Move Over, Glucose!

The effects of ketogenic diets and ketosis on cognition in Alzheimer's disease

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ABSTRACT

BACKGROUND: Alzheimer's disease (AD) is a neurodegenerative disorder that destroys brain cells and causes deterioration of cognitive ability and memory. Alzheimer's affects roughly seven percent of Canadians over 65 years of age. There is no cure for the disease and current care is primarily focused on symptom management. A dietary approach to treat AD may potentially provide an effective and low-cost intervention until the causative mechanism of disease is determined. The ketogenic diet is a high-fat, low carbohydrate diet that has been established as an effective, non-pharmacological treatment for epilepsy. Its use in inducing ketosis has also been implicated in a variety of neurodegenerative disorders, including Alzheimer's and Parkinson's disease. Ketosis results in the production of ketone bodies, an alternate fuel source to glucose for the brain when carbohydrates are unavailable.

OBJECTIVE: A review of the literature was conducted to assess the effectiveness of a ketogenic diet and ketosis induction in improving memory function in those with AD.

METHODS: A structured literature review was executed. Three databases were consulted: PubMed (Medline), Google Scholar, and the Cochrane Library (Wiley). The keywords used were "ketogenic diet" (or specific components including "ketosis" and "ketone bodies"), "Alzheimer's disease", and "memory function" (or synonyms).

RESULTS: Twenty-three relevant articles were chosen for review. However, only five studies met the inclusion criteria for analysis.

CONCLUSIONS: To date, only a limited number of studies on the effects of ketogenic diets specifically on Alzheimer's in humans have been conducted. The five studies that examined humans with AD did show improvement of memory performance after establishing ketosis, although not necessarily through traditional dietary means. However, animal models of Alzheimer's have shown an improvement in cognitive performance with ketogenic diets and ketosis induction. These results warrant more clinical trials in humans and overall further elucidation amongst individuals with Alzheimer's.

INTRODUCTION

ALZHEIMER'S DISEASE (AD): Clinically, AD is characterized by progressive decline in memory and language as well as the pathological accumulation of plaques and neurofibrillary tangles[1].

The human brain relies almost entirely on glucose for its energy. An early feature of AD is region specific declines in brain glucose metabolism (Figure 1)[2]. The hypometabolism that occurs in AD usually occurs early on and may contribute to both the cognitive decline as well as the pathological changes to the brain[1].

Therefore, interventions on this metabolic effect may potentially improve the AD patient's clinical symptoms and produce pathological decline[3].

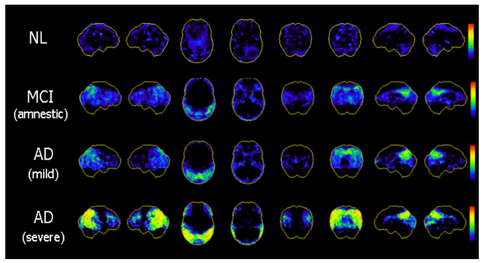

Figure 1: Colour coded PET scan images of brain regions showing statistical significance (Z-scores) of reduced metabolism. Normal (NL), Mild Cognitive Impairment (MCI), Alzheimer's disease (AD) – mild and severe[2 (p 133)].

KETOGENIC DIETS: The classic ketogenic diets (Figure 2) developed in the 1920's are high fat diets (at least 75%) designed to mimic the biochemical changes that occur during starvation[4]. The fats are biochemically converted to the ketone bodies β-hydroxybutyrate, acetoacetate, and acetone, which serve as alternative energy sources to glucose[3].

KETOSIS: Under certain situations, such as prolonged starvation, the liver will produce ketone bodies to be used as alternative fuel to glucose for extrahepatic tissues, including the brain[1].

Reduced glucose concentration may lead to specific adverse effects on the hippocampus – the brain structure responsible for the consolidation of memory[5].

Ketone bodies can cross the blood-brain barrier, enter the neuronal mitochondria and serve as an alternative energy source to glucose. The extra available energy can improve neuronal metabolism and survival and therefore, potentially lead to improved cognitive function in people with AD[5].

For the purposes of this review, all manners of ketosis induction were considered for inclusion because of the limited studies on classic ketogenic diets in humans in relation to AD. Further, both dietary means and "food-drug" / ketogenic agent means were considered. Medium Chain Triglycerides (MCTs) including the "medical food" Axona® are metabolized to ketone bodies once ingested[5]. Medical foods are substances that provide a specific nutrient need that cannot be satisfied by diet modification alone[5]. The inclusion of "food-drugs" as well as dietary ketosis was done due to the lack of studies focusing on traditional ketogenic diets but also because the mechanism of action on the brain remains the same. Therefore, it was assumed that any effect on cognition in AD would occur in the same manner through any means of ketone body production and utilization by the brain.

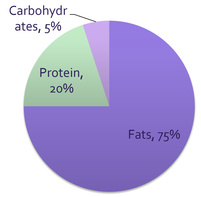

Figure 2: Typical macronutrient distribution of a traditional ketogenic diet[4].

RESEARCH QUESTION

In individuals with or at risk for Alzheimer's disease, can compliance to a ketogenic diet and the induction of ketosis improve memory function?

METHODS

STRUCTURED LITERATURE REVIEW: Three databases were searched for the keywords "ketogenic diets", "ketosis" AND "Alzheimer's disease" AND "cognition", "memory function", or synonyms. All manners of peer-reviewed articles published after 2004 were included. Table 1 below identifies the specific inclusion and exclusion criteria utilized to assess the articles.

Table 1: Inclusion and exclusion criteria for literature analysis.

Inclusion Criteria	Exclusion Criteria
Disease Examined	
Alzheimer's disease (or risk of development)	Effects of ketosis solely on other neurological disorders (e.g. epilepsy or Parkinson's disease)
Population	
People with Alzheimer's disease or at risk thereof (e.g. Mild Cognitive Impairment)	Animal models only
Intervention	
Ketogenic Diets, Ketosis or Ketosis-inducing agents (dietary and non-dietary)	Other diets, dietary lifestyles, calorie restriction
Primary Outcome	
Changes in Alzheimer's disease Assessment Scale –Cognitive Subscale (ADAS-Cog), Mini-Mental State Exam (MMSE), or other cognition assessment measures	No outcome measurements of cognitive function
Study Characteristics	
Publication date between 2004 and March 2015	Publication date before 2004
English language paper	Not English
Peer-reviewed	Not peer-reviewed (editorials or opinion reports)
Accessibility	
Available through the University of Ottawa Library Network	Unavailable through the University of Ottawa Library Network

RESULTS

Of the 416 papers found in the initial search, five were eventually analyzed in this review. Figure 3 depicts the search process and Table 2 provides a summary of the findings from the papers. The Jadad Scale was consulted to judge the quality of the RCT's reviewed[6].

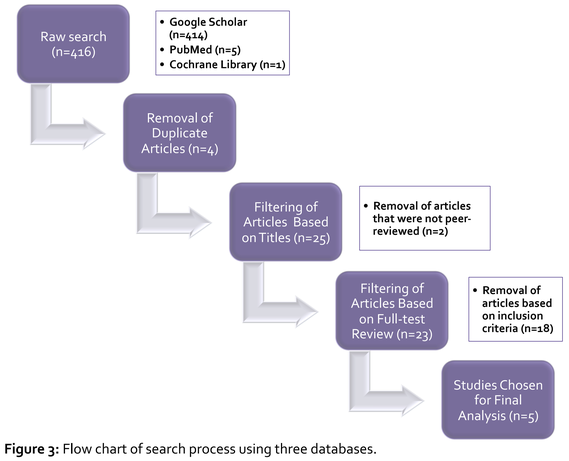

Figure 3: Flow chart of search process using three databases.

Table 2: Summary of literature review results.

Study	Population Examined	Design of Study	Primary Outcome Measures (Memory Function)	Commentary
Reger et al[7], 2004	20 subjects with AD or amnestic mild cognitive impairment (MCI)	RCT	- MCT (medium chain triglyceride) treatment facilitated performance on the ADAS-Cog for APOε4 allele negative subjects, but not for APOε4 allele positive subjects (P = 0.04). - APOε4 allele presence is known risk factor for AD. - Higher ketone values → greater improvement in paragraph recall with MCT treatment relative to placebo across all subjects (r=0.50, p = 0.02).	- MCT ketogenic agent - Same kind of results as Henderson et al[8], 2009. - APOE4 related differences in ketone body metabolism. - Small number of subjects. - Benefits in e4- group even though e4+ group had much higher serum ketone levels. Jadad Score: 4 (method used to generate the sequence of randomization not described).
Henderson et al[8], 2009	152 subjects diagnosed with mild to moderate Alzheimer's disease	RCT	Among patients without the APOE4 allele, those administered AC-1202 performed significantly better on the ADAS-Cog relative to placebo at both Day 45 (p=0.0005) and Day 90 (p=0.0148).	- Ketogenic agent AC-1202 - 80% of subjects were on currently approved AD meds. - Chronic induction of ketosis may offer a novel strategy for AD that can be used with current therapies. - Small number of subjects. - Adverse GI effects to agent! - More rigorous than Reger et al[7] study: Jadad Score: 5
Krikorian et al[3], 2012	23 older adults with mild cognitive impairment (MCI)	Clinical Trial: - Random assignment - Not placebo-controlled - Not blinded	Urine ketone body levels were related to memory performance, r = 0.45, p = 0.04.	- Dietary ketosis (low carbohydrate diet ONLY; no effect on high fats examined). - Exploratory/pilot study.
Maynard & Gelblum[9], 2013	55 outpatients aged 50 years with probable mild-to-moderate AD who had received CT for 6 months	Retrospective Cohort Study	- Caregiver assessments indicated that most patients were stable or improved with respect to memory and ability to carry out activities of daily living. - MMSE results stable over 15 months of therapy (p=0.5233).	Caprylic triglyceride only (CT) → type of MCT. Adverse effects to CT were mainly GI related.
Maynard & Gelblum[10], 2013	Eight patients aged 50 years with probable mild-to-moderate AD who had received CT for 6 months	Retrospective Case Studies → Chart Review/ Caregiver survey	Several patients had stabilization (cases 3 and 6) or modest improvements (cases 2 and 5) after CT was added to therapy, while MMSE scores in others continued to decline (cases 1, 4, 7, and 8).	- MMSE measure only. - Caprylic triglyceride only (CT) → type of MCT.

DISCUSSION

Overall, all five studies analyzed showed improved or stabilized cognitive function when patients with AD or those at increased risk for AD were administered ketogenic agents in the form of medical food or when they adhered to a ketosis inducing low carbohydrate diet. However, no evidence was found that suggested that following a classic ketogenic diet (Figure 2) benefits AD patients in terms of memory. Surprisingly, the increased cravings for sweets and high-carbohydrate foods that occurs in AD may make it impossible for patients to comply to a strict ketogenic diet. Further, a high fat diet may actually be impractical in the elderly population[5].

Limitations:

- Review of only English studies and only those available through the uOttawa Library Network.
- Not enough available studies to answer the research question solely based on ketogenic diets. Other ketosis inducing compounds and non-dietary agents had to be examined.
- It would have been preferable to only analyze clinical trials. However, most research on the relationship between ketogenic diets and AD has been done on animals.

Potential Biases and Conflicting Interests:

Four of the studies analyzed were funded by Accera Inc., a pharmaceutical company. Further, Dr. Samuel Henderson, a co-author in two of the studies is Accera Inc.'s VP of Research and Development.

CONCLUSIONS AND FUTURE IMPLICATIONS

"Medical foods" or ketogenic agents such as MCTs provide ketone bodies in the presence of high-carbohydrate diets, making them ideal additions to a regular dietary regimen. This review determined that ketogenic agents and ketosis induction can improve cognitive ability in AD patients. More studies must be conducted to determine the long term safety of ketogenic agents such as MCTs as well as their role in the treatment of AD.

REFERENCES AVAILABLE ON HANDOUT