

Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Medium Chain Triglycerides (MCTs)

Evidence Summary

Rationale exists for the use of MCTs for general cognitive health, the early stages of Alzheimer's disease, and aging. Unfortunately, there is a lack of quality clinical data.

Neuroprotective Benefit: Raising ketone levels is an attractive strategy to enhance brain metabolism, but there is a lack of human data and mixed animal data suggesting that it will have a clinically meaningful benefit.

Aging and related health concerns: A *C. elegans* study suggests ketone supplementation at the correct dose can increase lifespan. No studies in humans.

Safety: MCTs and ketone esters have gastrointestinal side effects that may be prohibitive to their long-term use. Few studies have investigated the long-term use of MCTs/ketone esters.

What is it?

Ketone bodies (such as beta-hydroxybutyrate [BHB]) can be used by cells for energy metabolism. They enter the tricarboxylic acid (TCA) cycle directly, bypassing the glycolytic pathway, where mitochondria can generate ATP. It is suggested that they may be an alternative energy source for the brain in situations of glucose hypometabolism (e.g. Alzheimer's disease).

Medium-chain triglycerides are fatty acids with a 6-12 carbon tail. They diffuse through the GI tract through the hepatic portal system where they are readily metabolized in the liver into ketone bodies. Ketone monoesters are also broken down into ketone bodies in the GI tract and liver. Both subsequently raise plasma ketone levels with ketone monoesters seemingly more efficient ([Clarke et al 2012](#), [Cunnane et al 2016](#)).

Plasma ketone levels are usually low (~0.2mM), and glucose supplies almost all of the brain's energy. When carbohydrate consumption is low, such as when fasting or on the ketogenic diet, plasma ketone levels can rise to 5mM, and ketone bodies can supply nearly two-thirds of the brain's energy ([Chourchesne-Loyer et al 2013](#)). Glucose brain metabolism decreases in patients with Alzheimer's disease but ketone metabolism remains to a certain extent, and raising plasma ketone levels might be an alternative strategy to supply the brains of dementia patients with energy ([Castellano et al 2015](#)). Since fasting and the ketogenic diet are difficult and unpleasant to adhere to, MCTs or ketone esters might be an alternative strategy to raise plasma ketone levels.

Neuroprotective Benefit: Raising ketone levels is an attractive strategy to enhance brain metabolism, but there is a lack of human data and mixed animal data suggesting that it will have a clinically meaningful benefit.

Types of evidence:

- No meta-analysis, systematic review, or observational study
- Three RCTs using MCTs in MCI or mild/moderate Alzheimer's patients, one RCT using MCTs in elderly with cognitive decline but not dementia
- Two case studies using a ketone ester in Alzheimer's patients
- Multiple animal studies

Human research to suggest MCTs or exogenous ketones can prevent dementia or cognitive aging

None

Human research to suggest MCTs or exogenous ketones can benefit patients with Alzheimer's disease/dementia?

[Reger et al, 2004](#) and [Henderson et al, 2009](#) examined the effects of an MCT solution developed by [Accera, Inc.](#) In a double-blind cross-over trial, [Reger et al, 2004](#) reported that in 20 patients (15 probable AD, 9=ApoE4; 5 aMCI, 1=ApoE4) MCTs increased plasma beta-hydroxybutyrate (BHB) levels in all patients and improved ADAS-Cog scores in ApoE4(-) patients ($p=0.04$) but not in ApoE4(+) patients. No groups scored better in the Stroop test and MMSE scores were not reported. In a phase II study ([NCT00142805](#)) of 152 patients with mild-to-moderate Alzheimer's disease (MMSE avg. 19.5), [Henderson et al, 2009](#) reported that daily MCT consumption ([Accera, Inc's](#) AC-1202, also known as [Axona](#)) in dosage compliant ApoE4(-) subjects improved ADAS-Cog scores over placebo (day 45, 6.26 points; $p=0.001$; day 90, 5.33 points; $p=0.006$). These improvements disappeared after a 14-day washout period. There was no improvement in ApoE4(+) patients. The increase in ApoE4(-) group might be slightly exaggerated since ApoE4(-) placebo patients scored worse on the ADAS-Cog at day 45 and 90 while ApoE4(+) placebo patients remained at baseline. Also, there was a high dropout rate in MCT patients (MCT dropout = 23.3%; placebo = 6.1%). This is likely due to gastrointestinal effects commonly caused by MCT supplementation, but if non-responders dropped out, the results could be further skewed.

In contrast to the previous results, a cross-over study from GlaxoSmithKline reported [no significant improvement](#) in cognition ([NCT01702480](#)) in 96 elderly subjects with cognitive decline but not dementia taking 30g of an MCT powder for 14 days. An additional MCT study ([Rebello et al, 2015](#)) was unable to recruit enough patients to report significant results.

Three studies testing the effects of Axona have been completed but reported no results ([NCT00355550](#) (2007), [NCT01538212](#) (2012), [NCT01122329](#) (2015)). These studies examined cognitive benefits in older adults with memory complaints but no dementia, benefits in mild-to-moderate Alzheimer's patients, and regional cerebral blood flow in probable Alzheimer's, respectively.

MCTs might provide acute benefits in patients with Alzheimer's disease/dementia, but plasma BHB levels soon drop back to baseline and the positive benefits seem to disappear soon after MCT supplementation is suspended. In addition, since no long-term MCT study has been conducted, it is unclear whether patients taking MCTs will see sustained, long-term benefits.

Two case studies ([Newport et al 2015](#), [Chu and Jiao, 2015](#)) reported beneficial effects of a ketone ester in a total of three ApoE4(+) Alzheimer's disease patients. Unfortunately, [Newport et al 2015](#) reported

no objective cognition measures after ketone ester treatment (it was reported “the patients could remember better”, etc.). In addition, [Newport et al 2015](#) reported an incredibly high improvement in MMSE score (8 points) after a 75 day MCT treatment (prior to the ketone ester treatment) accompanied by an impairment of ADAS-Cog score. The reason for this discrepancy is unknown. The second publication came out soon after the first and reported similar findings.

Low-carbohydrate and ketogenic diets also raise plasma BHB levels, and [Krikorian et al \(2012\)](#) found that overweight, hyperinsulinemic, older adults with cognitive decline given a low carbohydrate diet (carbs < 5-10% of calories – 20-50 grams) for six weeks scored better on tests of long-term memory but not working memory or executive function. It is unclear whether these results are due to increased BHB levels, per se, or decreased carbohydrate and caloric consumption. In addition, reported daily caloric intake levels were low for both groups (1592 kcal/day high carbohydrate group; 1042 kcal/day for low carbohydrate group). Inaccurate reporting of daily food intake is a common problem in dietary studies.

Mechanisms of action for potential neuroprotection identified from laboratory and clinical research

An early indicator of Alzheimer's disease/dementia is brain glucose hypometabolism. This decrease might be caused by synaptic dysfunction and neuronal death, but recent imaging studies suggest that glucose hypometabolism might precede synaptic dysfunction. In individuals with presenilin 1 mutations, APOE4, a maternal history of Alzheimer's disease or type II diabetes, regional brain glucose hypometabolism precedes cognitive dysfunction ([Cunnane et al 2011](#), [Cunnane et al 2016](#)). Since imaging studies show that brain ketone metabolism is directly related to plasma ketone concentration, even in early Alzheimer's patients ([Chourchesne-Loyer et al 2013](#); [Castellano et al 2015](#)), and MCTs and ketone esters raise plasma BHB levels ([Reger et al, 2004](#); [Henderson et al, 2009](#); [Clarke et al \(2012\)](#)), the brains of pre- or early-Alzheimer's patients may be able to use ketones, even in the face of glucose hypometabolism.

Animal studies suggest that a shift from glucose metabolism to ketone metabolism is an early event in Alzheimer's disease and aging ([Yao et al, 2009](#); [Yao et al, 2011](#); [Ding et al, 2013](#); [Yin et al, 2016](#)) and that glucose hypometabolism might accelerate the progression of Alzheimer's disease ([Velliquette et al 2005](#)). In addition, there is evidence from animal studies that ketones might compensate for glucose hypometabolism in aging and Alzheimer's disease. In the parietal cortex of aged beagles (~9 years), short-term (2 months, 2g/kg/day) MCT treatment increased mitochondrial respiration, the ability to drive electrons through mitochondrial complex 1, decreased protein oxidation and nitration, decreased APP levels, and increased non-sterol lipids, phospholipids, saturated fatty acids, and n-3

polyunsaturated fatty acids. There were no differences in BACE1 levels or mitochondria uncoupling proteins ([Studzinski et al, 2008](#); [Taha et al, 2009](#)). Long-term treatment in aged beagles (8 months, 5.5%) improved visuospatial functions, learning ability, and attention – improvements that were more pronounced with increased difficulty ([Pan et al, 2010](#)).

Additional animal and cell culture studies support the notion that ketones might be beneficial in Alzheimer's disease. In cultured cells, raising plasma ketone levels acted as an HDAC 1 inhibitor, raised antioxidant capability possibly through induction of Nrf2, protected neurons from A β 42 toxicity and prevented the entry of oligomeric A β 42 into cultured cells ([Kashiwaya et al 2000](#), [Yin et al 2016](#), [Shimazu et al 2013](#), [Xie et al, 2015](#)). In healthy male rats, ketone esters decreased plasma glucose and insulin levels and increased levels of mitochondrial uncoupling proteins 4 and 5 (which are thought to reduce oxidative stress) ([Kashigawa et al 2010](#); [Ramsden et al 2012](#)). In Alzheimer's disease mouse models, raising plasma ketone levels had an anxiolytic effect, improved some measures of memory (but not others), decreased apoptosis and lipid peroxidation levels, decreased reactive oxygen species, enhanced mitochondrial complex 1 activity, restored mitochondrial membrane potential, decreased amyloid beta and phosphorylated tau levels, and increased soluble APPa levels ([Kashigawa et al, 2013](#); [Zhang et al 2013](#), [Van der Auwera et al, 2005](#), [Yin et al 2016](#)).

This evidence supports a role for MCT/ketone supplementation for patients with early Alzheimer's disease/dementia. However, a number of questions still remain. First, some studies suggest that enzymes downstream of ketone metabolism decrease in the later stages of Alzheimer's disease at which point ketones supplementation might not be useful ([Yao et al, 2009](#); [Correia et al 2012](#)). Also, although ketones seem to have a protective role against A β toxicity, the mechanism of action for this protection is still unclear. Finally, in some of the experiments described above, weight loss or a reduction in caloric intake that occur as a side effect of MCT/ketone ester supplementation might be a cause of the benefit rather than increased ketones, per se ([Clark et al, 2012](#)).

APOE4 interactions:

Two RCTs ([Reger et al, 2004](#); [Henderson et al, 2009](#)) reported greater effects of MCTs in ApoE4(-) patients. The patients in the ketone ester case studies were ApoE4(+) ([Newport et al 2015](#), [Chu and Jiao, 2015](#)). More research needs to be done to discover whether MCTs/ketone esters are beneficial in only certain patient populations.

Aging and health related concerns: A *C. elegans* study suggests ketone supplementation at the correct dose can increase lifespan. No studies in humans.

Types of evidence:

- One *C. elegans* study

BHB supplementation (20mM) increased *C. elegans* lifespan by 26%. ([Edwards et al 2014](#)). Lifespan extension did not occur in conjunction with dietary restriction, suggesting that BHB acted as a dietary restriction mimetic. In addition, similar to mouse studies above, BHB acted as an HDAC 1 inhibitor and increased the expression of the *C. elegans* homolog of Nrf2 (Skn-1). Nrf2 is a transcription factor that increases the expression of antioxidant proteins. Two caveats to consider: first, there is [evidence](#) that prolonged activation of Nrf2 may increase the chances of cancer metastasis ([Wang et al, 2016](#)); second, higher levels of BHB in the *C. elegans* study, 50mM and 100mM, *decreased* lifespan by ~20% and 30%, respectively.

Safety: MCTs and ketone esters have gastrointestinal side effects that may be prohibitive to their long-term use. Few studies have investigated the long-term use of MCTs/ketone esters.

Types of evidence:

- Two human studies
- Multiple animal studies

MCT supplements are generally safe with the most common side effects being [gastrointestinal effects](#). Patients in the trials above given MCTs and ketone esters reported gastrointestinal effects but no severe adverse effects ([Henderson et al, 2009](#); [Clark et al, 2012](#)). However, 90 days for MCTs and 5 days for ketone monoesters are the longest reported dosing schedules (except for [Newport et al, 2015](#); and [Chu and Jiao 2015](#)). Animal studies using up to ~8 months of MCTs/ketone esters ([Pan et al, 2010](#); [Kashiwaya et al, 2013](#)) reported no adverse effects. That being said, coconut oil (an MCT supplement) is widely used, and MCTs are listed by the FDA as Generally Recognized as Safe.

Diabetic ketoacidosis is a life-threatening condition where low levels of insulin lead to an uncontrolled increase in blood ketone levels (and subsequent decrease in blood pH). Although the use of MCTs and ketone esters has not been shown to raise plasma ketones near dangerous levels, those at risk for

elevated blood ketone levels (e.g. [diabetics](#)) should consult with their doctor before considering supplementation.

Sources and dosing:

Ketone esters and ketone salts are becoming very popular in the general public and are becoming more widely available. Ketone salts can be purchased at <http://prototypenutrition.com/> and <http://pruvitnow.com/products/ketoos/>. The ketone esters used in the [Newport et al \(2015\)](#) study and many of the animal studies are being developed by a company spun out from the University of Oxford (<http://www.tdeltas.com/site/>).

MCTs are also widely available. Coconut oil is the most well-known source. In addition, [Axona](#) (based on AC-1202, the supplement used in the [Accera, Inc](#) studies, \$69.50/month) is available with prescription as a medical food, and a concentrated coconut oil beverage, [Fuel for Thought](#) (\$94.95/24 pack), is also available.

In general, studies raised BHB levels to 5-9mM with ketone esters and ~0.4mM with MCTs. Participants in [Clark et al \(2012\)](#) took 140, 357, or 714mg/kg of body weight three times a day for the low, medium, and high doses, respectively. Participants in [Henderson et al \(2009\)](#) took up to 20 g of AC-1202/day.

BHB levels can be measured in a number of ways including directly through the [blood](#), in the [breath](#), or in the [urine](#). Each way has different advantages/disadvantages in terms of accuracy and cost.

Research underway:

A number of studies are currently underway investigating the effects of MCTs in patients. Accera is testing the effects of Axona (AC-1202) in a six month study in patients with mild-to-moderate Alzheimer's ([NCT01538212](#)) and a new formulation, AC-1204 in a 26 week Phase 2 study in patients with mild-to-moderate Alzheimer's which is estimated to be complete in October 2017([NCT01741194](#)). One trial testing AC-1204 was withdrawn ([NCT01211782](#)) to be redesigned. The company is also testing caprylic triglycerides for 90 days in patients with Multiple Sclerosis ([NCT01848327](#)). Another medical food company, Fuel for Thought, has a 6 months study in patients with mild-to-moderate Alzheimer's that is still recruiting ([USF IRB Study #Pro00012233](#)) as of 2013.

A number of other studies are testing the cognitive and/or metabolic effects of MCTs in patients with MCI ([NCT02551419](#), [NCT01669200](#)), Alzheimer's ([NCT02709356](#)), and healthy patients ([NCT02357550](#), [NCT02679222](#), [NCT02679235](#)).

Search terms:

Pubmed

- hydroxybutyrate + Alzheimer
- hydroxybutyrate + dementia
- ketone + alzheimer (filters: case reports, clinical study, clinical trial, meta-analysis, observational study, pragmatic clinical trial, rct, systematic review)
- Ketone + dementia (filters: clinical trial, meta-analysis, observational study, rct, systematic review)
- cognition + hydroxybutyrate (filters: CT, MA, OS, RCT, SR)
- cognition + ketone [Title/Abstract] (filters: CT, MA, OS, RCT, SR)
- cognitive + ketone [Title/Abstract] (filters: CT, MA, OS, RCT, SR)
- mitochondrial + biogenesis + ketone
- lifespan + hydroxybutyrate
- hydroxybutyrate + aging [title/abstract]
- medium chain triglyceride + lifespan
- MCT + aging [title/abstract]
- aging + ketone [title/abstract]
- ketone + mortality [title/abstract]
- medium chain + mortality [title/abstract]
- ketone + atherosclerosis [title/abstract]
- medium-chain + cardiovascular (filters: case reports, clinical study, clinical trial, meta-analysis, observational study, rct, systematic review, review)
- apoe + hydroxybutyrate
- mct + insulin [title/abstract]

Clinicaltrials.gov

- medium-chain triglyceride cognition

Clinicaltrialsregister.eu

- medium chain triglyceride
- ketone

NIH Reporter

- Ketone

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