Commentary

Pilot feasibility and safety study examining the effect of medium chain triglyceride supplementation in subjects with mild cognitive impairment: A randomized controlled trial

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ABSTRACT

Background: Impaired brain glucose metabolism appears to be a potential pathogenic feature of mild cognitive impairment (MCI). This study examined the potential for increasing circulating ketone bodies through medium chain triglyceride (MCT) supplementation, as a means to beneficially modulate brain homeostasis in subjects with MCI.
Methods: Six participants with MCI were enrolled in a randomized placebo-controlled trial. Participants received 56 g/day of either medium chain triglycerides (MCTs) or placebo for 24 weeks. Serum β-hydroxybutyrate concentrations, apolipoprotein-E4 status, and cognitive assessments were carried out. Due to the small number of participants only the raw scores were examined.
Results: Intake of MCT oil increased serum ketone bodies and improved memory, while intake of placebo did not show improvement in any of the cognitive measures tested.
Conclusions: Consumption of 56 g/day of MCTs for 24 weeks increases serum ketone concentrations and appears to be a candidate for larger randomized control trials in the future that quantify the modulation of cognitive function through supplementation with ketone precursors, in patients with MCI.
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1. Introduction

Alzheimer's disease (AD) is the result of slow progressive neurodegenerative changes that develop in the brain and is initially characterized by selective impairments of the cognitive domains related to learning and memory [1]. Apolipoprotein E ε4 allele (ApoE4) increases the risk of AD by three times in heterozygotes and by 15 times in homozygotes [2]. The presence of cognitive impairment that is not sufficient to affect social function or activities of daily living is generally referred to as mild cognitive impairment (MCI), with MCI being generally recognized as one of the earliest stages of AD.

Several pathogenic mechanisms that underlie the changes observed in AD have been proposed, and an emerging body of evidence points to significantly lower brain glucose metabolism as being a general feature of AD which precedes cognitive dysfunction and pathological alterations [3]. It has been hypothesized that perturbations in cell energy metabolism cause the clinical and histologic changes observe in AD [4].

There is increasing evidence of a functional response leading to improved brain function in response to the consumption of nutritional supplements that increase energy sources in the brain, especially, the elevation of ketones [5,6]. This study evaluated the effect of the daily consumption of an oil, composed of medium chain triglycerides (MCTs) for 24 weeks on serum ketone body concentrations (β-hydroxybutyrate [BHB]) and cognitive performance assessed by the Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog), Trail Making Test, and Digit Symbol Test, in MCI subjects.

2. Study design and methods

Six individuals ≥ 50 years, with MCI were enrolled in a pilot and feasibility, randomized double blind placebo-controlled parallel trial. MCI was defined using the 2011 National Institute on Aging and Alzheimer's Association work group [7] and related clinical guidelines. Briefly, diagnosis was made on: (1) identification of a concern for

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change in cognition (clinical observation and/or patient history corroborated by care giver), (2) mini mental state examination score of 25–28, (3) preservation in independence of functional abilities, and (4) lack of dementia (significant impairment of social or occupational functioning). Subjects were excluded if they had major depression as determined by the Geriatric Scale for Depression in Dementia score ≥ 6, were on medication for MCI less than 90 days, and had uncontrolled hypothyroidism, B_{12} deficiency, or clinically significant hepatic disease or insufficiency. The study was approved by the Institutional Review Board of Pennington Biomedical Research Center, where the study was conducted, and records maintained. Subjects recruited from Baton Rouge and the surrounding areas provided written informed consent. The trial was registered on ClinicaTrials.gov (NCT01669200).

Psychological testing which included the ADAS (Cog), Trail making, and Digit Symbol tests was done just prior to the baseline visit. Subjects reported for the baseline visit fasting from 9 p.m. the prior night, and blood was drawn for ApoE4 status, serum BHB, blood glucose and insulin. Subjects then consumed 56 g of MCT's (MCT oil, Nestle™) or placebo (canola oil, color matched) added to six ounces of Yoplait™ 99% fat-free fruit yogurt. Randomization was conducted by the study pharmacist using a random number table and was revealed to study staff and investigators only at the conclusion of the study. Blood was drawn 90 min later to assess post-prandial serum BHB. In addition, subjects' diet was assessed by a registered dietitian and they received instruction on incorporation of the study products into the diet. Study products were dispensed at each visit in excess of requirements, and re-issued at every visit. Returned product was measured to assess compliance.

The post-baseline visits at weeks 4, 8, 12, 16, and 20 included dispensation of study products, compliance assessment, and instruction by a registered dietitian. In addition, at week 4, baseline blood testing for glucose, insulin, and pre/post-prandial BHB were repeated. At week 24, the clinical tests except ApoE4 status, and the psychological tests done at baseline were repeated. Subjects were asked about adverse events at all post-baseline visits. Weight and vital signs were measured at all visits.

2.1. Statistical analyses

Twenty subjects were to be randomized to two groups of ten each; however, the trial concluded after six subjects were enrolled due to a preference among them for enrolling in other MCI studies, including drug trials. Since only four subjects completed the study there was insufficient data for assessing statistical significance in the differences between the two groups. Therefore, the raw scores were examined.

3. Results

Subjects ranging in age from 58 to 78 years were enrolled and followed from October 2012 to August 2013. One subject with a history of gastrointestinal dysfunction dropped out due to a recurrence of these events and one subject was dropped due to non-compliance. There were no other adverse events. Two of the remaining subjects received MCT oil (one male, one female) and two received the placebo (one male, one female). Subjects were able to easily incorporate the MCT oil into their diet, without changes in their usual intake or weight gain.

Of the two subjects who received the MCT oil, one had ApoE4 negative status, and memory performance as measured by the memory subtests of the ADAS-COG (word recall, word recognition, remembering test instruction) increased from baseline to week 24. No improvements in language or praxis of the ADAS-COG were observed in this individual. Consequently, there was an increase in the overall ADAS (Cog) score in this individual. In the second participant who was homozygous for ApoE4, memory performance as measured by word recall, word recognition, remembering test instruction also improved from baseline to week 24, but a decline in orientation led to a decrease in overall ADAS (Cog) scores (Table 1). There were no improvements in the Trail Making

Table 1
Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS [Cog]) scores from baseline to week 24.

	Memory	Language	Praxis	Overall ADAS (Cog)	
Test					
ApoE4$^{(-)}$	4	1	0	5	Week 0
	10	0	0	10	Week 24
ApoE4$^{(+)}$	9	1	1	18	Week 0
	12	0	2	14[a]	Week 24
Placebo					
Subject 1	6	0	1	7	Week 0
	5	0	1	7	Week 24
Subject 2	14	2	1	17	Week 0
	8	2	1	13	Week 24

[a] Decline in orientation reduced the overall ADAS (Cog).

Test, and Digit Symbol Test. Post-prandial BHB concentrations increased in the subject with negative ApoE4 status at baseline, but the increase in post-prandial BHB was progressively less when the tests were repeated at week four and week 24. In the participant with positive ApoE4 status, there was a consistent increase in post-prandial serum BHB from baseline to week 24 (Table 2). Blood glucose and insulin concentrations were in the normal range. Subjects in the placebo group showed no improvement in memory or overall ADAS (Cog) scores (Table 1).

4. Discussion

Supplementation with MCT oil for 24 weeks increased post-prandial serum BHB concentrations and improved memory in a participant with negative ApoE4 status, and to a lesser extent in a participant with positive ApoE4 status. In the subject with ApoE4 positive status, the post-prandial BHB concentrations progressively increased over the course of the study. However, the increase in post-prandial BHB in the participant with ApoE4 negative status progressively lessened over the course of the study suggesting an adaptation whereby ketones were used at an increased rate as an energy source.

When consumed in sufficiently large quantities MCTs promote the generation of ketone bodies from excess acetyl-CoA. Ketone bodies are transported across the blood brain barrier for oxidative metabolism by neuronal mitochondria, and serve as an energy source. However, the adult brain does not usually metabolize ketone bodies unless uptake of glucose in the brain is reduced [8]. Cerebral glucose metabolism is therefore dependent upon both glucose transportation and the rates of intracellular oxidative catabolism, with ketone bodies potentially serving as an auxiliary energy source when glucose concentrations are reduced [1].

Positron emission topography (PET) using F-fluorodeoxyglucose (FDG) as a tracer shows that AD is characterized by reductions in cerebral glucose metabolism in the parietal, temporal, and frontal lobes [9,10] which are preceded by hypometabolism in memory-related regions such as the hippocampal structures [11]. Patients with

Table 2
Serum β-hydroxybutyrate concentrations before and after eating yogurt containing medium chain triglyceride oil.

	Week 0 mM	Week 4 mM	Week 24 mM	
Test				
ApoE4$^{(-)}$	0.19	0.02	0.01	Fasting
	0.64	0.26	0.15	Post-prandial
ApoE4$^{(+)}$	0.06	0.26	0.13	Fasting
	0.32	0.39	0.54	Post-prandial
Placebo				
Subject 1	0.04	0.08	0.06	Fasting
	0.01	0.03	0.02	Post-prandial
Subject 2	0.04	0.02	0.03	Fasting
	0.04	0.03	0.03	Post-prandial

MCI suffer isolated memory damage. Previous evidence from FDG-PET scans indicates that there is an apparent decrease in glucose metabolism in hippocampal structures in MCI [12]. The expression of glucose transporters Glut-1 and Glut-3, which play a key role in modulation of brain glucose transportation, is also decreased in AD patients [13]. Physiologically, ketone bodies are a potential replacement fuel for the brain enabling the preservation of brain function during periods of low glucose availability. Moreover, the brain has a transport system for ketones that is independent of glucose transport [3].

In a study investigating the effects of a single 40 ml dose of MCT oil an elevation of serum BHB to 0.5 mM was induced after two hours and led to a significant correlation with performance on a paragraph recall test in the overall sample. Further, subjects lacking the ApoE4 gene variant also showed significant improvements in the ADAS (Cog) [5]. In another study, daily consumption of 20 g of MCTs resulted in significant improvement in cognitive effects in subjects lacking the ApoE4 gene variant, at the end of 90 days. However, the cognitive effects were not significant in the overall sample [6]. Placing subjects with MCI on a low carbohydrate diet to induce ketosis has also been shown to improve memory [14].

In the present study, MCT oil intake induced an increase in BHB concentrations and led to an improvement in memory in subjects with MCI. The study is limited in that it was not possible to show statistical significance due to the small number; however, based on the estimate of effect size provided by this study a power analysis showed that 16 subjects in each group are needed to provide 80% power to detect differences in the improvement in memory. The calculations assume a t-test for comparing means of two independent samples with $\alpha = 0.05$, to test equality of mean change score against a two-directional alternative of unequal change.

Approved drugs only treat the symptoms of the disease and drug trials focusing on a single mechanism do not seem to have had much success. Alzheimer's disease is a multifactorial disease, but, a common feature of many systemic processes linked to AD is involvement in energy metabolism [15]. Anecdotal evidence indicates that MCTs as part of a comprehensive therapeutic system are effective in reversing cognitive decline [16]. It is likely that targeting multiple aspects of the pathophysiology may prove successful in treating AD; however, optimizing the therapeutics of each of these targets is of paramount importance [16].

5. Conclusions

Intake of MCT oil for 24 weeks increases serum post-prandial BHB concentrations and improves memory in patients with MCI. At a plasma concentration of 1.5 mM, 18% of the brain's energy needs which is the deficit observed in MCI, can be met [3,17]. However, palatable more readily convertible forms of BHB or keto-esters may be a more effective treatment.

6. General significance

Improvement in memory through supplementation with MCT oil offers support to the hypothesis that ketones counteract the effects of impaired cerebral energy metabolism.

Transparency document

The Transparency document associated with this article can be found, in the online version.

Conflicts of interest

The authors declare no conflicts of interest.

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