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Ketogenesis and Alzheimer's Disease: Literature Review

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Abstract

Context Whilst Alzheimer's Disease (AD) aetiology is unclear, diet has been implicated as a modifiable risk factor. Despite this, current AD dietary advice is vague. Recent research has suggested ketone bodies can be used to slow or even improve the rate of AD deterioration.
Aim This literature review evaluates the role of ketones in AD amelioration through the Ketogenic Diet (KD) and Medium-chain triglyceride (MCT) therapy. This review also analyses potential mechanisms by which ketone bodies improve AD pathophysiology.
Method Three searches were carried out on PubMed database covering: KD effectiveness in animal models of AD and AD patients, and MCT effectiveness in AD patients. Animal studies focused on both physiological and behavioural/cognitive functioning outcomes whilst human studies solely focused on the latter.
Findings Studies in this review generally support the link between KD and AD cognitive improvement, through the induction of ketogenesis in the body. Similar results have been achieved for MCT therapy. However, effects of both seem to be largely limited to mild, APOE4- AD patients.
Conclusions Whilst the ketosis effects of the ketogenic diet seem promising, more research needs to investigate why cognitive improvement is lacking in APOE4 positive patients. MCT emulsion therapies could be a welcome alternative to achieve ketosis, considering strict adherence needed in KD for similar effects.

1 Introduction

Alzheimer's Disease (AD) is a neurodegenerative disorder characterised by amyloid-beta $(A\beta)$ plaque deposition and neurofibrillary tau tangles within neurons, leading to cortical degeneration. Over time, this presents with cognitive and behavioural impairments, starting with mild memory loss (Weller & Budson, 2018).

AD pathophysiology implicates many biological processes e.g. glucose hypometabolism, free-radical damage, and gut dysbiosis leading to neuroinflammation (Seneff, Wainwright, & Mascitelli, 2011).

Whilst AD aetiology is unclear, diet has been implicated as a modifiable risk factor. Despite discrepancies in which macronutrients exacerbate AD risk, a low fat and high carbohydrate diet has been cited. (Seneff et al., 2011) suggested that this diet leads to cholesterol deficiency which causes increased oxidative damage and ultimately, neuronal apoptosis. Cholesterol enables the cell membrane to form a closer configuration. This protects membrane fatty acids from oxidative damage caused by excess glucose exposure from high carbohydrate intake. Insufficient fatty acid supply, through

low fat intake, reduces neuronal ability to repair damaged cell membranes. This suggests that AD progression is exacerbated by diet as people with AD have a greater preference for foods high in carbohydrates (Mungas et al., 1990).

Current AD dietary advice is vague (Yerstein & Mendez, 2020), however, if low fat and high carbohydrate intake is suggested to worsen AD outcomes, the inverse (low carbohydrate and high fat (LCHF)) could slow or even improve the rate of AD deterioration.

In this literature review, I will focus on research regarding the ketogenic diet, an LCHF diet, as a potential way of improving AD symptoms. There has been increased interest in this area, using this diet as an adjunct to current Alzheimer's Disease treatment. Previous reviews have focused on its role on improving cognitive symptoms, but few have further explored the practicalities of implementing the ketogenic diet (KD) in AD patients. Therefore, I will also focus on potential objections to KD implementation and future steps research could take, such as the use of medium-chain triglyceride therapy as an adjunct to Alzheimer's Disease treatment.

2 Background

2.1 Ketogenic diet

The Ketogenic Diet (KD) was a term coined by Dr Wilder in 1921. It is an LCHF diet which involves substantial carbohydrate reduction. This minimises glucose stores and replaces them with dietary fat, inducing ketogenesis. A standard ketogenic diet (SKD) involves a macronutrient divide of 55-60% fat (mainly saturated fat), 30-35% 63 protein and 5-10% carbohydrates (20-50g/day) (Dhamija, Eckert, & Wirrell, 2013).

Carbohydrates are the main energy source in the body. They are metabolised via glycolysis, the TCA cycle and oxidative phosphorylation to produce ATP. When carbohydrate intake is reduced to $\leq 50g$, insulin secretion is reduced, and glucagon is used to access glycogen stores to provide energy. Once glycogen stores are depleted, gluconeogenesis and ketogenesis are initiated. During ketogenesis, ketones become the main energy source for both peripheral tissue and the brain. They are produced by the liver from excess fatty acid oxidation. This leads to elevated circulating levels of ketones: β-hydroxybutyrate (BHB) and acetoacetate, as seen in Figure 1.

2.2 KD and AD Pathophysiology

2.2.1 Fuel Exchange

In AD, global cerebral glucose metabolism is reduced by 20-25%, in turn, reducing ATP output. Presumably, this starts from the hippocampus and precedes clinical symptom onset, resulting in reduced synaptic function and atrophy (Cunnane et al., 2016). This leads to a further reduction in energy demand, forming a vicious cycle of hypometabolism and neuropathology. As amyloid precursor protein (APP) cleavage is also ATP-dependent, a lack of ATP could lead to increased Aβ plaque accumulation, a hallmark of AD (Maloney, Minamide, Kinley, Boyle, & Bamburg, 2005). As brain ketone uptake remains the same in AD patients compared to cognitively healthy aged-matched controls (Hartman et al., 2007), it can be used to supplement neural ATP demand.

2.2.2 Anti-oxidant properties

There is evidence of free-radical oxidative damage in AD, caused by reactive oxygen species (ROS). The brain is especially vulnerable to this due to its high content of readily oxidised fatty acids, high oxygen consumption and low antioxidant levels. Aβ_{1-42} plaques and their high copper concentration are thought to mediate ROS generation and lead to mitochondrial damage and lipid peroxidation, a prominent feature of AD degeneration (Huang, Zhang, & Chen, 2016). Both BHB and acetoacetate have been shown to have an antioxidant effect against ROS, preventing neuronal ATP decline (McPherson & McEneny, 2012).

2.2.3 Gut Microbiota

The microbiota-gut-brain axis describes the interaction between commensal microbiota and brain function via multiple pathways. Research suggests age-related changes to the gut contribute to neuroinflammation, which is amplified by AD pathology. Over time, there is a decrease in 'beneficial' gut bacteria e.g. *Bifidobacteria* and *Lactobacillus*, which maintain gut barrier integrity and contribute to anti-inflammation. Low *Bifidobacterium* levels have been correlated with elevated plasma LPS concentration, a component of gram-negative bacteria (Ling, Linglong, Weixia, & Hong, 2016). LPS production is shown to increase IL-6 and TNF-α levels – pro-inflammatory cytokines. (Zhang et al., 2009) found LPS concentrations 3 times higher in AD patients than healthy, age-matched controls.

Ageing is also linked to low-grade chronic inflammation termed 'inflammaging', which can contribute to increased gut permeability and blood-brain barrier compromise (Jiang, Li, Huang, Liu, & Zhao, 2017). This would allow proinflammatory cytokines more access to the brain, causing neuroinflammation.

Studies in healthy mice have found KD enhances neurovascular functions after 16 weeks, by increasing relative abundance of *Lactobacillus* and decreasing pro-inflammatory taxa (Ma et al., 2018). Theoretically, this could reduce neuroinflammation. However, conflicting evidence in young epilepsy patients shows that KD reduces the relative abundance of beneficial bacteria and increases pro-inflammatory *Escherichia coli* abundance after 3 months (Lindefeldt et al., 2019). This would suggest that KD promotes inflammation, worsening AD pathology. It could be argued that AD gut microbiota changes may not be seen in younger patients so they cannot be used as a valid comparison however, more research needs to be done on KD-induced microbiota changes.

2.2.4 Upregulation of Protein Channels directly involved in Amyloid Clearance

More recently, Versele et al. (2020), using human in vitro blood-brain barrier (BBB) models and brain-like endothelial cells (BLECs), have found that the combined use of ketone bodies (acetoacetate and BHB) promotes Aβ efflux through

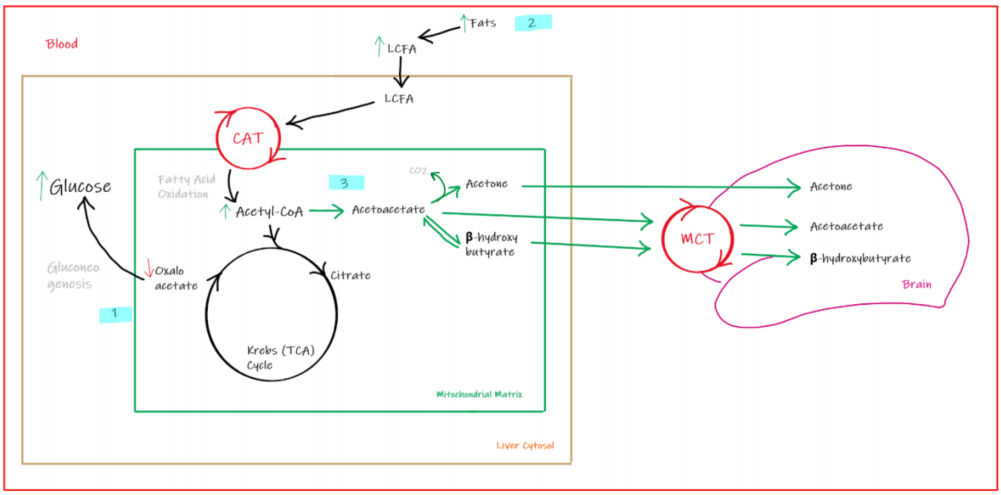

Figure 1: Ketone effect on TCA (Krebs) Cycle (Hartman et al., 2007). (1) Low blood glucose causes oxaloacetate (Krebs Cycle) conversion to glucose in the liver via gluconeogenesis. (2) Increased long chain fatty acid (LCFA) intake (from high saturated fat diet e.g. KD) increases acetyl CoA concentrations. Due to low oxaloacetate levels caused by gluconeogenesis, it cannot be combined with excess acetyl CoA to make citrate needed in the TCA cycle. (3) As a result, excess acetyl CoA is converted to acetoacetate, a ketone; this spontaneously degrades to acetone. It can also be reversibly converted to β-hydroxybutyrate, another ketone, via β-hydroxybutyrate dehydrogenase. Ketones can readily cross the Blood-Brain Barrier (BBB) either via simple diffusion (acetone) or via Monocarboxylic Acid Transporters (MCT) (β-hydroxybutyrate and acetoacetate) to be used for energy metabolism; MCT expression in the brain responds rapidly to hyperketonaemia. CAT: Carnitine-acetylcarnitine translocase

upregulation of protein channels involved in amyloid clearance, such as low-density lipoprotein receptor-related protein 1 (LRP1). This suggests that KBs can have a direct effect on the blood-brain barrier which has not been previously demonstrated. More research into the direct effect of KBs on protein channels would be appreciated to corroborate results shown in this study.

3 Methods

3.1 Data Sources and Search Methods

Two separate PubMed searches were conducted in October 2018 and March 2020 to find relevant, up-to-date papers. Previous literature reviews were used to form the basis of the initial search, using backwards citation to identify useful papers. This search investigated the following topic areas:

1. KD effectiveness in animal models of Alzheimer Disease
2. KD effectiveness in Alzheimer patients
3. Medium-chain triglyceride (MCT) therapy effectiveness in Alzheimer's patients

The primary literature search utilised studies published from January 2004 to March 2020. This sixteen-year span was used as a starting point for the topics mentioned above due to a general lack of studies in these areas.

3.2 Inclusion and Exclusion Criteria

English-language only papers (print or electronic) were included in this review. Randomised controlled trials and clinical trials were looked on more favourably, as these are stronger levels of evidence. However, case reports were also included, if relevant, due to a general scarcity of evidence in the topic areas listed below. Reviews were excluded from reporting as they are not primary research.

Both MeSH heading and free text searches were combined to find papers. All three searches included *'alzheimer*'* as a search term, to encompass all iterations of Alzheimer's Disease spellings. The screening process was refined for each topic area following the initial search:

3.2.1 KD effectiveness in animal models of Alzheimer Disease

The inclusion criteria were as follows:

1. English-language papers (print or electronic) published between 1 January 2004 - 1 March 2020. This span was selected due to the paucity of studies in this area.
2. Papers including ('ketogenic diet') AND ('alzheimer*') AND ('animal studies OR animal models') in either title or abstract.
3. Papers assessing physiological or behavioural/cognitive functioning outcomes in animal models of Alzheimer's Disease.

Studies were excluded if:

1. Animals were given ketones or additional supplements to induce ketosis
2. Animals were given vitamin supplementation

3.2.2 KD effectiveness in Alzheimer patients

The inclusion criteria were as follows:

1. English-language papers (print or electronic) published between 1 January 2012 - 1 March 2020. The initial sixteen-year search span detailed above was later refined to seven years due to increased research interest in this area in the recent decade.
2. Papers including ('ketogenic diet') AND ('alzheimer*') AND ('human studies') in either title or abstract.
3. Studies with populations of AD and/or mild cognitive impairment (MCI), as MCI patients are at increased risk of AD.
4. Papers assessing cognitive or behavioural changes in patients with AD.

Studies were excluded if:

1. A non-human study population was investigated
2. Lack of primary or secondary behavioural/cognitive functioning outcomes investigated
3. Use of MCTs without patient achieving ketosis
4. Combined use of MCT therapy with adjuncts such as vitamin/protein supplementation seen

4 Results

See Appendix A for full table summary of findings.

4.1 KD Effectiveness in Animal Studies

van der Auwera et al. (2005) found that KD can reduce amyloid deposition by 25% in transgenic mice brains over 43 days, compared to controls on a standard diet (high carbohydrate/low fat). This suggests that KD could reverse AD pathology. However, it may not reverse clinical symptoms as, despite ketone and Aβ level changes, no cognitive improvements were seen.

Brownlow et al. (2013) found KD-fed transgenic mice performed better on motor tasks than controls. Yet, tissue measures of amyloid and tau deposition showed no difference between mice fed on KD or control diet over 3 months. Similar results were corroborated by (Beckett, Studzinski, Keller, Paul Murphy, & Niedowicz, 2013). This again shows that symptom improvement and pathology improvement can be separate phenomena.

Going forward, if these are separate, perhaps non-human studies should focus on human trial endpoints i.e. symptom improvement, as it is more practical to measure patient outcome.

4.2 KD Effectiveness in Human Studies

Krikorian et al. (2012) found that mild AD/MCI patients randomly assigned to a very low carbohydrate diet significantly improved verbal memory after 6 weeks, compared to controls on a high carbohydrate diet. High blood ketone levels positively correlated with memory performance. However, depressive symptoms were not affected suggesting that KD might have better efficacy in cognitive impairment.

One problem found in KD studies is that efficacy is largely tested on mild AD patients. In a 3-month medium chain triglyceride (MCT)-supplemented KD, patients had significant cognitive improvement, which reverted to their baseline post-1-month washout (Taylor, Sullivan, Mahnken, Burns, & Swerdlow, 2018). Despite positive results, all diagnosed with moderate AD (Clinical Dementia Rating (CDR) = 2.0) withdrew due to caregiver burden. This highlights that KD may not be practical for moderate to severe AD patients, as strict adherence is needed to achieve ketogenesis. Further, neither study was able to demonstrate similar cognitive improvements in APOE4 positive patients, suggesting a genetic difference in treatment effectiveness. The APOE4 genetic variation is the strongest genetic risk factor for AD and is associated with increased levels of amyloid deposition in both early and late stage AD (M. Di Battista, M. Heinsinger, & William Rebeck, 2016).

However, a recent case study has shown that a 10-week carbohydrate restricted,high-fat KD has been linked to cognitive improvement in a heterozygous APOE4 positive, mild AD patient (Morrill & Gibas, 2019). Whilst it is unclear how much the KD contributed to cognitive improvement, as the patient had also been prescribed time-restricted eating and low-impact physical/cognitive exercise, which have been shown to improve cognition in mild AD (Du et al., 2018); (Jia, Liang, Xu, & Wang, 2019), this still suggests that KD could have a role in cognitive improvement in APOE4 positive patients.

4.3 MCT Therapy

Medium-chain triglyceride (MCT) therapy involves the consumption of medium chain triglycerides (6-12 carbons long), a form of saturated fat, to induce ketogenesis. This is administered via capsules or liquid emulsions.

Medium-chain triglyceride therapy is an alternative to strict KD as AD patients can achieve ketogenesis with limited dietary modification. In contrast to LCFAs in KD, MCTs are oxidised readily in the liver regardless of nutrient consumption. Therefore, macronutrient restrictions are unnecessary as described in Figure 2 (Cunnane et al., 2016).

MCTs have been shown to increase serum ketone levels in both APOE4+ and APOE4- AD patients (Reger et al., 2004). It also significantly improved cognition and paragraph recall in APOE4- AD subjects, compared to placebo. The lack of cognitive improvement in APOE4+ patients despite increased ketone levels could be investigated, because this indicates that ketones might be used differently to the proposed methods above. Other MCT-based ketogenic formulas have shown to improve verbal memory and processing speed in mild to moderate AD patients after 12 weeks of consistent administration along with their usual diet (Ota et al., 2019). If MCT supplements can be taken alongside patient's normal diets, this can improve adherence as it is not a substantial disruption to their normal routine, compared to the challenges the KD might pose.

Studies have also investigated the effects of Caprylidene

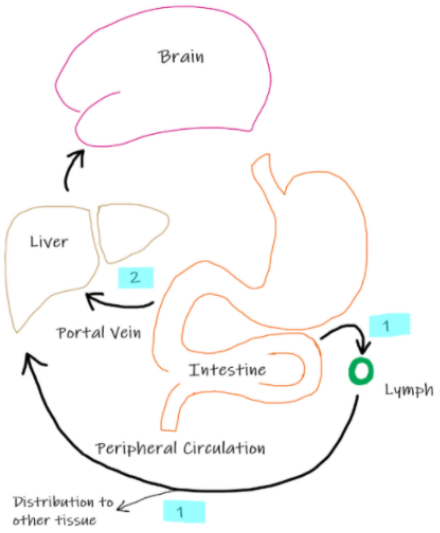

Figure 2: LCFA metabolism is different to MCFA metabolism (Cunnane et al., 2016). Long chain fatty acids (LCFAs), used mainly in KD, are absorbed into the intestinal villi (1) where they are packaged into chylomicrons. These are transported via the lymphatic (lacteal) system into peripheral circulation where they are either distributed to adipose tissue or other organs (excluding the brain), for storage. They are utilised once glucose stores are depleted. Medium chain fatty acids (MCFAs), used in MCT emulsion therapy, directly pass into the portal vein (2) via diffusion across the intestinal villi, leading to the liver. Here, MCFAs undergo complete fatty acid oxidation. Excess acetyl CoA from thisreaction is converted into ketones which can be used as an energy substrate for the brain.

(Axona®), an American Food and Drug Administration (FDA)-approved, MCT-rich medical food for AD treatment. Henderson et al., (2009) found significant cognitive improvement from baseline in ADAS-cog (Alzheimer's Disease Assessment Scale-Cognitive Subscale) scores over 90 days in compliant mild APOE4- AD subjects, compared to placebo, highlighting Caprylidene's effectiveness. In a similar trial, Kimoto et al., (2017) also found cognitive improvements in mild APOE4-AD subjects through Caprylidene. Kimoto et al. also found that patients with more severe cognitive decline (Mini-mental State Exam (MMSE) scores <15) did not show cognitive improvement. These studies suggest that MCTs are most impactful in early AD stages. The next step in implementing MCT therapies may be to investigate how early in AD the therapy is most effective.

Reported side effects of MCT therapies such as Caprylidene are gastrointestinal limited: diarrhoea, flatulence and dyspepsia – especially if not taken with meals. Diarrhoea, especially, can lead to long term problems in frailer patients with AD. Whilst results are mixed, studies have suggested these side effects can be mitigated through putting MCTs into an emulsification (e.g. in a smoothie) rather than a straight oral dose (Courchesne-Loyer et al., 2017). Caprylidene is further contraindicated in type 1 diabetes mellitus due to ketoacidosis risk, and in those with renal dysfunction(Roman, 2010). Moreover, the effects of MCT supplementation, on long-term lipid levels and CVD risk factors need to be established before recommendations can be made.

Overall, as MCT therapy produces similar effects to KD, it might help patients who may be less compliant with KD, to obtain similar results. Furthermore, it may be more convenient than KD as the patient can avoid diet changes which reduces caregiver burden.

5 Potential Objections to KD

Despite much research, it is still unclear why a standard KD works as studies have also found correlations between high saturated fat intake and AD risk (Ruan, Tang, Guo, Li, & Li, 2018). Mice studies have found that high saturated fat diets can increase amyloid levels in microvasculature and exacerbate cognitive deficits (Thériault, ElAli, & Rivest, 2016). Diets high in saturated fat are also shown to increase plasma LPS levels 2-3-fold, contributing to neuroinflammation, according to the gut microbiota hypothesis (Jiang et al., 2017).

It could be argued that saturated fat intake associated to AD risk, is related to the Western Diet where it is coupled with high levels of simple carbohydrates (Thériault et al., 2016). This could mean that it is not saturated fat alone which increases risk but its links to other poor eating habits. This also suggests that KD success is due to carbohydrate-fat (LCHF) interaction.

Furthermore, as high saturated fat is linked to high cholesterol, it could theoretically increase cardiovascular disease (CVD) risk. However, studies show KD is associated with significant reductions in variables associated with high CVD risk, such as: total cholesterol, triglycerides and LDL cholesterol in both obese and normal weight participants (Kosinski & Jornayvaz, 2017). This could be explained theoretically as fat is used as a main energy source in KD so it will be utilised immediately, rather than stored. Longitudinal studies would be ideal to assess long term CVD risk in KD.

6 Future Research

Overall, research generally supports the link between KD, a form of high fat diet, and AD cognitive improvement. How-

ever, effects seem to be limited to mild, APOE4- AD patients.

This poses two further research interests:

1. **Stratification of mild AD patients to assess KD effectiveness.** There is currently a lack of standardisation when assessing AD severity. The studies above either used CDR or MMSE to stratify patients. If this can be standardised, more studies could investigate KD effectiveness at these stratified levels (based on score) to discover which AD stage the diet is most effective.

2. **Differences in APOE4+ cognitive outcomes despite ketone elevation.** More research needs to investigate why cognitive improvement is lacking in these patients despite treatment producing the same ketone level increases seen in APOE4- participants. In the meantime, if this form of treatment were to be implemented, genetic screening should be done to determine the patient's APOE4 status as this may influence treatment outcome.

As strict KD adherence is needed to achieve ketogenesis, it may reduce patient compliance and thus the effectiveness of the treatment presented in findings. MCT emulsion therapies could be a solution as one's usual diet can be maintained. There is yet to be a direct comparison between MCT therapy and the KD, regarding clinical outcomes – this could be investigated via clinical trial, comparing MMSE cognitive scores. Additionally, longitudinal trials are impact to investigate both the impact of MCT-induced ketogenesis on AD improvement and any long-term cardiovascular risks.

Generally, many KD efficacy studies only look for cognitive improvement whilst AD is a multi-faceted disease, including behavioural components e.g. apathy. Research could expand to investigate the KD effect on other symptoms apart from cognitive impairment.

Lastly, as it is unclear which mechanism KD uses to improve AD symptoms, more research needs to be done to understand this. That way, more insight can be shed into the pathophysiology of AD, which could lead to further treatment discovery.

Author statements

Conflicts of interest statement

No conflicts of interest have been declared by any authors.

Authorship statement

All authors fulfill ICMJE authorship criteria, which can be accessed at http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html. All authors have read and approved the final version, and accept responsibility for information published.

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7 Appendix A

Table 1: Summary findings of studies assessing effectiveness of KD and MCT therapies

**CDR - Clinical Dementia Rating; **ADAS-cog - Alzheimer's Disease Assessment Scale-Cognitive Subscale; ***MMSE - Mini-Mental State Examination*

KD Effectiveness in Animal Studies			
Study Details	Participants	Diet Composition and Study Length	Key Findings
Van der Auwera et al., 2005 Randomised Controlled trial	Sixteen, 3 months old, transgenic (London APP mutation) female mice	KD chow: 1. 79% fat (29% of this is saturated fat) 2. 8% protein 3. 0.76% carbohydrate 4. 12% water, fibre and ash Compared with standard chow: 1. 4.5% fat 2. 21% protein 3. 35% carbohydrate 4. 39.5% water, fibre and ash Fed for 43 days ad libitum	Compared to controls, KD-fed mice found: 1. 25% reduction in total brain Aβ levels 2. No changes in behaviour
Brownlow et al., 2013 Randomised Controlled trial	Five months old APP (model of amyloid deposition) and Tg4510 (model of tau deposition) mice.	KD chow: 1. 77% fat (especially MCT-rich) 2. 22% protein 3. 1% carbohydrate Compared with NIH-31 control diet: KD chow: 1. 14% fat 2. 24% protein 3. 62% carbohydrate Fed for 3 months. Food replaced 3 times a day.	Compared to controls, KD-fed mice found: 1. Improved motor performance independent of genotype. 2. No difference in amyloid or tau deposition on tissue examination.
Beckett et al., 2013 Randomised Controlled trial	1–2 months old APP/PS1 knock-in mice	LCHF, KD diet: 1. 79% fat 2. 8% protein 3. 1% carbohydrate Compared with control diet: KD chow: 5. 5% fat (29% of this is saturated fat) 6. 20% protein 7. 62% carbohydrate Fed for 1-month ad libitum.	Compared to controls, KD-fed mice found: 3. Improved motor performance on rotarod apparatus. 4. No difference in amyloid deposition or APP levels in the brain.
KD Effectiveness in Human Studies			
Study Details	Participants	Diet Composition and Study Length	Key Findings
Krikorian et al., 2012 Randomised control trial	23 older adults with mild cognitive impairment and mild AD (CDR*) = 0.5 or 1). Mean age = 70.1 years.	Very low carbohydrate (VLC) diet: 1. 5-10% of total calorie intake 2. Fat and protein intake allowed to vary 3. No total calorie intake restrictions Compared with high carbohydrate diet (50% of total calorie intake). Diet lasted 6 weeks.	Compared with controls, VLC group found: 1. 2.8-mean point increase in V-PAL score (verbal memory test) 2. No difference in depressive symptoms
Taylor et al., 2018 Randomised, single-arm controlled trial	15 AD participants with CDR ratings: 1. 0.5 (very mild AD) 2. 1 (mild AD) 3. 2 (moderate AD). Mean age 73.1 years. 5 participants withdrew due to caregiver burden	Very high-fat KD diet: 1. 73.4% fat (MCT-rich) 2. 17.6% protein 3. 9% carbohydrates Diet lasted 3 months. Later followed by 1-month washout (reverting back to normal diet).	Participants found, compared to preintervention: 1. 4.1-mean point reduction in ADAS-cog** scores 2. 1.1-mean MMSE*** score increase. Improvements reverted to baseline post-washout. Note: Point reduction in ADAS-cog assessment is seen as cognitive improvement.
Morrill & Gibas, 2019 Case report	Morbidly obese 71-year-old female, APOE4 positive. Family history of AD. Diagnosis: Mild AD and metabolic syndrome.	LCHF ketogenic diet (composition unspecified), time-restricted eating and physical/cognitive exercise. Diet lasted 10 weeks.	After 10 weeks: 1. Triglycerides and VLDL: 50% reduction 2. HbA1c reduction from 5.7& to 4.9%. 3. 7-point increase in Montreal Cognitive Assessment score

MCT Effectiveness in Human Studies			
Study Details	Participants	Diet Composition and Study Length	Key Findings
Reger et al., 2004 Double-blinded randomised control trial	20 subjects with mild AD or mild cognitive impairment. Mean age = 74.7 years old 50% participants were APOE4+	Emulsified MCT drink: 1. 40ml MCT oil 2. 152ml heavy whipping cream Compared with placebo: 232ml of heavy whipping cream Study conducted under isocaloric conditions (690 calories) over 2 visits.	MCT-fed participants found, compared with controls: 1. Improved paragraph recall and 1.5-mean point reduction of ADAS-cog score in APOE4- participants 2. 1-point increase in ADAS-cog scores in APOE4+ participants
Henderson et al., 2009 Double-blinded randomised controlled trial	152 subjects with mild to moderate AD. Mean age = 76.8 years old. 52 withdrew before end of study. 55.6% participants were APOE4+.	Oral ketogenic compound AC-1202 (Axona®) – 30g powder sachet mixed with liquid (e.g. water, milk, juice): 1. 33% AC-1202: Glycerine and caprylic acid 2. 64% gum acacia Compared to placebo: 1. 51% gum acacia 2. 37% dextrose 3. 10% safflower oil Given daily for 90 days.	Dosage compliant, AC1202 (Axona®) participants found, compared to controls: 1. 2.6-mean point reduction in ADAS-cog scores in APOE4- participants from day 45 2. No significant ADAS-cog changes in E4+ participants throughout study.
Kimoto et al., 2017 Randomised clinical trial	24 patients with sporadic mild to severe AD. Mean age = 63.9 years old. MMSE scores pre-treatment range = 10 – 25 2 patients withdrew from study 7 patients were APOE4+.	Axona® (40g of powder containing 20g of caprylic triglycerides) administered to all patients. Given daily for 3 months.	Study found during treatment: 1. No significant difference between APOE4- and E4+ patients. 2. Participants with MMSE >15: Improved mean orientation and memory in ADAS-cog test (0.5-point reduction) 3. Participants with MMSE <15: Decreased orientation (0.6-point increase in ADAS-cog)
Ota et al., 2019 Randomised clinical trial	20 patients with mild-to-moderate AD Mean age = 73.4 years old 4 withdrew from study due to side effects (diarrhoea)	Patients given 50g Ketoformula® (contains 20g MCTs) or isocaloric placebo formula (370 calories each), as a control. Taken daily for 12 weeks.	Compared with controls, Ketoformula® participants found: 1. At 8 weeks: Mean 4-point in immediate and delayed logical memory tests 2. At 12 weeks: Mean 7-point increase in digit-symbol coding test and mean 4- point increase in immediate logical memory test