ketogenic diet, ketogenic oils and/or ketone salts or esters for aging, Parkinson's disease, Lewy body dementia, ALS, prediabetes, diabetes, heart failure, recovering from myocardial infarction, TBI, obesity, alcohol use disorder, PCOS, COVID-19, muscle atrophy, sleep, etc.

Reversing and Bypassing Insulin Resistance:

Brain insulin resistance with abnormal brain glucose uptake and related inflammation are key pathologies in AD (De la Monte, *J Alzheim Dis* 2005), certain dementias, Parkinson's, and in some people with MCI. GLUT1 and 3 (Simpson *Ann Neuro* 1994), and PDH Complex 1 (Hoshi *Proc Natl Acad Sci* 1996) are also decreased in AD. Mild nutritional ketosis through adjustment of the fat:carb+protein gram ratio can reverse insulin resistance (Hallberg *Diabetes Ther* 2018) and could provide therapeutic benefit in neuro and other disorders with insulin resistance since ketones are an alternative fuel to glucose for the brain and most other organs through production of ATP via the Kreb's cycle (Veech *IUBMB Life* 2001).

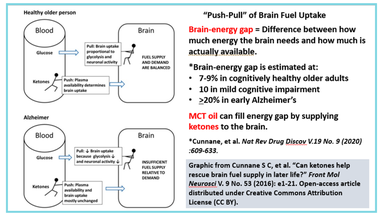


Glucose and ketones can drive TCA cycle to produce ATP

Right figure from: Newport, et al. "A new way to produce hyperketonemia: use of ketone ester in a case of Alzheimer's disease." *Alzheimers Dement.* 2015 Jan;11(1):99-103.

Brain-Energy Gap:

Using dual tracer ketone (acetoacetate) and glucose PET imaging in more than 300 young and older adults, Stephen Cunnane, PhD and group have identified a "brain-energy gap" in cognitively healthy older adults (7 to 9%) that worsens with MCI (>10%) and AD (>20%). Ketone uptake is normal in brain regions affected by abnormal glucose uptake in AD (Castellano, et al. *J Alzheim Dis* 2015) in direct proportion to blood ketone levels.



Strategies to Achieve Mild to Moderate Nutritional Ketosis:

Optimal blood betahydroxybutyrate (BHB) levels of 0.5-2 mmol/L are many times lower than in diabetic ketoacidosis and can be achieved by adopting ketogenic strategies alone or in combination. Sustained improvement and stabilization has been reported anecdotally in people with AD, MCI, and Parkinson's for years using a multi-strategy approach.

(1) **Low-carb and ketogenic diets (KD)** with carbohydrates ≤50 grams per day, fat ≥50% of calories and protein of at ~ 0.4-0.8 g/lb (1-2 g/kg) body weight (too much protein can increase blood glucose levels). A low-glycemic whole-food Mediterreanean-style diet will provide important nutrients and help control blood glucose.

(2) **Overnight fasting**: Ketone levels begin to increase after 10 to 12 hours of fasting (calorie free liquids and coffee/tea with coconut or MCT oil will not stop ketosis).

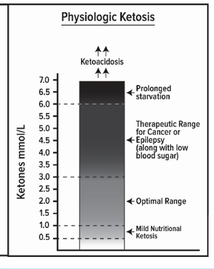
(3) **MCT oil** ≥18 gm/day and/or **Coconut oil** ≥ 35 gm/day (more as tolerated) divided into 3 or 4 doses with meals/snacks could help sustain mild continuous ketosis.

(4) **Exogenous ketone supplements,** such as salts and esters, containing the ketone betahydroxybutyrate (BHB) result in a transient increase in ketone levels.

(5)**Caffeine** (Vandenberghe *Can J Physiol Pharmacol* 2017), 175 to 350 mg/day, will provide a small bump in ketone levels.

(6) **Exercise** can further increase ketosis and ketone uptake in the brain (Vandenberghe *Appl Physiol Nutr Metab* 2019).

KETOGENIC STRATEGY :	KETONE LEVELS mmol/L:
Caffeine	→ 0.2 to 0.3
Coconut Oil	→ 0.3 to 0.5
Vigorous Exercise	→ 0.3 to 0.5
Overnight Fast	→ 0.3 to 0.5
MCT Oil	→ 0.3 to 1.0
Branched Chain Amino Acids	→ 0.3 to 1.0
Ketone Mineral Salts	→ 0.5 to 1.0
Classic Ketogenic Diet	→ 2 to 6
Starvation	→ 2 to 7
Ketone Esters (Oral or IV)	→ 2 to 7 or higher
Diabetic Ketoacidosis	→ 10 to 25



Studies & Case Reports of Improved Cognition with Ketogenic Interventions:

MCT oil (C8:0 alone or C8:0/C10:0 Combinations):

Crossover study – n=20, mild to moderate AD – single dose 40 g C8:0 MCT or placebo at separate visits – at 90 m, with MCT, ↑ trend paragraph recall, ↑ ADAS-Cog in ApoE4⁻ people (Reger *Neurobio Ageing* 2004).

Double-blind RCT – Mild to moderate AD – 20 g C8:0 MCT n=77) versus placebo (n=63) for 90 d. With MCT, ↑ ADAS-Cog Score (3.4 points) in ApoE4⁻ people (Constantini *Nutr & Metab* 2009).

Chart review, n=55 mild to moderate AD - C8:0 MCT oil (Axona) - MMSE stable or improved in 80% after 15 mo (Maynard *Neuropsych Disease Treat* 2013).

Crossover study - n=11, type 1 diabetes and hypoglycemic episodes – single-dose MCT (C8:0/C10:0) 40 g versus placebo at two separate visits. MCT prevented autonomic, cognitive, and behavioral symptoms of acute insulin-induced hypoglycemia, placebo did not. (Page, et al. *Diabetes* 2009).

RCT – 38 frail elderly, 1/3 assigned to MCT (C10:0/C8:0) 6 gm + leucine + vit D, 1/3 to LCT oil + leucine + vit D, 1/3 to regular diet/no supplement. After 3 months, MCT group ↑10.6% on MMSE, ↑30.6% Nishimura Geriatric Rating Scale; cognitive scores ↓ in LCT and control groups. MCT group had ↑ hand grip by 13.1%, ↑ speed of walking by 12.5%, ↑leg open and close test by 68.2%, ↑peak expiratory flow by 28.2% compared to LCT and control groups. (Abe. *J Nutr Sci Vitaminol* 2017; Abe. *J Nutr* 2016).

Open label, n=10 (completed), mild to moderate AD - MCT oil (C8:0/C10:0) modified-KD for 12 weeks, ↑ ADAS-Cog Score; no cardiovascular safety or other metabolic concerns (Taylor, et al. *Alzheimers Dement* 2017).

Double-blind RCT, n=46, mild to moderate AD - MCT oil jelly (C10:0/C8:0) 6 gm vs. 3 x daily for 30 d, 30-d washout, then canola oil placebo jelly 3 x daily for 30 d, or reverse sequence. On MCT ↑ ADAS-Cog Score by 2.62 points; on placebo ↓ ADAS-Cog Score by 2.52 points, improved lipid metabolomics (Xu et al. *Clin Nutr* 2020).

RCT, n=65 people with MCI - MCT oil (C8:0/C10:0) 30 g (15 g twice per day) for 6 months vs. LCT oil placebo. With MCT, ↑ brain ketone levels; cognitive improvement in four domains; no change in lipid profile or serious adverse effects (Fortier *Alzheimers Dement* 2021).

Keto Diet with Coconut Oil Recipes - 21 people with AD, 2 x 12 week periods of keto or usual diet with 10 week washout period. KD program included coconut oil in most recipes. ACDS/ADL ↑, QOL-AD ↑ compared to usual diet (Phillips *Alz Research & Therapy,* 2021).

Coconut Oil: RCT – 44 people with mild to severe AD – half assigned to coconut oil 40 g (20 g twice per day) for 21 days versus controls on usual diet. ↑ orientation, ↑ language-construction with coconut oil (De la Rubia Orti *Nutr Hosp* 2017).

Low Carb MeDi Ketogenic diet: Crossover study – 20 people with subjective cognitive impairment (n=11) or MCI (n=9) - Mediterranean KD (MMKD) for 6 wks, washout 6 wks, AHA diet 6 wks. For MMKD only: ↑ CSF Aβ42 level, ↓ CSF tau level, ↑ brain ketone levels, and ↑ cerebral perfusion. In both groups: ↑ levels of metabolic markers and ↑ memory. (Neth *Neurobiol Aging* 2020).

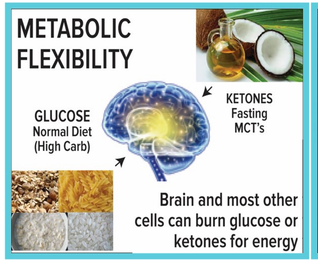
Modified Atkins KD (n=9) or NIA low-fat diet (n=5) for 12 weeks, RCT for AD - ↑ composite cognitive score, esp. memory domain in adherent participants and only with KD (Brandt *J Alz Dis* 2019).

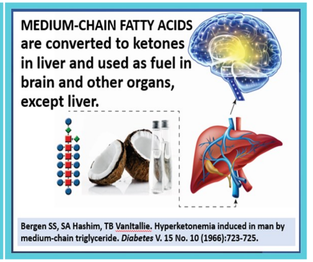
Cases reports MCT Oil (Axona)—8 cases of mild to moderate AD - cognitive stabilization or improvement while taking C8:0 MCT oil (Axona) (Maynard *Neuropsych Dis and Treat* 9 2013).

Case Report KD – 68 yo male, mild AD, ApoE4+, type 2 DM, obesity - 10 weeks KD + exercise + cognitive training, improved insulin-resistance biomarkers, ↓ LDL & TGs, weight loss, ↑MoCA from 23 to 29 of 30 points (Stoykovich, Gibas. *Alzheimers Dement* 2019).

Case Report KD– 71 yo female, mild AD, ApoE4+, metabolic syndrome, obese - 10 weeks KD + exercise + cognitive training, improved insulin-resistance biomarkers, ↓ LDL & TGs, weight loss, ↑MoCA from 21 to 28 of 30 points (Morrill, Gibas. *Diab Metab Syndr:Clin Res & Rev* 2019).

MCTs and Ketone monoester: Case Report –In 2008, 58 yo male, moderate EOAD, ApoE 4/3, began coconut then MCT oil, eventually in a 4:3 ratio of MCT oil/Coconut oil up to 165 ml/d. ↑ MMSE from 14 to 20 of 30 points over 2 months. Over 1st year, improved ADAS-Cog by 6 pts and Activities of Daily Living by 14 pts. 2010 MRI: no change in atrophy x 2 years. In 2010, 2 years after starting coconut oil, in NIH pilot study (n=1), added ketone ester ((R)-3-Hydroxybutyl (R)-3-Hydroxybutyrate) 28.5 g 3 x daily – improved self-care, mood, affect, abstract thinking, insight (Newport *Alzheim Dement* 2015). Stable for 20 more months until hospitalization for drug reaction in 2012. Brain donation in 2016 showed AD Braak stage 6 and Lewy bodies, amygdala predominant.





Ketones are anti-inflammatory, reduce oxidative stress, and reduce AD pathologies in animal models

The ketone betahydroxybutyrate (BHB) inhibits activation of the NLRP3 inflammasome (Shippy *Front Cell Neurosci* 2020; Kim *Frontiers Immunol* 2022), prevents perforation of neurons by beta amyloid (Yin, et al. *Neurobiol Aging* 2016), acts as an antioxidants and scavenger of free radicals, and improved survival of neurons and neurites in neurons subjected to beta-amyloid in cultures (Kashiwaya *PNAS* 2000). BHB also reduced beta amyloid plaques and tau tangles in AD animal models (Kashiwaya *Neurobiol Aging* 2013; Wu et al. *FASEB* 2020).

Complete list of references for ketones and cognition, including *in vitro*, animal, and human studies of ketones and cognition, and clinical trials of ketogenic diet, coconut oil, and MCT oil for MCI and AD.

CONCLUSIONS:

Given the lack of any FDA-approved drug that brings about meaningful improvement in people with Alzheimer's, adopting strategies to achieve mild to moderate nutritional ketosis could provide a safe and reasonable therapeutic approach to improve symptoms and potentially slow down progression of the disease, and could also provide a strategy for prevention. A ketogenic lifestyle could help reverse insulin resistance and aid blood glucose control, fill in the brain-energy gap by providing fuel to insulin-resistant neurons, astrocytes, and other glia to produce ATP, improve mitochondrial function and reduce oxidative stress, and reduce neuroinflammation by blocking activation of the NLRP3 inflammasome. A whole-food Mediterranean-style KD can be adapted to most diets in nearly all cultures by eliminating obvious sweets, added sugar, and sugary drinks, which accelerate brain aging (Pase *Alz Dement* 2017), eating mainly vegetables and small portions of whole grains, legumes, and low-sugar fruits for carbs, while increasing healthy fats/oils and foods with high-fat content such as fatty fish, avocados, nuts, cheese, seeds, and olives. Ketogenic MCT and coconut oil, as well as exogenous ketone supplements, exercise, and intermittent fasting could further enhance ketosis.

PLEASE ALSO SEE VIDEO FOR THIS POSTER AND POSTER P3-582

More on ketones and ketogenic strategies at:
https://coconutketones.com/alzheimers-dementia

Scientific References" website page—list of references on ketones & cognition, and many complete articles on ketones and the brain.

Books on ketones and Alzheimer's by Mary T. Newport, MD
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