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Research article

Effects of a medium-chain triglyceride-based ketogenic formula on cognitive function in patients with mild-to-moderate Alzheimer's disease

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ABSTRACT

Clinical and animal studies suggested that a medium-chain triglyceride (MCT)-based ketogenic diet provides an alternative energy substrate to the brain and has neuroprotective effects, but the clinical evidence is still scarce. Here we examined the effect of an MCT-based ketogenic formula on cognitive function in patients with Alzheimer's disease (AD). The subjects were 20 Japanese patients with mild-to-moderate AD (11 males, nine females, mean age 73.4 ± 6.0 years) who, on separate days, underwent neurocognitive tests 120 min after consuming 50 g of a ketogenic formula (Ketonformula®) containing 20 g of MCTs or an isocaloric placebo formula without MCTs. The patients then took 50 g of the ketogenic formula daily for up to 12 weeks, and underwent neurocognitive tests monthly. In the first trial, although the patients' plasma levels of ketone bodies were successfully increased 120 min after the single intake of the ketogenic formula, there was no significant difference in any cognitive test results between the administrations of the ketogenic and placebo formulae. In the subsequent chronic intake trial of the ketogenic formula, 16 of the 20 patients completed the 12-week regimen. At 8 weeks after the trial's start, the patients showed significant improvement in their immediate and delayed logical memory tests compared to their baseline scores, and at 12 weeks they showed significant improvements in the digit-symbol coding test and immediate logical memory test compared to the baseline. The chronic consumption of the ketogenic formula was therefore suggested to have positive effects on verbal memory and processing speed in patients with AD.

1. Introduction

Alzheimer's disease (AD) is one of the most common causes of dementia, and is associated with progressive decline in memory, language, and visuospatial abilities. Pathologically, AD is characterized by the progressive accumulation of neuritic plaques of amyloid-beta (Aβ) followed by neurofibrillary tangles of hyperphosphorylated tau. Individuals with AD show impaired glucose utilization in the brain, i.e., a consistent pattern of reduction in the cerebral metabolic rate of glucose in the hippocampus, posterior cingulate, precuneus, and prefrontal locations by positron emission tomography with ^{18}F-fluorodeoxyglucose (FDG-PET) [1]. The presence of insulin resistance in the brains of AD patients has also been suggested [2]. Anti-dementia drugs, such as cholinesterase inhibitors and N-methyl-D-aspartate (NMDA) receptor antagonists, have been used to delay the progression of AD. However, the etiology of AD is still elusive and no cure has been found.

Medium-chain triglycerides (MCTs), which are the main constituents of coconut and palm kernel oils, are absorbed and metabolized via medium-chain fatty acids into ketone bodies. Usually, the main energy substrate for the brain is glucose. However, under certain circumstances such as extended fasting or a very high-fat ketogenic diet, the liver produces ketone bodies as an energy substrate for extrahepatic tissues including the brain [3]. Ketone bodies are composed of β-hydroxybutyrate, acetoacetate, and acetone, and the former two

Abbreviations: AD, Alzheimer's disease; ADAS-cog, AD Assessment Scale-Cognitive Subscale; MCT, medium chain triglycerides; TMT, Trail Making Test; WAIS-III, Wechsler Adult Intelligence Scale-3rd; WMS-R, Wechsler Memory Scale-Revised

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molecules get to the brain via the blood-brain barrier and are oxidized in astrocytes as an alternative fuel under ketogenic conditions [4,5].

Several studies have indicated that ketone bodies have neuroprotective effects in the brain and may improve cognitive function (for a review see [6]). In mouse models of AD, ketone bodies were reported to show a cognition-sparing property and to reduce Aβ and tau pathology [7,8]. In humans, ketone bodies may have beneficial effects on cognitive outcomes in AD and mild cognitive impairment (MCI), although the findings of previous studies are sometimes conflicting [9–12]. Reger and colleagues initially reported that a single intake of an MCT drink (NeoBEE®) containing 40 ml of MCTs (mainly caprylic triglycerides) significantly facilitated performance on the AD Assessment Scale-Cognitive Subscale (ADAS-cog) among subjects without the ε4 allele of *APOE* (apolipoprotein E), but not among those who carried the ε4 allele [9].

Thereafter the same research group organized a relatively large-scale randomized controlled trial of the MCT known as AC-1202 (20 g of caprylic triglycerides per day) in mild-to-moderate AD patients, and they observed significantly beneficial effects at day 45 but not day 90 in the total patient series, although such effects remained at day 90 among the patients who did not carry the ε4 allele [10]. Ohnuma and colleagues performed an open label trial of Axona® containing 20 g of caprylic triglycerides for 3 months in mild-to-moderate AD patients, and they failed to find significant improvement of any cognitive function compared to the baseline, although they observed that some ApoE4-negative AD patients with a baseline Mini-Mental State Examination (MMSE) score ≥14 showed improvement in their MMSE and ADAS scores [12]. When the same research group re-analyzed that study's data, they found that the AD patients with a baseline MMSE score ≥15 showed significant improvement of memory and orientation [13]. Another research group reported that older adults with MCI exhibited ketosis and showed superior verbal memory performance after receiving a very-low-carbohydrate diet for 6 weeks compared to their performance after receiving a high-carbohydrate diet for the same period [11]. Based on the inconsistency of these results, further investigations are warranted.

Recently, we reported that a single dose of an MCT-based ketogenic formula (Ketonformula®) had cognition-enhancing effects on working memory, visual attention, and task switching in non-demented elderly individuals [14]. We conducted the present study to examine the possible effect of single and chronic (12-weeks) administrations of this formula on cognitive function in patients with mild-to-moderate AD.

2. Materials and methods

2.1. Patients

We studied 20 patients (11 males, nine females; mean age 73.4 ± 6.0 years) who were diagnosed with AD based on the criteria of the U.S. National Institute of Neurological and Communicative Disease and Stroke and the Alzheimer's Disease and Related Disorder Association [15]. The patients' characteristics are summarized in Table 1. The use of anti-dementia drugs (e.g., cholinesterase inhibitors) was allowed; however, changes in dose were not allowed during the trial. All 20 of these patients participated in the first trial of this study, which examined the possible effect of a single administration of ketogenic formula on cognitive function.

For the second trial, which was a longitudinal, open-label 12-week trial, 19 of the 20 patients gave their consent to participate, and three dropped out prior to the end of the 12-week administration period. All three dropouts were due to diarrhea, which is the most frequently reported side effect of MCT intake [10], though MCTs in doses up to 1 g/kg/day have a robust safety record in humans [16,17]. Written informed consent for participation in the study was obtained from every patient. In 18 of the 20 patients, we also obtained written informed consent from a family member. For the remaining two patients, no family member was available to come to the laboratory. However, these patients' MMSE scores were > 20 and they were considered to be able to understand and agree to participate in the study based on their free will. This study was performed in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the National Center of Neurology and Psychiatry, Japan.

Table 1
Baseline demographic and clinical parameters of the 20 Japanese patients with Alzheimer's disease.

Age (years)		73.4	±	6.0
Men / women		11	/	9
MMSE		20.0	±	4.3
Onset of disease (years)		69.1	±	8.2
Anti-dementia drugs				
	Donepezil (mg/day)	2.5	±	3.0
	Rivastigmine (mg/day)	0.9	±	4.0
	Galantamine (mg/day)	0.6	±	2.7
	Memantine (mg/day)	2.3	±	5.7
Plasma measurements				
	BUN (mg/dL)	15.5	±	4.5
	Creatinine (μmol/L)	0.8	±	0.2
	AST (IU/L)	24.4	±	4.9
	ALT (IU/L)	19.8	±	7.1
	γ-GTP (IU/L)	25.8	±	17.0
	Total cholesterol (mmol/l)	189.0	±	47.8
	Triacylglycerols (mmol/l)	137.2	±	64.1
	Glycated hemoglobin (%)	5.9	±	0.7
	Glucose (mmol/l)	106.5	±	22.3

MMSE: mini mental state examination, BUN: blood urea nitrogen, AST: aspartate aminotransferase, ALT: alanine aminotransferase, γ-GTP: γ-glutamyl transpeptidase.

2.2. Procedures

The first study followed a double-blind placebo-controlled design with two study visits for each patient. During each visit, the patient received (in a randomized sequence) one of two isocaloric formulae (370 calories each): a ketogenic formula containing emulsified MCTs, or a placebo formula containing emulsified long-chain triglycerides as a substitute for MCTs. Ketonformula®, which is used in ketogenic diet therapies [18], was used as the ketogenic formula (see [14] for its composition). A single serving of the ketogenic formula provided 20 g of MCTs in 35.9 g of total fat. The fatty acid compositions of caprylic acid and capric acid are 30.3 and 9.8 (g/100 g total fatty acid), respectively.

The ketogenic formula was suspended in hot water to emulsify the sample. The patients fasted from 10:00 p.m. on the night prior to the study visit and arrived at 10:00 a.m. for an immediate blood draw to determine their plasma ketone body levels (acetoacetate and β-hydroxybutyrate). The patients then consumed one of the test formulae, and blood was drawn again 120 min after the intake. After the second blood sampling, cognitive tests were administered. The blood samples were centrifuged and stored at −20 °C. The plasma concentrations of ketone bodies were measured by an enzymatic method at SRL Corp. (Tokyo).

We next performed a longitudinal, open-label 12-week trial for 19 patients. Each patient was instructed to intake 50 g of the ketogenic formula containing 20 g of MCTs daily along with his or her usual diet. Blood samples were obtained every 4 weeks in all patients. Cognitive functions were tested at weeks 4, 8, and 12.

2.3. Cognitive measures

We selected cognitive tests while considering the possible ceiling or floor effects in our patients with mild-to-moderate AD. The test battery consisted of immediate logical memory, delayed logical memory, digit span and visual memory span tests from the Wechsler Memory Scale-Revised (WMS-R) [19], block-design and digit-symbol coding tests from

Table 2
Cognitive test scores after a single administration of ketogenic or placebo formula and plasma ketone body levels before and after the administration.

			Ketogenic formula			Placebo formula			d.f.	t	p value
			score (mean ± standard deviation)								
Cognitive test score (120 min after administration)											
	WAIS-III										
		Block design	24.4	±	12.8	24.3	±	12.0	19	0.11	0.92
		Digit-symbol coding	35.8	±	17.4	37.9	±	17.6	18	−0.52	0.61
	WMS-R										
		Logical memory (immediate)	6.9	±	7.3	6.9	±	7.7	19	0.00	1.00
		Logical memory (delayed)	2.6	±	5.1	2.4	±	6.3	19	0.31	0.76
		Digit span	10.4	±	2.9	10.3	±	2.6	19	0.14	0.89
		Spatial span	12.3	±	3.6	12.7	±	4.9	19	−0.55	0.59
	Stroop test										
		Stroop effect (second)	101.4	±	45.0	104.9	±	53.2	18	−0.50	0.62
		Correct (number)	41.1	±	14.9	42.1	±	14.8	18	−2.45	0.025
	Trail-making test										
		A (second)	110.7	±	124.1	105.9	±	129.5	17	−1.51	0.15
		B (second)	191.3	±	128.4	203.1	±	122.2	13	−0.93	0.372
Plasma											
	Pre-treatment										
		Acetoacetate (μmol/L)	31.0	±	22.3	46.1	±	42.3	19	−1.86	0.08
		β-hydroxybutyrate (μmol/L)	64.8	±	58.7	111.7	±	99.1	19	−2.54	0.020
	Post-treatment										
		Acetoacetate (μmol/L)	138.0[a]	±	69.0	62.7	±	45.8	19	5.95	< 0.001
		β-hydroxybutyrate (μmol/L)	470.9[a]	±	292.6	149.3	±	131.2	19	5.54	< 0.001

WAIS-III: Wechsler Adult Intelligence Scale-3rd Edition.
WMS-R: Wechsler Memory Scale-Revised.
[a] There was a significant difference ($p < 0.05$), compared to the pre-treatment by paired t-test..

the Wechsler Adult Intelligence Scale-3rd (WAIS-III) [20], the Stroop test [21], and the Trail Making Test (TMT) [22]. The logical memory, digit span, and visual memory span tests measure the subject's memory functions, and the block-design test evaluates the subject's spatial visualization ability and motor skill. The digit-symbol coding test estimates multiple cognitive functions, including processing speed, working memory, visuospatial processing, and attention. The subscales of the WMS-R and WAIS-III are the raw score, with higher scores indicating better cognitive function.

The Stroop test is widely used to assess the mental processes of attentional fatigue and the decreased ability to inhibit ongoing competing conflicts; in this test, the reaction time represents the "attentional process," and the error number is associated with impulsivity. The TMT is a neuropsychological test of visual attention and task -switching ability. Subjects who take a long time to finish the TMT-A task are deemed to have low visual attention, and those requiring a long time to finish the TMT-B task are considered to have poor visual attention and task-switching ability.

2.4. Statistical analyses

In the first trial, the effect of a single administration of the ketogenic formula on cognitive tests and that of the placebo formula were compared by paired-t test. In the second trial, the changes in cognitive measurement scores over 12 weeks of treatment with MCTs were analyzed by a repeated analysis of variance (ANOVA). Statistical analyses were performed using IBM SPSS Statistics ver. 23.0 for Windows software (IBM Japan, Tokyo).

3. Results

3.1. Double-blind placebo-controlled single trial

We first evaluated the effects of a single administration of the ketogenic formula on the patients' plasma ketone body levels and their cognitive measurement scores. As expected, the administration of the ketogenic formula induced significant increases of both the plasma acetoacetate and β-hydroxybutyrate levels compared to that of the placebo formula (Table 2). However, we found no significant difference between scores after taking the ketogenic formula and those after the placebo formula in any cognitive test after the correction for multiple testing (Table 2).

3.2. Open-label chronic trial

We next estimated the influences of the chronic consumption of ketogenic formula on the patients' plasma ketone body levels and their cognitive functions. In regard to ketone body levels, we found no significant increase at week 4, 8, or 12 from the baseline level of the initial assessment, probably because the patients did not take the ketogenic formula prior to the blood sampling in the morning of each assessment day. In the 16 CE patients who completed the 12-week trial, significant improvements in the digit-symbol coding test and immediate logical memory test were revealed when we compared the cognitive scores at 12 weeks with those at baseline, and significant improvements in the immediate and delayed logical memory tests between the scores at 8 weeks and baseline were identified even after the correction for multiple comparisons (Table 3).

4. Discussion

In the first placebo-controlled single trial, the plasma levels of ketone bodies were successfully increased after the ketogenic formula intake, but there was no significant change in the cognitive test scores after its consumption. In contrast, in the subsequent open-label chronic trial, the ketogenic formula had significant cognition-enhancing effects in the AD patients, although the increases in ketone body levels were not statistically significant. To our knowledge, this is the first study to examine the influences of acute-single and chronic continuous administrations of a ketogenic formula in the same participants.

We found increased acetoacetate and β-hydroxybutyrate levels in the patients' plasma after the single administration of the ketogenic

Table 3
The changes in cognitive test scores and plasma ketone body levels during 12-week trial of ketogenic formula intake.

			Initial	Post 4 weeks	Post 8 weeks	Post 12 weeks	d.f.	f	p value
			score / concentration (mean ± standard deviation)						
Cognitive test									
	WAIS-III								
		Block design	25.7 ± 11.7	24.6 ± 11.8	26.9 ± 11.9	25.4 ± 13.6	1.70	0.86	0.47
		Digit-symbol coding	37.4 ± 19.0	39.9 ± 21.7	42.6 ± 20.0	44.0* ± 21.6	3.00	5.24	0.004[a]
	WMS-R								
		Logical memory (immediate)	7.1 ± 8.3	9.0 ± 9.1	11.7* ± 10.6	11.2** ± 11.1	1.81	9.55	0.001[a]
		Logical memory (delayed)	2.9 ± 7.0	4.4 ± 7.7	6.9* ± 9.6	6.4 ± 10.2	1.88	6.67	0.005[a]
		Digit span	10.6 ± 2.5	10.9 ± 2.4	10.6 ± 2.7	10.7 ± 2.9	3.00	0.20	0.90
		Spatial span	13.1 ± 5.2	13.1 ± 4.8	12.8 ± 4.4	12.5 ± 5.5	3.00	0.27	0.85
	Stroop test								
		Stroop effect (second)	108.8 ± 57.2	94.5 ± 39.6	99.3 ± 55.2	94.4 ± 40.6	1.52	4.38	0.009[a]
		Correct (number)	43.4 ± 12.3	43.8 ± 12.0	44.9 ± 8.9	47.5 ± 1.1	1.37	1.03	0.39
	Trail-making test								
		A (second)	75.6 ± 41.9	65.1 ± 26.3	64.2 ± 37.2	71.0 ± 48.2	3.00	0.69	0.57
		B (second)	175.3 ± 98.9	129.0 ± 65.9	151.8 ± 73.6	153.9 ± 97.4	3.00	2.47	0.09
Plamsa									
	Acetoacetate (μmol/L)		33.0 ± 23.9	42.8 ± 39.5	35.2 ± 18.2	43.4 ± 40.3	3.00	0.53	0.66
	β-hydroxybutyrate (μmol/L)		67.6 ± 64.4	103.4 ± 138.8	76.8 ± 82.3	106.3 ± 157.3	3.00	0.49	0.69

WAIS-III: Wechsler Adult Intelligence Scale-3rd Edition.
WMS-R: Wechsler Memory Scale-Revised.
* Significant difference (post hoc; $p < 0.05$) compared to the initial score (after Bonferroni correction).
** Trend toward a significant difference (post hoc; $p = 0.053$) compared to the initial score (after Bonferroni correction).
[a] $p < 0.05$.

formula compared with those after the administration of the placebo formula. These results are congruent with our previous data in a study of non-demented elderly subjects [14]. However, there were no significant differences in the cognitive test scores between the single intake of the ketogenic and placebo formulae. In another study, a single administration of MCTs facilitated the performance on the ADAS-cog in *APOE* ε4− subjects, but not in *APOE* ε4+ subjects [9]. The APOE ε4 allele has been shown to influence energy metabolism in cognitively normal, older subjects [23], individuals with MCI [24], and AD patients [25]. Further examinations of the pharmacokinetic response patterns in AD patients with differing *APOE* genotypes may confirm our findings.

In the second trial on the effects of a chronic consumption of the ketogenic formula, we found no significant change in the plasma ketone body levels after the formula consumption. Some of the patients showed increased plasma levels, but the others did not. These differences were likely attributable to the lack of standardization in the timing or division of the formula consumption, i.e., some patients took all of the formula at once in the morning, some took it all at once in the evening, some took half the formula in the morning and half in the evening, and so on. Although we did not observe a significant increase in plasma ketone body levels, we did detect significant improvements of some cognitive functions in our mild-to-moderate AD patients. A similar chronic trial of MCTs demonstrated a significant improvement in the AD Assessment Scale-Cognitive Subscale (ADAS-cog), but only in *APOE* ε4- AD subjects [10]. However, another study found no significant effects of MCTs in the participants with AD, including *APOE* ε4- patients [12]. On the other hand, ketosis induced by a very-low-carbohydrate diet was shown to ameliorate the verbal memory performance in MCI patients [11].

The mechanism by which ketones affect cognition is unclear. Some studies showed rapid improvements in cognitive function after only a single administration of a ketogenic drink [9,14]. Several research groups have suggested that ketones function at least partly as an alternative fuel for cerebral neurons; there is an increasing amount of evidence that ketones can significantly improve glucose homeostasis, reducing both metabolic dysregulation and insulin resistance [26–28]. Impairment of the brain's glucose utilization is an early feature of AD, and clinical AD symptoms almost never occur without decreases in the cerebral metabolic rate of glucose, which may be associated with local brain insulin resistance [2]. The metabolism of ketone bodies mimics some actions of insulin [29] and can overcome insulin resistance [30], suggesting a potential therapeutic benefit of ketone bodies in AD [31]. From this perspective, our results may be derived from a chronic beneficial effect of the ketogenic formula on insulin resistance rather than from the acute effect of the ketogenic formula as an alternative fuel.

It is well known that the cerebral metabolic rate of glucose is reduced in hippocampal and parietal regions many years before the onset of AD [1]. However, a 2015 PET study showed that the regional brain ketone metabolisms were preserved in AD patients, and that there were large dissociations of the cerebral metabolic rate of glucose and ketone in the parietal, thalamus, and posterior cingulate cortex [32]. Another study revealed relationships between impairments in memory, visuospatial processing, and attention and gray matter atrophy in the temporal lobe, thalamus, and posterior cingulate cortex [33]. In the present study, we observed improvements of verbal memory (immediate and delayed recall) and processing speed in AD patients who were chronically administered a ketogenic formula. These cognitive changes would be derived from an amelioration of the AD-related regional brain dysfunctions.

Regarding the limitation of our present study, the number of participants (n = 20) was small, which is makes the study vulnerable to type II error. Secondly, some of the patients had already been treated with anti-dementia drugs. However, because we evaluated the improvement of cognition and clinical symptoms after the adjunctive administration of the ketogenic formula, previous medications would likely have affected our results minimally, if at all. Thirdly, the chronic study was an open-label one (single arm design), and we did not prepare a placebo group. We thus cannot rule out the influence of placebo effects. A further study with a double-blind design is necessary to clarify the effectiveness of ketogenic formula intake. Finally, we did not obtain information on the patients' APOE genotype, which may have influenced the results [9,10].

5. Conclusion

Although we failed to detect an acute effect of a ketogenic formula on any cognitive function, the chronic consumption (2–3 months) of the ketogenic formula was suggested to have positive effects on working memory, short-term memory, and processing speed in patients with mild-to-moderate AD. However, the results must be interpreted with caution because the study was limited by the small sample size and the single-arm design of the trial measuring the chronic effect.

Author contributions

M.O. and H.K. bore the responsibility for the study design and analysis of the data. M.O. wrote the original draft of the article. J.M., I.I., H.T., Y.Y., H.H., and S.Y. participated in the study design and acquired the data. K.A., K.N., T.T., and H.K. participated in the study design and revised the article. All authors contributed substantially to this work and approved the final manuscript.

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