Enhanced cerebral bioenergetics with dietary ketosis in Mild Cognitive Impairment

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Abstract

BACKGROUND: Metabolic disturbance is associated with risk for neurodegeneration, and cerebral glucose hypometabolism is prominent in Alzheimer’s disease (AD). Ketone metabolism can compensate for glucose hypometabolism and confer other benefits pertinent to neurodegeneration, among them reduction of oxidative stress and AD pathological factors, suggesting its potential as a therapeutic intervention. In a prior controlled trial, we showed that six weeks’ carbohydrate restriction induced ketogenesis and produced improvements in metabolic parameters and memory performance in older adults with Mild Cognitive Impairment (MCI). Those benefits were attributed to the correction of hyperinsulinemia and to the presumed enhancement of cerebral bioenergetic function associated with ketone metabolism.

OBJECTIVE: To assess the effect of dietary ketosis on cerebral metabolites in older adults with MCI.

METHODS: We enrolled a sample of five MCI participants in a ketogenic dietary regimen and performed pre- and post-intervention proton magnetic resonance spectroscopy to investigate changes in neurochemical metabolites. We also assessed cognitive function and metabolic and anthropometric factors.

RESULTS: We observed a significant increase in myo-inositol ($p=0.02$) and trends for increases in N-acetyl-aspartate ($p=0.09$) and creatine + phosphocreatine ($p=0.11$) after six weeks on the ketogenic regimen. Working memory ($p=0.01$) and long-term memory ($p=0.07$) performances also improved.

CONCLUSIONS: This study offers novel, preliminary evidence of cerebral bioenergetic enhancement with mild dietary ketosis in aging humans. Further investigation in controlled trials is warranted to assess the preventive and treatment implications of this intervention for age-related memory decline and dementia.

Keywords: Ketones, proton MRS, glucose hypometabolism, memory, Mild Cognitive Impairment, Alzheimer’s disease

1. Introduction

Insulin resistance syndrome is a common condition among older adults, affecting more than 40% of individuals at age 60, with increasing prevalence with aging [1]. Older adults with insulin resistance and related hyperinsulinemia have been associated with mitochondrial dysfunction [3] as well as with acceleration of beta amyloid deposition [4] and tau hyperphosphorylation [5], characteristic neuropathological features of Alzheimer’s disease (AD). Cerebral glucose hypometabolism is prominent in neurodegenerative disorders including AD [6, 7] and Parkinson’s disease [8], and has been observed as an early indicator

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of neuronal dysfunction in at-risk individuals well in advance of clinically evident cognitive disturbance [9].

Late-life, sporadic AD develops over a preclinical period of many years during which neuropathological changes accumulate before the appearance of clinical impairment [10]. In higher risk individuals, cerebral glucose hypometabolism is evident during the extended pre-dementia period before other early pathological signs [9]. In Mild Cognitive Impairment (MCI), a condition marked by mild memory decline and increased risk for AD, the proportion of dead to dysfunctional neurons is lower than in AD [11], suggesting the possibility that progression of neurodegeneration could be slowed if dysfunctional neurons could be rescued.

Ketosis has been shown to produce benefits with respect to metabolic function and fatty acid metabolism in humans [12] and neuroprotection in cellular and animal studies [13–15]. Reduced ß-amyloid [16] as well as increased mitochondrial uncoupling protein and decreased reactive oxygen species in the hippocampus [17] have been demonstrated after administration of the ketogenic diet for six weeks and 12 days, respectively. Genetic and biochemical evidence of increased mitochondrial biogenesis has been demonstrated after three weeks’ administration of a ketogenic diet in rodents [18]. There have been few human trials assessing neurocognitive benefit in response to dietary ketosis, which can be achieved through carbohydrate restriction or supplementation with medium chain triglycerides (MCT). Older adults with MCI and AD exhibited increased ß-hydroxybutyrate (ßHB) levels and acutely improved cognitive function after consumption of MCT [19]. A larger, multicenter intervention also demonstrated cognitive benefit in AD with longer-term MCT consumption [20]. In addition, there are indications that ketone bodies enhance human cerebral circulation [21] and may signal neuroprotective effects mediated through inhibition of histone deacetylases [22].

The brain is capable of utilizing ketone bodies as an alternate energy substrate to glucose for up to 60% of its energy requirement [23], offsetting a substantial portion of the bioenergetic deficit attributed to glucose hypometabolism in MCI and AD. Accordingly, one might consider ketosis a plausible intervention with the potential to restore neuronal bioenergetic function by providing an alternate energy substrate to compensate for impaired glucose metabolism and by protecting against neuropathological insults such as generation of ß-amyloid and hyperphosphorylated tau [14, 27].

In a prior controlled trial, we demonstrated improved memory function in older adults with MCI following six weeks’ carbohydrate restriction designed to induce ketogenesis [28]. In conjunction with elevated ketone body levels, improvements of metabolic function and anthropometric factors also were evident, including correction of peripheral hyperinsulinemia and reductions of serum glucose levels, weight, and waist circumference. It was postulated that enhanced bioenergetic function and neuroprotection associated with ketone metabolism contributed to improved memory function, although data were not obtained to assess these factors in that trial. We have followed that study with a trial designed to examine the effects of dietary ketosis on cerebral metabolites associated with neuronal health and bioenergetic function using proton magnetic resonance spectroscopy (1H MRS) in a small sample of MCI participants. 1H MRS allowed us to examine in vivo changes in markers of cerebral bioenergetic function in response to the same six-week ketogenic diet intervention in a noninvasive manner. We performed pre- and post-intervention 1H MRS with spectra acquired from the dorsolateral region of the right prefrontal cortex. The metabolites of interest were: myo-inositol, N-acetyl-aspartate, creatine + phosphocreatine, choline, glutamate, and glutamate + glutamine. We present data showing change in metabolites implicating enhanced cerebral bioenergetic function and performance on cognitive tasks.

2. Material and methods

2.1. Participants

The study protocol was approved by the University of Cincinnati Medical Institutional Review Board, and each enrolled participant signed the informed consent document. Prospective participants were recruited
from the greater Cincinnati area with print advertise-
ing in the form of flyers posted at senior centers and
advertisements placed in the Cincinnati Enquirer, the
major daily newspaper. The recruitment ads solicited
participation of older adults with mild, acquired mem-
ory decline for a dietary intervention study. There
was no stipulation in the recruitment material as to
weight or metabolic status with the exception that those
with diabetes were to be excluded. We enrolled seven
participants. However, 1H MRS data for two of the par-
ticipants possessed insufficient signal-to-noise ratio to
permit robust quantification. The final sample included
five participants (two men, three women). The mean
age of the sample was 72 (±7.1) years, and the mean
educational level was 16 (±2.0) years.

2.2. Procedure

Prospective participants were assessed with struc-
tured interview instruments to determine eligibility
for study inclusion. All reported age-related mem-
ory decline such as forgetfulness and prospective
memory difficulty and inefficiencies in everyday activ-
ities but not substantial functional decline. None of
the participants required assistance with every-
day functioning that might imply advanced cognitive
impairment or dementia. The Academic and Medi-
cal History Questionnaire [29] was used to obtain
demographic information and information regarding
academic attainment, current and past medical condi-
tions, and medication and substance use. Those who
reported substance abuse or who had been diagnosed
with diabetes or psychiatric or neurological condi-
tions were excluded as well as those treated regularly
with medications such as benzodiazepine and stimu-
lation drugs that might affect outcome measures. Level
of memory impairment as manifested in everyday activ-
ities was determined with the Clinical Demen-
tia Rating (CDR), which elicited information from
the participant and an informant (typically, spouse or
adult child) concerning the nature and extent of cogni-
tive decline at home and in the community [30]. The
functional domains of memory, orientation, problem
solving, community affairs, home activities, and per-
sonal care were evaluated, and the ratings for each
domain contributed to a global CDR classification with
the memory domain weighted most heavily. Global
CDR classifications included no impairment, mild
decline, and mild, moderate, and severe dementia. We
enrolled individuals with mild decline (coded 0.5), cor-
responding to MCI, and excluded those with CDR
classifications indicating no impairment or dementia.
In addition to the global CDR classification, we derived
the sum of box score from the arithmetic sum of the
category ratings across the six domains of functioning,
which served as a means of quantifying overall level
of functional decline [31].

Qualifying participants were administered the brain
imaging and neurocognitive protocols at the enroll-
ment visit, which occurred one day before the dietary
intervention was initiated, and at the final visit, which
was scheduled to occur after the intervention had been
performed for six weeks. Anthropometric measures and
blood samples also were obtained at the enrollment
and final visits.

Brain imaging and spectroscopy measurements
were performed at the University of Cincinnati Col-
lege of Medicine Center for Imaging Research using a
4.0 Tesla Varian Unity INOVA Whole Body MR/MRS
system (Agilent, Palo Alto, CA). All MRI and MRS
pulse sequences were controlled by VnmrJ graphic user
interface.

A 3-D, whole-head image was acquired using a
Modified Driven Equilibrium Fourier Transform
(MDEFT, T MD 1.1 s, TR 13 ms, TE 6 ms, FOV
25.6 × 25.6 × 19.2 cm, flip angle 20°) pulse sequence
[32] to allow for selection of the MRS voxel based
don anatomical structure and for the quantification of
tissue content. 1H MRS data were obtained from a
2 cm × 2 cm × 2 cm voxel placed in the dorsolateral
region of the right prefrontal cortex. After MRS voxel
positioning, the magnetic field homogeneity was opti-
mized using FASTMAP (Fast Automatic Shimming
Technique by Mapping Along Projections) [33]. The
localized, single-voxel spectrum was acquired with
a PRESS sequence (Point Resolved Spectroscopy)
with water suppression using TR 3000 ms, TE 30 ms, 128
averages, 1500 Hz spectral width, and 1024 data
d points with water suppression by the VAPOR (vari-
able pulse powers and optimization relaxation delays)
method [34]. For the purposes of determining abso-
late concentrations for metabolites, the water signal
from the same voxel served as an internal reference.
The unsuppressed water signal spectra were acquired
using the same acquisition parameters with the quali-
fication that only four averages and a lower receiver
gain were used [35]. Tissue contents (percent gray
matter, white matter, and cerebrospinal fluid) of the
MRS voxel were obtained through tissue segmenta-
tion of the MDEFT images using SPM5 software.
The $^{1}$H MRS spectra were analyzed using LCModel software to quantify the following cerebral metabolite levels: myo-inositol (mlnos), a cell membrane component; N-acetyl-aspartate (NAA), a marker of neuronal integrity; creatine + phosphocreatine (Cr), a marker of mitochondrial energy turnover; choline (Ch), representing choline-containing compounds glycerophosphocholine and phosphocholine; glutamate (Glu); and glutamate + glutamine (Glx). Metabolite levels were further corrected for tissue dependence with tissue segmentation and corrected for the relaxation loss with transverse and longitudinal relaxation times [37, 38]. Metabolite levels are presented in concentration (mM) relative to unsuppressed water signal from the same MRS voxel.

Neurocognitive assessments included measures of working memory, long-term memory, and mood. The Trail-making Test part B [39] was used to assess working memory with respect to ability to switch mental set in accordance with changing task demands [40]. In this timed, paper and pencil procedure, participants were presented with a two dimensional array of randomly arranged alphanumeric characters and asked to alternate sequence digits and letters by drawing connecting lines with a pencil. The outcome measure was time on task so that a lower score reflected better performance. We evaluated secondary or long-term memory ability with the California Verbal Learning Test (CVLT) [41]. This is a list-learning task consisting of presentation of 16 common words over five learning and testing trials. Among a number of learning and retention measures, we used list recall after a delay period as an index of long-term memory. Alternative forms of the CVLT were administered at the enrollment and final visits to eliminate the possibility of retention or priming of specific item content at the second administration. Mood was assessed with the Geriatric Depression Scale (GDS) [42], a 30-item inventory designed to evaluate symptoms of depression in older adults.

We also gathered data on potential mediators of neurocognitive function and the dietary intervention. We measured body weight and waist circumference at the narrowest waist between the lowest rib and iliac crest. Blood samples were obtained after overnight fast for determinations of serum glucose and insulin values by radioimmunoassay and enzymatic assays by the Biochemistry Laboratory of the University of Cincinnati Clinical Translational Research Center. BHB concentration in serum was measured from samples obtained at the enrollment and final visits by enzymatic quantification at the University of Cincinnati Mouse Metabolic Phenotyping Center.

2.3. Dietary intervention

The prescribed dietary intervention involved carbohydrate restriction intended to promote ketogenesis. Diabetic regimens with 20 g to 50 g carbohydrate per day have been shown to produce adaptation to ketone metabolism and are associated with the detectable presence of ketone bodies [43]. Adaptation to ketone metabolism begins after several hours of carbohydrate restriction. Within three to four days, the brain begins to utilize ketone bodies for energy with full adaptation occurring after two to three weeks [44, 45]. Carbohydrate was the only restricted macronutrient. Consumption of protein and fat was allowed to vary, and total energy intake was not constrained. Very high levels of fat (90% of total kilocalorie intake) have been prescribed traditionally to induce ketosis for seizure management [46]. However, recent trials have indicated that consumption of moderate levels of protein does not suppress ketogenesis [47, 48] or seizure control [49, 50], allowing for a less severe regimen.

Participants were given information as to the macronutrient constituents of common foods and counseled as to sources of carbohydrate, fat, and protein. The participants were advised to consume not more than 20 g carbohydrate per day as a target level in order to help insure adaptation to ketone metabolism. Fruit was prohibited and carbohydrate consumption was limited to moderate portions of vegetables. Specific foods that might be included or eliminated were discussed with each participant in light of information as to food items typically consumed based on pre-intervention diet diaries and consultation with each participant. We maintained weekly contact with participants throughout the intervention to answer questions and promote adherence to the protocol.

Participants also completed daily diet diaries during the entire intervention. This was done not only to provide information concerning food intake but also to increase participant attention to food items consumed and, thereby, promote adherence to the regimen. In addition, diet records were completed the week before the enrollment visit as a record of pre-enrollment consumption habits. Participants received oral and written instruction for recording quantities of all foods.
and beverages consumed and used portion posters (Nutrition Consulting Enterprises, Framingham, MA, USA) to estimate food and beverage portions. The completed diet records were reviewed with each participant to clarify ambiguities related to particular foods and portion sizes. Three-day records were extracted for analysis from the seven-day periods before the enrollment and final visits to derive pre- and post-intervention data concerning change in energy and macronutrient intake. These records were selected based on temporal proximity to the study visits and consisted of diaries for three consecutive days including one weekend day. Food records were analyzed for kilocalorie and macronutrient content by the BioNutrion Core of the Cincinnati Children’s Hospital Medical Center Clinical Translational Research Center using the Nutrition Data Systems for Research (NDSR) software (Nutrition Coordinating Center, University of Minnesota, Minneapolis, MN, USA).

3. Results

As noted, all participants were classified with Mild Cognitive Impairment on the basis of a CDR global score of 0.5. The mean (SD) CDR sum of boxes score was 0.8 (0.44), consistent with this level of memory decline. Table 1 contains information obtained prior to and during the final week of the intervention concerning anthropometric variables, metabolic factors, total daily energy and macronutrient consumption, and ketone body concentration. At enrollment, anthropometric and metabolic measures were typical of US adults aged 60 years and older with respect to abdominal obesity, hyperinsulinemia, and elevated fasting glucose [51, 52]. The pre-intervention mean serum ßHB concentration was at the level expected after overnight fast [24]. Dependent sample t-tests were performed to assess change in the outcome measures. At the end of the intervention the mean ßHB concentration was significantly increased (p = 0.03), and elevations relative to pre-intervention were apparent for each participant with values ranging from +0.21 mM to +0.90 mM indicating that the level of carbohydrate restriction maintained by the participants was adequate to increase ketone body concentrations. As shown in Table 1, we observed statistically significant anthropometric and dietary changes across the six-week intervention including reductions of body weight (−7.5%), waist circumference (−3.9%), daily energy intake (−43%), carbohydrate intake (−80%), and fiber intake (−54%). Notably, overall protein and fat consumption did not change appreciably with the intervention. With the decline in carbohydrate intake, the amount of animal protein increased and non-animal protein intake decreased. Glucose and insulin values also declined, although not significantly.

After six weeks’ carbohydrate restriction there was a significant increase in minos (p = 0.02) and trends for increased NAA (p = 0.09) and Cr (p = 0.11). There was no change in Ch (p = 0.36), Glu (p = 0.51), and Glx (p = 0.23). Figure 1 shows change from the enrollment to final visit in minos, NAA, and Cr values for each participant. All of the participants demonstrated increases in minos and four of the five participants showed increases in NAA and Cr. Notably, the fifth participant showed the smallest increase in minos and no change in NAA and Cr.

We also observed cognitive performance changes at the end of the six week intervention. Dependent t-test analyses indicated that executive ability, as measured by task switching efficiency on the Trail-making part B, was significantly improved (t = 4.39, p = 0.01). In addition, there was a trend for improved performance on the CVLT list recall task (t = 2.44, p = 0.07). There was no change in level of mood symptoms (t = 0.53, p = 0.62).

We examined the relationship of change in the anthropometric, dietary, and metabolic factors with

<table>
<thead>
<tr>
<th></th>
<th>Pre-intervention</th>
<th>Final</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight, kg</td>
<td>81.9 (20.6)</td>
<td>75.7 (18.8)</td>
<td>7.85</td>
<td>0.0001*</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>92.7 (19.4)</td>
<td>89.0 (20.0)</td>
<td>6.29</td>
<td>0.003*</td>
</tr>
<tr>
<td>Fasting glucose, mg/dL</td>
<td>108.7 (22.7)</td>
<td>104.3 (13.4)</td>
<td>0.98</td>
<td>0.37</td>
</tr>
<tr>
<td>Fasting insulin, μU/mL</td>
<td>23.0 (10.7)</td>
<td>20.5 (5.8)</td>
<td>1.07</td>
<td>0.34</td>
</tr>
<tr>
<td>Total energy, kcal</td>
<td>1844 (453)</td>
<td>1950 (138)</td>
<td>4.32</td>
<td>0.01*</td>
</tr>
<tr>
<td>Carbohydrate, g</td>
<td>203 (80)</td>
<td>40 (22)</td>
<td>4.18</td>
<td>0.01*</td>
</tr>
<tr>
<td>Protein, g</td>
<td>68 (16)</td>
<td>64 (18)</td>
<td>0.88</td>
<td>0.42</td>
</tr>
<tr>
<td>Animal, g</td>
<td>46 (14)</td>
<td>58 (22)</td>
<td>2.18</td>
<td>0.04*</td>
</tr>
<tr>
<td>Non-animal, g</td>
<td>27 (5)</td>
<td>6 (4)</td>
<td>6.99</td>
<td>0.002*</td>
</tr>
<tr>
<td>Fat, g</td>
<td>67 (26)</td>
<td>60 (11)</td>
<td>0.46</td>
<td>0.66</td>
</tr>
<tr>
<td>Fiber, g</td>
<td>24 (5)</td>
<td>11 (8)</td>
<td>3.71</td>
<td>0.02*</td>
</tr>
<tr>
<td>ß-hydroxybutyrate, mM</td>
<td>0.09 (0.10)</td>
<td>0.49 (0.3)</td>
<td>3.09</td>
<td>0.03*</td>
</tr>
</tbody>
</table>

Note. All values are mean (SD). Statistical analyses are dependent sample t-tests. *indicates significant effect at p ≤ 0.05. Daily energy and macronutrient intake were calculated from three-day diet diaries generated during the week before enrollment and during the final week of the intervention.
Fig. 1. Change from enrollment to final study visits in proton MRS metabolites, myo-inositol (mInos), N-acetyl-aspartate (NAA), and creatine + phosphocreatine (Cr), for each participant. Participants 1 through 4 showed increases in all metabolites at the final visit. Statistical tests are dependent sample t-tests and indicate a significant effect for mInos and trends for NAA and Cr.

change in working memory and long-term memory performance using regression analyses. In these analyses, the dependent variable was the final visit cognitive performance score (either Trail-making or CVLT recall) and the predictor variables were the corresponding enrollment visit cognitive score and the biological or dietary factor change score (final visit less enrollment visit). These analyses were intended to isolate the association of change in the biological or dietary factor with the increment in cognitive performance. Body weight, waist circumference, and total daily energy intake decreased significantly, but were not associated with the cognitive improvements. Change in body weight was not related to Trail-making (standardized
making time on task (ß

list recall (ß

and associated with impaired cognitive function. How-

sidered representative of pathology in MCI and AD

observational studies, increased mInos has been con-

enhanced bioenergetic function in this population.

Further investigation with larger MCI samples is neces-

bility that neuronal function may have been improved.

two metabolites were marginal, they suggest the possi-

ation [53]. Accordingly, while the increments in these

size, we observed marginal trends for increases in the

cerebral metabolites NAA and Cr, which are asso-

Factors in an effort to identify differences in any of these

variables that might be related to the relatively weaker

neurochemical response in these two participants. The

only other factor that was different for participants 4

and 5 was the change in ßBB. For each these partic-

ipants, the increase in ßBB concentration was higher

(0.81 mM and 0.59 mM, respectively), whereas the dif-

ference for the other three subjects was in the range of

0.2 mM.

4. Discussion

To our knowledge, this is the first study to investi-

gate the effect of dietary ketosis on cerebral metabolites

in individuals with MCI. Despite the small sample

size, we observed marginal trends for increases in the

cerebral metabolites NAA and Cr, which are asso-

associated with neuronal integrity and cellular energy

turnover. These observations are contrary to what has

been reported in non-interventional and cross-sectional

MRS studies of AD and MCI in which decreased levels

of NAA and Cr are viewed as markers of neurodegener-

ation [53]. Accordingly, while the increments in these

two metabolites were marginal, they suggest the possi-

bility that neuronal function may have been improved.

Further investigation with larger MCI samples is neces-

sary to corroborate and extend these observations and

substantiate the notion that moderate-term ketogene-

sis is associated with improved neuronal integrity and

enhanced bioenergetic function in this population.

In addition, there was a significant effect for mInos

with increases for all participants. In some but not all

observational studies, increased mInos has been con-

sidered representative of pathology in MCI and AD

and associated with impaired cognitive function. How-

ever, a meta-analysis examining magnetic resonance

spectroscopic imaging findings in MCI noted that alter-

ations in mInos were not uniform across brain regions

and that effect sizes were small relative to alterations

in NAA [54]. A number of longitudinal studies have

reported no change in mInos in MCI subjects [53,

55–57] or found mInos increased specifically in the

context of decreased Cr [58]. This raises doubt about

whether increased mInos can be considered a common

or central finding in MCI, especially in the absence

of reduced NAA, which has been determined to be a

reliable marker of neuronal integrity [54]. The 1H

MRS signal arises from free mInos and is reflective of

either membrane substrate or membrane breakdown

product [59]. Decreased NAA and Cr concentrations

in MCI have been thought to indicate neuronal death

and impairment of mitochondrial function [54, 58].

However, in the context of stable or increased markers

of energy substrate (Cr) and neuronal viability (NAA)

and improved cognitive performance, our finding of

increased mInos likely does not reflect cell membrane

breakdown. Also, the dietary regimen involved, de

facto, a decrease in mInos intake because of reduced

vegetable consumption and elimination of fruit [60]

so that the observed increase in mInos occurred in spite

of reduced dietary intake. Again, the increments in NAA,

Cr, and in cognitive performance suggest neuronal via-

bility while in dietary ketosis and it is unlikely that the

measured increase in mInos was the result neuronal

degradation.

Despite the small sample size we found positive

changes in cognitive performances on the executive

set-shifting and list recall tasks improved. The level of

depressive symptoms endorsed by the participants in

this sample was quite low and well below the threshold

for clinically significant mood disturbance [42].

From the point of view of metabolic function and

dietary habits, our participants were similar to those

enrolled in other trials involving older adults with

MCI [61, 62]. Our recruitment efforts were aimed at

enrolling individuals with mild memory decline and,

with the exception of diagnosed diabetes, we did not

consider metabolic status as an inclusion or exclusion

factor. The pre-enrollment anthropo-

metric and metabolic values were consistent with

those observed in metabolic syndrome [51, 52], and

insulin resistance and hyperinsulinemia characteristic

of that syndrome have been implicated in cerebral glu-

cose hypometabolism [2, 3, 7] as well as increased

risk for neurodegeneration [4, 63]. The reductions of

ß (ß

= −0.05, p = 0.84) or list recall (ß

= −0.02, p = 0.90) performance. Change in waist circumfer-

dence was not related to Trail-making (ß

= 0.04, p = 0.88) or list recall (ß

= 0.33, p = 0.37) performance. However, change

in serum ßBB was associated inversely with Trail-

making time on task (ß

= −0.38, p = 0.05) but not list recall (ß

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As is evident in Fig. 1 the increases in the brain

metabolites mInos, NAA, and Cr were smaller or

absent for participants 4 and 5. We examined demo-

graphic, anthropometric, metabolic, and cognitive

factors in an effort to identify differences in any of these

variables that might be related to the relatively weaker

neurochemical response in these two participants. The

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two metabolites were marginal, they suggest the possi-

bility that neuronal function may have been improved.

Further investigation with larger MCI samples is neces-

sary to corroborate and extend these observations and

substantiate the notion that moderate-term ketogene-

sis is associated with improved neuronal integrity and

enhanced bioenergetic function in this population.

In addition, there was a significant effect for mInos

with increases for all participants. In some but not all

observational studies, increased mInos has been con-

sidered representative of pathology in MCI and AD

and associated with impaired cognitive function. How-
weight and waist circumference observed at the end of the intervention suggest metabolic benefit, although changes in glucose and insulin were not statistically significant, possibly because of the high variability of values in the small sample. We did not find statistical support for the notion that improving insulin sensitivity was beneficial with respect to neurocognitive function, although it will be of interest to assess the potential benefit of metabolic factors in a larger sample.

We observed a significant decrease in total daily energy intake that almost certainly contributed to the reductions of body weight and waist circumference. The fact that protein and fat consumption did not change appreciably with the intervention indicates that essentially all of the reduction in energy intake was attributable to the reduction in carbohydrate consumption. This recapitulates the dietary behavior observed in the prior trial [28], in which the low carbohydrate group exhibited reductions in carbohydrate and total calorie intake but no change in protein and fat consumption. Also, as in that prior trial, we found no relationship between change in weight or change in calorie intake and cognitive performance.

With regard to ketogenesis, elevation of ßHB concentration was evident for each of the participants. The individual values and the significant elevation of mean ßHB concentration at the end of the intervention were in the expected range, consistent with mild dietary ketosis, and well below the concentration indicative of pathological ketocidosis [64]. These data provide evidence that the level of carbohydrate restriction was adequate to stimulate mild ketosis, and the post-intervention ßHB concentration was in the range considered sufficient to provide cerebral bioenergetic recovery [23]. Although change in ßHB level did not predict the cerebral metabolite levels, it was associated with performance on the Trail-making task (but not list recall). It is possible that a longer intervention period or stricter regimen might have generated higher ßHB concentrations indicative of pathological ketoacidosis [64]. These data provide evidence that the level of carbohydrate restriction was adequate to stimulate mild ketosis, and the post-intervention ßHB concentration was in the range considered sufficient to provide cerebral bioenergetic recovery [23]. Although change in ßHB level did not predict the cerebral metabolite levels, it was associated with performance on the Trail-making task (but not list recall). It is possible that a longer intervention period or stricter regimen might have generated higher ßHB concentrations indicative of pathological ketoacidosis [64].

The major limitations of this study are the small sample size and uncontrolled design, and the study results must be judged to be preliminary. However, we did observe positive increments in the primary outcome measures, and the findings are consistent with other evidence supporting the notion that mild dietary ketosis is associated with bioenergetic enhancement. One would expect stronger effects with a larger sample, and it will be of interest to determine the extent to which neurocognitive enhancements associated with the ketogenic diet intervention are related to enhanced bioenergetic function in distinction from other putative benefits [13, 16, 17, 22, 65]. On balance, these findings are novel and provocative and consistent with our prior research [28] and with empirically-derived expectations concerning the neurobiological benefits associated with ketone metabolism.

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References


