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Featured Article

A ketogenic drink improves brain energy and some measures of cognition in mild cognitive impairment

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Abstract

Introduction: Unlike for glucose, uptake of the brain's main alternative fuel, ketones, remains normal in mild cognitive impairment (MCI). Ketogenic medium chain triglycerides (kMCTs) could improve cognition in MCI by providing the brain with more fuel.

Methods: Fifty-two subjects with MCI were blindly randomized to 30 g/day of kMCT or matching placebo. Brain ketone and glucose metabolism (quantified by positron emission tomography; primary outcome) and cognitive performance (secondary outcome) were assessed at baseline and 6 months later.

Results: Brain ketone metabolism increased by 230% for subjects on the kMCT ($P < .001$) whereas brain glucose uptake remained unchanged. Measures of episodic memory, language, executive function, and processing speed improved on the kMCT versus baseline. Increased brain ketone uptake was positively related to several cognitive measures. Seventy-five percent of participants completed the intervention.

Discussion: A dose of 30 g/day of kMCT taken for 6 months bypasses a significant part of the brain glucose deficit and improves several cognitive outcomes in MCI.

Keywords: Acetoacetate; Alzheimer's disease; Beta-hydroxybutyrate; Decanoic acid; Fluorodeoxyglucose; Glucose; Ketone; Medium chain triglyceride; Mild cognitive impairment; Octanoic acid; PET imaging

1. Introduction

Several conditions that increase the risk of Alzheimer's disease (AD) are associated with a regional deficit in brain glucose uptake on the order of 10%. These conditions include carrying the Presenilin-1 mutation, presence of one or two alleles of apolipoprotein E4 (*APOE4*), family history of AD, insulin resistance, or being ≥65 years old [1].

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Because the brain glucose deficit in these conditions is present before the onset of any cognitive deficit, by definition, it is presymptomatic, so may be contributing to deteriorating brain structure and function associated with the onset of AD [2–7].

The brain's main fuel is glucose but when plasma glucose declines for at least 12 hours, which is long enough to deplete glycogen stores, the brain also readily uses an alternative fuel—ketone bodies (or simply ketones: acetoacetate [AcAc] and beta-hydroxybutyrate [BHB]). In long-term fasting, ketones can supply ≥60% of the brain's energy requirements [8,9], so they are the brain's most important replacement fuel for glucose. When brain glucose uptake is decreased, basal brain ketone uptake is still normal not only in cognitively healthy older people, but also in mild cognitive impairment (MCI) and in mild to moderate AD compared with healthy younger adults [10–13]. Plasma ketones normally contribute to <5% of the brain's energy requirements, but when they are available in moderately increased amounts they actually displace glucose as a brain fuel because ketones are preferentially taken up over glucose by the brain [14,15]. In response to consuming a drink providing 30 g/day of ketogenic medium chain triglycerides (kMCTs) for one month, brain ketone uptake increased in patients with AD as it would in cognitively normal adults [16]. Because the brain energy deficit in MCI and AD is specific to glucose, some degree of brain energy rescue by ketones appears to be the mechanism by which cognitive outcomes improve with ketogenic interventions in both MCI and AD [17–21].

Dietary supplementation with kMCTs is a simpler and more convenient method to moderately increase plasma ketones than dietary energy or severe carbohydrate restriction [1]. Unlike long-chain fatty acids, the shorter chain length of kMCT allows them to reach the liver directly via the portal vein, and to cross the mitochondrial inner membrane without carnitine-dependent transport. Hence, kMCTs are more rapidly β-oxidized than long-chain fatty acids [22,23] thereby permitting them to be ketogenic. The 8-carbon MCT, tricaprylin, is more ketogenic than the 10-carbon tricaprin or coconut oil [24], so we refer here to kMCT as one that contains at least 50% tricaprylin.

Our goal was to address two questions about kMCTs in MCI: (1) If cognitive improvement occurs with a kMCT drink, is it a function of the increase in ketone or energy availability to the brain? (2) Is a kMCT drink well enough tolerated to make it a feasible strategy to improve cognition in older people? The primary objective of the Brain ENErgy Fitness, Imaging and Cognition (BENEFIC) trial was therefore to assess whether global or regional metabolic rate of AcAc and glucose in the brain, measured by positron emission tomography (PET) with the carbon-11 (^{11}C) AcAc and [^{18}F]-fluorodeoxyglucose (^{18}F-FDG) tracers, would increase in MCI when consuming a kMCT drink for 6 months. Our secondary objectives were to assess whether a kMCT drink changes (1) global brain energy supply; (2) performance on a neurocognitive battery; (3) cognitive outcomes relative to increased delivery of ketones to the brain; and (4) whether the kMCT drink was well tolerated. Exploratory objectives included assessing whether regional brain volumes, cortical thickness, functional connectivity, or cerebral blood flow change after kMCT in MCI.

2. Methods

2.1. Participants

The BENEFIC trial was conducted with the informed written consent of all the participants and was approved by our institutional ethics committee (CIUSSS de l'Estrie–CHUS, Sherbrooke, Quebec, Canada). It is registered at ClinicalTrials.gov with identification number NCT02551419 under the title "Proof of Mechanism of a New Ketogenic Supplement Using Dual Tracer PET." Inclusion criteria were male or female aged ≥55 years and the presence of MCI [25]. Criteria for MCI were (1) subjective memory complaint plus objective cognitive impairment in one or more domains compared with appropriate normative data (≥1.5 standard deviation less than the mean); (2) a Montreal Cognitive Assessment (MoCA) score of 18 to 26 of 30 or a Mini-Mental State Examination (MMSE) score of 24 to 27 of 30; (3) absence of depression (General Depression Scale score <10/30 [26]); and (4) full autonomy for daily living based on a score of ≤15 of 24 on the instrumental activities of daily living score (functional autonomy measurement system [27]). Exclusion criteria included diagnosis of a major cognitive disorder according to criteria in the Fifth Edition of the Diagnostic and Statistical Manual of Mental Disorders [28], use of an acetylcholinesterase inhibitor, major depression or history of alcohol or substance abuse within the past 2 years, smoking, uncontrolled diabetes (fasting plasma glucose >7 mM or glycated hemoglobin >6.5%), overt evidence of heart, liver or renal disease, vitamin B12 deficiency, uncontrolled hypertension, dyslipidemia, or thyroid disease, inability to lie down without moving for 60 minutes (for the brain imaging), or the presence of implanted metal objects or devices contraindicated for magnetic resonance imaging (MRI). Screening tests for all participants were reviewed by a collaborating physician before enrollment.

2.2. Experimental design

Eligible participants were assigned to the active (kMCT) or placebo treatment using a randomization sequence (Excel 2010, Microsoft, Redmond, WA) with 1:1 allocation and six consecutive blocks of 10 participants and then scheduled for a dual tracer brain PET scan, an MRI, and a neurocognitive battery. At enrollment, participants received their first months' supply of the bottled drink and a daily logbook. They returned monthly to meet the study coordinator to have a blood sample drawn and to receive their next months' supply of the drink. A second

and final dual tracer brain PET scan, an MRI, and a cognitive assessment were scheduled during the final week of the sixth (final) month of intervention.

2.3. Neurocognitive battery

General cognitive status was estimated with the MMSE [29] and the MoCA [30]. Episodic memory was assessed by the French version of the 16-item free and cued word learning and recall test (Rappel Libre/Rappel Indicé [RL/RI-16]) [31] and the Brief Visual Memory Test-Revised [32]. The Trail Making, Stroop Color and Word Interference (Stroop), and Verbal Fluency (VF) tests from the Delis-Kaplan Executive Function System [33] and Digit Symbol Substitution tests from the Wechsler Adult Intelligence Scale [34] provided information on executive function, attention, and processing speed, respectively. The Boston Naming Test (BNT) [35] was used for language ability. A table of normative scores for each test was used to determine a Z-score for each subtest and to calculate composite *Z*-scores [33,34,36,37]. Tests used for each composite *Z*-score are specified in Table 1.

2.4. Ketogenic MCT and placebo drinks

The active kMCT drink was an emulsion containing 12% Captex 355 (60% caprylic acid, 40% capric acid; Abitec Corp, Columbus, OH) in lactose-free skim milk. The drink provided 30 g kMCT in 250 mL bottles (Nalgene, New York) and was prepared under aseptic conditions at the dairy pilot plant at Université Laval (Quebec City, Quebec, Canada) using our proprietary process. The placebo drink contained refined, bleached, winterized, and deodorized high-oleic acid sunflower oil as the nonketogenic lipid and was also prepared under aseptic conditions. It was provided to the participants in the same 250 mL bottles and was

Table 1
Raw scores on the cognitive tests

	Placebo					Active					
	PRE		POST			PRE		POST			ΔPlacebo versus active
Cognitive tests	Mean	SD	Mean	SD	*P* value*	Mean	SD	Mean	SD	*P* value*	*P* value†
Episodic memory											
RL/RI16—Trial 1 Free Recall (/16)	6.4	2.5	6.6	2.4	.638	6.3	2.0	7.6	2.7	.013	.370
RL/RI16—Total Free Recall (/48)	23.3	6.5	22.7	7.8	.844	23.5	6.9	25.4	7.2	.169	.563
RL/RI16—Total Recall (/48)‡	42.7	3.6	40.1	7.1	.232	43.4	4.9	42.3	5.2	.130	.751
RL/RI16—Delayed Free Recall (/16)	9.0	3.4	8.6	3.1	.529	9.8	3.0	9.6	3.1	.703	.908
RL/RI16—Delayed Total Recall (/16)‡	14.8	1.1	13.5	2.5	.026	14.8	1.7	13.9	2.3	.081	.954
BVMT-R—Trial 1 (/12)	3.1	1.9	4.2	2.2	.051	2.6	1.8	3.9	2.4	.027	.908
BVMT-R—Total (/36)‡	13.4	5.5	15.8	6.9	.098	13.8	6.2	16.6	8.2	.066	.795
BVMT-R—Delayed Recall (/12)‡	4.8	2.4	5.6	2.8	.221	5.9	2.4	6.1	3.1	.688	.435
Composite Z-score‡	−0.98	0.74	−1.08	1.08	.673	−0.87	0.79	−0.69	0.98	.446	.499
Executive function											
Trail Making—Switching‡ (s)	150	55	152	71	.877	136	60	133	57	.705	.885
Stroop—inhibition‡ (s)	93	36	92	39	.629	87	27	83	25	.443	.686
Stroop—inhibition/switching‡ (s)	112	48	118	64	.673	93	29	88	25	.351	.191
VF—letter (total correct)‡	28.3	5.9	27.0	7.0	.477	29.3	10.5	27.9	11.9	.208	.863
VF—categories (total correct)‡	31.5	7.0	29.4	8.3	.047	30.8	6.8	31.1	6.3	.777	.075
VF—switching (total correct)‡	9.8	1.9	9.2	2.9	.423	10.7	3.6	10.6	2.8	.981	.603
VF—switching accuracy‡	7.2	2.5	7.2	3.1	.979	9.6	4.4	8.5	3.0	.294	.370
Composite Z-Score‡	−0.72	0.82	−0.72	0.97	.763	−0.33	0.98	−0.32	0.81	.862	.954
Attention and processing speed											
Trail Making—Visual Scanning (s)	29	8	33	9	.022	31	11	31	8	.983	.154
Trail Making—number sequencing (s)	60	27	63	33	.809	55	31	44	21	.043	.385
Trail Making—letter sequencing (s)	55	21	59	21	.144	59	30	62	42	.983	.325
Trail Making—motor speed‡ (s)	47	24	41	16	.226	42	29	34	13	.420	.773
Stroop—color naming‡ (s)	35	7	36	7	.087	37	10	36	12	.617	.085
Stroop—reading‡ (s)	26	5	27	6	.659	28	9	28	7	1.000	.402
Digit symbol substitution test‡ (/133)	44.9	11.9	47.2	14.9	.312	47.9	13.6	46.9	15.2	.452	.708
Composite Z-score‡	−0.02	0.57	−0.08	0.71	.840	−0.06	0.87	0.08	0.79	.171	.191
Language											
BNT—total correct responses (/60)‡	52.7	4.5	51.5	5.2	.018	53.3	4.6	54.3	4.4	.054	.003
Composite Z-score‡	−2.16	1.44	−1.97	1.56	.237	−1.59	1.13	−1.36	1.23	.234	.840

Abbreviations: BNT, Boston Naming Test; BVMT-R, Brief Visuospatial Memory Test–Revised; RL/RI-16, 16-item free/cued word learning and recall test; SD, standard deviation; Stroop, Stroop Color-Word Interference Test; VF, Verbal Fluency.

*Intragroup *P* value.

†Intergroup *P* value.

‡Specific tests used to calculate the composite *Z*-score for each cognitive domain.

visually and organoleptically indistinguishable from the active kMCT drink, as confirmed by a blinded visual inspection and taste test. The volume of active or placebo drink to be consumed was increased every few days from 50 mL/day to the final dose of 250 mL/day within 2 weeks, split evenly between two meals (usually breakfast and supper). Compliance was measured by a combination of bottle count (three to four extra bottles were provided monthly both for spillage and as a check on total intake), daily logs, and a blinded monthly blood test.

2.5. Neuroimaging protocol

The PET and MRI protocols were the same as those reported previously [12,13,16]. On the day of the post-intervention PET scan, 2 hours before injecting the [^{11}C]-AcAc tracer, participants consumed 125 mL of their usual drink. PET images were acquired on a PET/computed tomography scanner (Gemini TF, Philips Healthcare, Eindhoven, the Netherlands). Forearm blood was arterialized by warming with a heating pad at 44°C. [^{11}C]-AcAc (370 MBq) was injected followed by a 10-minute acquisition. One hour later, 185 MBq of [^{18}F]-FDG was injected with a 30-minute acquisition starting 30-minute after injection. The image-derived input function was calibrated against a series of blood samples as previously described [10,11]. The [^{18}F]-FDG input function was concatenated using the image-derived input function acquired during the scan and then cross-calibrated to plasma radioactivity (Cobra gamma counter, Packard).

MRIs were acquired on a 3 Tesla scanner with a 32-channel head coil (Ingenia, Philips Healthcare, Best, the Netherlands). For cerebral blood flow, a pseudo-continuous Arterial Spin Labelling sequence was used: scan duration = 5 minutes and 45 seconds, two-dimensional (2D) echo planar imaging, repetition time = 4200 milliseconds, echo time = 17.3 milliseconds, flip angle = 90°, postlabeling delay of 2000 milliseconds, label duration of 1650 milliseconds, 16 slices of 512 × 512 of 3.0 × 3.0 × 4.0 mm^3 pixel size with a gap of 1 mm between slices. A proton density image was acquired for the quantification of cerebral blood flow: repetition time = 12,000 milliseconds, echo time = 17 milliseconds, and flip angle = 90°. For resting state functional connectivity metrics, the protocol was: T2*-weighted 2D echo planar imaging sequence, scan duration = 5 minutes, repetition time = 2000 milliseconds, echo time = 30 milliseconds, flip angle = 90°, 150 averages, a 35 slices of 64 × 64 of 3.0 × 3.0 × 3.0 mm^3 pixel size with a gap of 1 mm between slices [38].

2.6. Image analysis

PET tracer kinetics were analyzed using PMOD 3.8 (PMOD Technologies Ltd, Zurich, Switzerland) as previously described [13]. The Patlak method was used to quantify the brain uptake rate constants for both tracers (K_{AcAc}, K_{Glu}; minute^{-1}) and their respective cerebral metabolic rates (CMR_{AcAc}, $CMR_{Ketones}$, and CMR_{Glu},; μmol/100 g/minute) [12,15,39]. Voxelwise parametric images were 3D surface-projected using MIMvista (6.4, MIM Software Inc, Cleveland, OH).

Regional and whole brain volumes and cortical thicknesses were determined using FreeSurfer Suite 6.0 (Martinos Center for Biomedical Imaging, Cambridge, MA). Regional volumes were normalized to the intracranial volume of each participant [40]. Cerebral blood flow was calculated using a one-compartment model (FSL version 4.1; FMRIB, Oxford, UK) [41]. Using PMOD software, partial volume correction was applied as described previously [42]. Data processing of resting state functional magnetic resonance images was performed using statistical parametric mapping and a resting state functional MRI data analysis toolkit [43]. Functional connectivity for the default mode network analysis was calculated using a spherical seed (radius = 8 mm), centered at coordinates (−8, −56, 26), within the posterior cingulate cortex [38].

2.7. Laboratory methods

Plasma glucose, cholesterol, and triglycerides (Siemens Medical Solutions USA, Inc, Deerfield, IL) as well as plasma ketones collected during the PET scan and at monthly follow-up [44] were analyzed by automated colorimetric assay on a clinical chemistry analyzer (Dimension Xpand Plus; Siemens, Deerfield, IL). Plasma BHB and AcAc were analyzed as previously described [45,46]. Plasma medium chain fatty acid analysis from monthly follow-up samples was performed by ultrahigh performance liquid chromatography (Nexera X2, Shimadzu) and tandem mass spectrometry (API-3000, ABSciex) as previously described [47]. The other blood metabolites were assayed at the biochemistry core laboratory of CHUS. *APOE* genotyping was performed by real-time polymerase chain reaction [48].

2.8. Statistics

Sample size was based on the primary outcome variable, which was change in CMR_{AcAc} and was calculated to detect an effect size of 0.5, with an alpha risk of 5% and 90% power (G*Power 3.1.9.2) [49]. As established from our previous work [11,15], the coprimary outcomes—plasma ketones and CMR_{AcAc}—typically increase 2- to 3-fold on 30 g/day of MCT, which is equivalent to an effect size of 0.5. Anticipating a priori a 30% dropout during the 6-month intervention, the total sample size for the study was 34 (N = 17 completers per group).

Data are presented as the mean ± standard deviation. All statistical analyses were performed using SPSS 24.0 software (SPSS Inc, Chicago, IL). Because assumptions of homogeneity and normality of the variance were not fulfilled for most of the dependent variables, nonparametric tests were used. A Wilcoxon signed rank test was used to compare

intragroup differences (PRE vs. POST) and a Mann-Whitney *U* test for the intergroup differences (placebo vs. active). Linear regression was used to identify a causal link in which variable "X" predicts the outcome variable "Y"; for example, whether a difference in plasma or brain ketones was associated with a change in cognitive scores.

3. Results

Of the 52 enrolled participants, $n = 8$ dropped out of the active group ($n = 6$ were intolerant to the drink; $n = 2$ discontinued for other reasons) whereas $n = 5$ dropped out of the placebo group ($n = 2$ were intolerant; $n = 3$ discontinued for other reasons). Thus, 75% completed the intervention, $n = 19$ in the active group and $n = 20$ in the placebo arm of the trial (Supplementary Fig. 1). All completers were protocol-compliant, that is, consumed a mean of 90 ± 8% of the planned daily dose of the kMCT, as measured by return bottle count. At baseline, the two groups were well matched for age, gender, *APOE4*, cognitive score, education, blood pressure, depression score, physical autonomy, clinical chemistry, and plasma metabolites (Table 2). Average plasma levels of the medium-chain fatty acids, octanoic acid (C8:0) and decanoic acid (C10:0), measured at monthly intervals were very significantly increased in the active group, 131 ± 95 and 159 ± 135 μmol/L for C8:0 and C10:0, respectively, compared with 5 ± 8 and 4 ± 6 μmol/L for C8:0 and C10:0, respectively, in the placebo group ($P < .001$ between active and placebo for both C8:0 and C10:0). There were no serious or severe adverse events in either group. About half the participants reported at least one side effect (abdominal or stomach discomfort [$n = 14$], reflux [$n = 8$], diarrhea [$n = 3$], nausea [$n = 2$], bloating [$n = 1$], headache [$n = 1$], and/or constipation [$n = 1$]). There were twice as many reported gastrointestinal side effects in the active as placebo group but most were transitory. There was no change in body weight or any clinically significant changes in plasma metabolites or clinical chemistry in either group.

3.1. Plasma and brain ketone and glucose metabolism

Compared with baseline, at the end of the study, plasma AcAc and BHB were 221% and 262% higher, respectively, in the active group but were unchanged in the placebo group (Table 3). Global brain CMR of AcAc (CMR_{AcAc}) was 211% higher in the active group but did not change over 6 months on placebo ($P < .01$; Fig. 1). Whole brain $CMR_{Ketones}$ (AcAc + BHB) also did not change on the placebo but was 230% higher post-treatment in the active group ($P < .01$; Fig. 2). In the active group, CMR_{AcAc} and CMR_{ketone} were 202% to 228% higher across the main brain regions (Fig. 1, Table 3).

Table 2
Participant characteristics at enrollment

	Placebo (N = 20)		Active (N = 19)		
Parameters	Mean	SD	Mean	SD	Intergroup *P* value
Gender (M/F)	8/12		10/9		.582
APOE4 carrier/total sample (%)	8/19 (42%)		6/18 (33%)		.429
Age (y)	75.4	6.6	73.8	6.3	.428
Education (y)	12.5	3.7	13.2	3.5	.687
GDS (/30)*	7.6	4.6	6.3	6.2	.163
SMAF-E (/24)†	1.5	2.0	2.1	4.0	.644
PASE (/793)‡	118.4	52.0	157.7	83.5	.134
McNair (/45)§	19.2	4.9	20.8	8.8	.558
MMSE (/30)¶	27.1	2.1	27.7	2.2	.284
MoCA (/30)#	22.4	2.4	23.5	3.5	.113
Blood pressure (systolic; mm Hg)	138.9	17.5	135.8	11.8	.422
Blood pressure (diastolic; mm Hg)	79.1	8.4	84.3	8.6	.081
Body mass index	25.8	4.0	28.2	4.3	.074
Plasma metabolites					
Total cholesterol (mM)	4.8	1.1	5.0	1.0	.753
Triglycerides (mM)	0.9	0.4	1.2	0.4	.064
Creatinine (μM)	74.1	13.4	76.6	25.1	.707
Glucose (mM)	4.8	0.7	4.8	0.8	.893
Glycated hemoglobin (%)	5.8	0.5	5.6	0.3	.573
Thyroid stimulating hormone (mUI/L)	2.4	1.4	2.3	0.9	.661
Vitamin B12 (pmol/L)	375	175	384	179	.860

Abbreviation: SD, standard deviation.
*Geriatric depression screening scale [26].
†Instrumental activity of daily living of the functional autonomy measurement system [27].
‡Physical Activity Scale for the Elderly [50].
§McNair Frequency of Forgetting Questionnaire [51].
¶Mini-Mental State Examination [29].
#Montreal Cognitive Assessment [30].

Table 3
Plasma ketone concentrations (μM) and regional changes in brain total ketone (acetoacetate + beta-hydroxybutyrate combined) uptake ($CMR_{Ketones}$; μmol/100 g/minute) before (PRE) and at the end (POST) of the intervention

	Placebo (N = 20)					Active (N = 19)					ΔPlacebo versus Δactive
	PRE		POST		Intragroup	PRE		POST		Intragroup	Intergroup
Parameters	Mean	SD	Mean	SD	*P* value	Mean	SD	Mean	SD	*P* value	*P* value
Plasma concentrations (μM)											
Acetoacetate	132	74	112	53	.546	123	56	272	141	.001	.001
Beta-Hydroxybutyrate	215	110	180	87	.421	207	133	543	321	.001	.001
$CMR_{Ketones}$ (μmol/100 g/min)*											
Frontal lobe	1.12	0.62	1.06	0.54	.970	1.14	0.77	2.59	1.75	<.001	<.001
Parietal lobe	1.17	0.64	1.11	0.56	.970	1.14	0.73	2.64	1.70	<.001	<.001
Temporal lobe	1.04	0.56	0.99	0.51	.970	1.02	0.66	2.39	1.58	<.001	<.001
Occipital lobe	1.24	0.71	1.17	0.63	.940	1.20	0.76	2.81	1.85	<.001	<.001
Cingulate cortex	0.90	0.50	0.87	0.45	.911	0.93	0.64	2.10	1.42	<.001	<.001
Subcortical regions	0.65	0.36	0.64	0.34	.852	0.68	0.47	1.52	0.92	<.001	<.001
Cortex (overall mean)	1.09	0.60	1.03	0.53	.940	1.08	0.71	2.49	1.66	<.001	<.001

Abbreviations: CMR, cerebral metabolic rate; SD, standard deviation.
*Calculated from brain acetoacetate uptake according to Blomqvist et al. [39] and Castellano et al. [12].

Postintervention, K_{AcAc} was 9% higher in the placebo group but unchanged in the active group ($P = .028$ and .133, respectively; Supplementary Table 1). Both globally and regionally, K_{AcAc} was different between active and placebo in almost all brain regions measured.

There was no change in whole or regional brain CMR_{Glu} or K_{Glu} in either group (Fig. 2 and Supplementary Table 2; all $P \geq .107$). Net global brain energy uptake (CMR_{Glu} + $CMR_{Ketones}$ combined) increased from 28.2 to 29.3 μmol/100 g/minute (+3.6%) in the active group ($P < .001$), but did not change in the placebo group ($P \geq .50$).

3.2. Cognitive outcomes

Cognitive outcomes are presented as raw scores (Table 1). The two groups had equivalent baseline performance on the cognitive tests. General cognition based on MMSE and MoCA scores did not change after 6 months in either group (data not shown; all $P > .1$). For the episodic memory domain (a key indicator of risk of

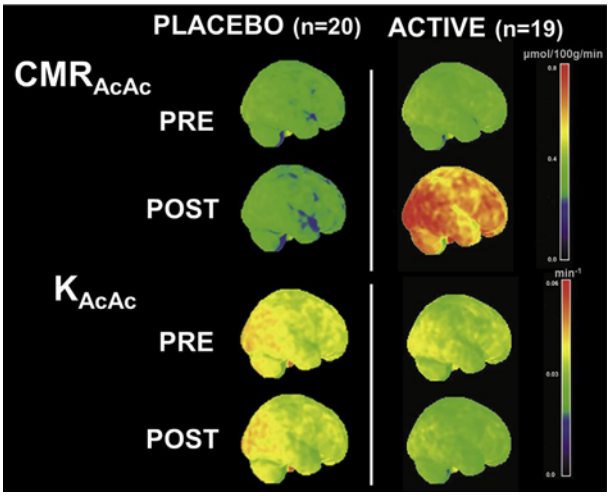

Fig. 1. Surface maps of brain AcAc uptake (CMR_{AcAc} [μmol/100 g/minute] and the rate constant of brain AcAc uptake (K_{AcAc} [$minute^{-1}$] before (PRE) and at the end of (POST) the intervention with the active or placebo drinks. Abbreviations: AcAc, acetoacetate; CMR, cerebral metabolic rate.

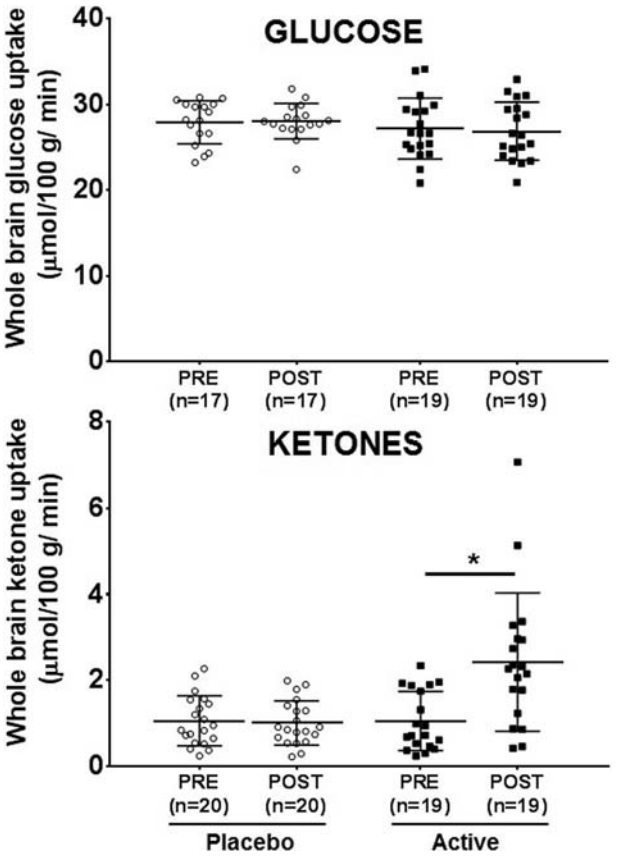

Fig. 2. Whole brain glucose (CMR_{Glu}) and ketone ($CMR_{Ketones}$) metabolism in the placebo and active groups before (PRE) and at the end of (POST) the interventions. Whole brain $CMR_{Ketones}$ increased by +130% at the end of the active treatment ($P < .001$) with no change in the placebo group. There was no change in whole brain CMR_{Glu} in the active or placebo group ($P \geq .687$). Mann-Whitney *U* test (*$P < .05$). * Represents the difference between PRE and POST in the active group. Abbreviations: AcAc, acetoacetate; CMR, cerebral metabolic rate.

progression to AD), the active group had 20% more words recalled on the first free recall trial of the 16-item free/cued word learning and recall test compare to baseline (French version, RLRI-16 test) (*Z*-score = +1.1; $P = .013$), whereas the placebo group had 9% fewer words recalled on the delayed total recall test (*Z*-score = −0.6; $P = .026$). There was also a significant increase in the score in first trial of the Brief Visual Memory Test-Revised for the active group (54% higher score; $P = .027$), and a tendency for improvement in preintervention to postintervention for the placebo group ($P = .051$).

The placebo group had a 7% lower postintervention score on the VF categories test ($P = .047$). In the active group, the number of self-corrected or noncorrected errors on the Stroop test decreased by 44% ($P = .046$) and 58% ($P = .036$), respectively, suggesting a modest improvement of inhibitory capacity post-treatment. Processing speed was 15% slower on the visual scanning task of the Trail Making Test for the placebo group ($P = .022$), but remained unchanged in the active group. Visual selective attention was better on the number sequencing condition for the active group post-treatment (20% less time to complete; $P = .043$). After normalization, the same cognitive tests remained statistically significant.

Comparing the placebo versus active groups, only language as measured by the BNT showed a significant intergroup effect for the total correct response (active +1.0 ± 2.2 and placebo −1.3 ± 2.0; $P = .003$).

3.3. Correlation of cognitive outcomes to ketone status

Scores on the following tests—Visual Scan task of Trail Making, BNT, and VF (categories)—all improved significantly and in direct relation to the increase in plasma ketones post-intervention (Fig. 3; all $P \leq .043$). Composite *Z*-scores of processing speed (Supplemental Table 3; $P = .035$) and performance on the Visual Scan task of the Trail Making test ($P = .034$; not shown) also improved in direct relation to the increase in brain ketone uptake. Both groups (active and placebo) were included in the scatter plots (Fig. 3) because our goal was to have enough statistical power to determine whether there was a link between ketone concentration and cognitive performance. We repeated the analysis of each group separately and the same significant relationship was observed for the active group but not for the placebo group (data not reported).

3.4. Exploratory outcomes

Postintervention, there was no change in global brain volume or in the volume of any brain region in either group with the exception of a 2% increase in the volume of the lateral ventricles in the placebo group (35.8 to 36.6 mL; $P < .007$). Global and regional cortical thickness, functional connectivity, and cerebral blood flow did not change globally or regionally in either group (data not shown).

4. Discussion

The BENEFIC trial demonstrated that a kMCT drink improves net brain energy status in MCI. The improvement in brain energy status was specifically due to brain ketone uptake doubling on the kMCT drink because the interventions did not change brain glucose uptake in either group. Cognitive scores in several domains linked to the risk of progressing to AD improved significantly and in direct relation to the increase in plasma ketones and/or brain ketone uptake on kMCT, suggesting that these functional improvements were because of brain energy rescue with ketones [47]. With 75% of enrolled participants completing this 6-month intervention trial, we demonstrate that this form of long-term ketogenic intervention is safe and feasible in MCI. Given that brain ketone uptake is also normal in mild to moderate AD [11,13,52,53], a kMCT drink could potentially also have beneficial effect on cognition in AD as previously reported [18].

The present results corroborate previous studies using different types of ketogenic interventions in both MCI

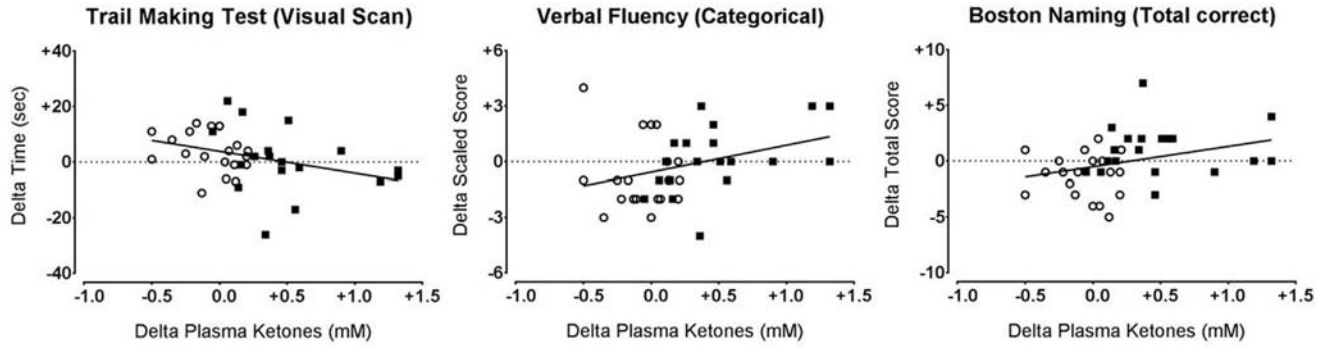

Fig. 3. Scatter plots of the change in plasma ketones (acetoacetate + beta-hydroxybutyrate; mM) and change in the score for the Trail Making (Visual Scan: $r = -0.351$, $P = .031$), Verbal Fluency (categorical: $r = +0.330$, $P = .043$), and Boston Naming ($r = +0.331$, $P = .042$) tests. Placebo (○) and active (■). N = 19 per group. Linear regression ($P < .05$).

[17] and mild-moderate AD [18,19]. Hence, not only is the brain energy deficit in MCI specific to glucose but at least partially correcting this deficit with ketones results in cognitive improvements. A very high fat ketogenic diet produces ketones from long-chain fatty acids in the diet or liberated from adipose tissue, whereas it is mostly the medium-chain fatty acid, caprylic acid, that is ketogenic in kMCT. Hence, it is likely that it is brain energy rescue by ketones themselves that drives the cognitive improvement observed here rather than any specific dietary fatty acid that changed brain membrane composition. Unexpectedly, the brain's capacity to extract ketones from the blood (K_{AcAc}) increased by 9% on the placebo but not on the active treatment. The reason for the change in K_{AcAc} in the placebo group remains unclear at this time.

To our knowledge, only one other study has reported the effect of kMCT versus placebo in MCI [54]. That feasibility study used a dose of 56 g/day in $n = 2$ per group who completed the intervention. The modest but significant cognitive benefit observed in the present MCI study is also consistent with three previous assessments of kMCT in AD, one of which was acute and uncontrolled [55], and the two other were placebo-controlled and of 2 to 3 months duration [18,21]. The present study had a better matched placebo than reported by Henderson et al. [18]. We also used a dose of kMCT that came closer to closing the brain energy gap caused by lower brain glucose uptake; participants in the other AD studies [18,21] took a single 20 g dose/day of kMCT whereas ours took two 15 g doses/day.

Plasma ketone half-life is relatively short, so peak brain ketone uptake after a dose of kMCT is 2- to 3-fold higher than brain ketone uptake when averaged over 24 h [45]. At peak plasma ketones, the 30 g daily dose of kMCT left approximately a 1% brain energy deficit compared with cognitively normal older people [13], a deficit that would be at least 3% when plasma ketones are averaged over 24 h. A higher daily dose of kMCT than 30 g, possibly up to 45 or 60 g, and/or a formulation that improves the ketogenic potential of MCT, is therefore probably needed to fully compensate for the brain glucose deficit in MCI.

The BENEFIC trial had several limitations. The sample size was not sufficient to obtain definitive cognitive results. Despite the fact that intergroup changes in cognition were limited to statistically better performance in the language domain (BNT) and that this change may not be clinically significant, the significant improvement PRE versus POST in the kMCT group encourages us to continue recruitment to double enrollment with the aim of better defining the impact of kMCT on cognitive function in MCI. Also, possible changes in measures of daily living should be measured in a future study. Unlike the reported detrimental effect of *APOE4* status on both the ketogenic effect and cognitive benefit of kMCT in MCI or AD [55,56], we did not see any significant effect of *APOE4* status on ketosis or cognitive outcomes; however, the present study was not adequately powered to assess this.

Most participants reported some gastrointestinal side effects during the project, especially in the active group. Providing the MCT as an emulsion and recommending it be taken with meals reduced the frequency and severity of these side effects but eight participants still dropped out principally for this reason. Tolerance and convenience should be taken into account when formulating a new approach with a higher dose of kMCT.

In conclusion, we demonstrate here for the first time that a dose of 30 g/day of kMCT taken for 6 months provides enough ketones to significantly improve brain energy status in MCI. Several aspects of cognitive function also improved in direct relation to the increase in brain energy status achieved with the kMCT. It remains to be seen whether a larger sample size will confirm the cognitive benefit of this dose of kMCT or whether a higher dose is required. Nevertheless, we show here that long-term clinical trials with kMCT and energy-equivalent placebo are feasible in older people. Further research to delay aging-related cognitive decline by optimizing brain energy rescue with ketones is warranted.

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Author contributions: M.F., C.A.C., and S.C.C. conceived the study design for the BENEFIC trial. M.F., C.A.C., and F.L. ran the cognitive assessments and analyzed and interpreted the cognitive data. V.S.P., C.V., M.B., M.D., K.W., M.R., and M.L. contributed to experimental methodology and image and biological analyses. C.A.C. conducted the statistical analyses. E.C., C.A.C., M.F., and V.S.P. conducted the PET and MRI scans. C.B., T.F., and E.T. provided medical supervision and assessments throughout the study. S.C.C. drafted and revised the manuscript. All coauthors reviewed and commented on the manuscript before submission.

Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jalz.2018.12.017.

RESEARCH IN CONTEXT

1. Systematic review: All peer-reviewed articles available on PubMed on the subject of ketones or brain ketone uptake and Alzheimer's, mild cognitive impairment (MCI) or dementia were reviewed. We found no published work describing measurement of the relationship between brain ketone uptake and cognitive outcomes after a ketogenic intervention in MCI.
2. Interpretation: This randomized controlled trial demonstrated for the first time that a ketogenic medium chain triglyceride drink increased certain cognitive outcomes in MCI in direct relation to the net change in brain energy status. Our results support previous reports showing that various ketogenic interventions can improve cognitive outcomes in both MCI and Alzheimer's disease.
3. Future directions: This study was powered to assess the change in brain energy status. A larger sample size is required to determine the robustness of the cognitive improvement we observed. The dose of ketogenic medium chain triglyceride needed to optimize cognitive outcomes may need to be higher.

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