Case Report

Ketogenic diet, high intensity interval training (HIIT) and memory training in the treatment of mild cognitive impairment: A case study

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ABSTRACT

Alzheimer’s disease (AD) deaths have increased by 89% since 2000. This alarming trajectory of neurological disease highlights the failure of current best practice. Deteriorating brain fuel supply is the nemesis of intact neurological health. Cerebral hypo-metabolism associated with AD occurs years before onset. Both the ketogenic diet and calorie restriction (fasting) lead to a compensatory rise in ketones to improve energy deficits in the brain derived from cerebral insulin resistance. Two forms of ketone bodies, \(\beta\)-hydroxybutyrate and acetoacetate, fuel the brain during starvation, fasting and strenuous exercise. Ketones are neuroprotective agents that shelter the aging brain from memory loss and neurodegeneration. Induced ketone production has been shown to ameliorate mitochondrial function, reduce the expression of apoptotic and inflammatory mediators and provide neuroprotection to cells (Lange et al., 2017). This case study highlights an innovative research design aimed at attenuating memory decline in a 57 year old female previously diagnosed with comorbid mild cognitive impairment (MCI) and metabolic syndrome (Mets). Mild cognitive impairment is a predementia syndrome known to precede AD (Michaud et al., 2017). The 12-week intervention included ketogenic nutrition protocol, high intensity interval training (HIIT) and memory training using the PEAK brain training app. Memory function was assessed via the MoCA (Montreal Cognitive Assessment) pre/post intervention. Physiological biomarkers for Mets including HOMA-IR (homeostatic model assessment of insulin resistance), triglyceride/HDL ratio, HgA1c, fasting triglycerides and HDL were measured pre/post intervention. MoCA baseline score was 22/30 (MCI); post intervention score: 30/30 (normal). MetS biomarker improvements also reflected statistical significance.

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1. Introduction

Every 66s, someone in the United States develops Alzheimer’s disease. It kills more than breast cancer and prostate cancer combined. The current 5.5 million cases of AD is projected to reach 16 million by 2050, costing the nation 1.1 trillion dollars. Neuroprotective strategies are critical to reversing this pandemic disease. Demetrius & Driver [2] posit that elucidating the origin of the disease is fundamental to prevention. The predominant amyloid cascade model contends that the imbalance in the production and clearance of beta-amyloid is responsible for the pathogenesis and progression of AD. An opposing bioenergetic theory posits that the primary cause of AD is age-induced mitochondrial dysregulation resulting in hypo-metabolic brain circuitry [2,3]. Supplying the brain with alternative fuel through nutritional treatments designed to raise plasma ketone levels, particularly in the early stages of AD, may not only prevent further degeneration but reverse the condition altogether [3,4]. Ketone delivery to the brain alleviates hypo-metabolism and ameliorates neuronal capacity. Ketone bodies protect neurons against neuronal injury caused by starvation and Aβ1-42, an amyloid precursor protein [5]. Aβ1-42 is toxic to hippocampal cells. Kashiyawa et al. exposed cultured hippocampal neurons to Aβ1-42, which reduced the number of cells as well as the neurite number and length compared control. The cells were simultaneously exposed to \(\beta\)-hydroxybutyrate. The surviving cell number doubled and the cell size and neurite outgrowth increased compared to the cells exposed exclusively Aβ1-42. The researchers exposed the surviving hippocampal neurons to ketone bodies for 14 additional hours. The cells increased in number and neurite number compared to control cells [5]. This finding suggests that ketones can act as growth factors to hippocampal neurons and protect against mitochondrial defects that contribute to the pathogenesis of AD.
The therapeutic potential of β-hydroxybutyrate for improving and restoring memory function is the topic of this case study.

2. Methods

A 57-year-old female previously diagnosed with comorbid MCI and MetS completed a 12-week therapeutic intervention designed to restore memory loss and reverse MetS biomarkers. A nutrition protocol utilized to increase plasma ketones through low carbohydrate/high fat diet, calorie restriction (fasting) and high intensity interval training was administered by healthcare professionals and the student researcher for 12 consecutive weeks. The patient was instructed to play the PEAK brain training games on a mobile device five days per week. PEAK brain training domains utilized were language, problem solving, memory, agility, memory and focus. The PEAK application is designed to strengthen the frontal, parietal, occipital, prefrontal cortex, temporal, angular gyrus, posterior cingulate cortex, and hippocampus [6]. Biomarkers for MetS were measured via blood serum pre/post intervention and included fasting insulin, blood lipids, blood ketones and risk ratios: HOMA-IR and the triglyceride/HDL. Memory function was assessed via MoCA at baseline and post intervention by a licensed professional clinical counselor (LPCC). Nutritional monitoring and blood ketones were measured each week by healthcare professionals. Twenty minutes of high intensity interval training was administered by the student researcher every other week for a total of six sessions. The high intensity exercise involved alternating periods of vigorous exercise with periods of recovery. Research has shown that HIIT can promote substantial improvements in insulin sensitivity, glucose control, and improvement in the biomarkers of a multitude of metabolic diseases [7].

3. Case report

The patient, a 57-year-old female presenting with comorbid mild cognitive impairment and metabolic syndrome is employed full-time as a pediatric respiratory nurse and stays active by swimming and participating in a multitude of exercise classes despite her measured cognitive and metabolic deficits. She joined the treatment program to prevent further cognitive decline. The memory complaints were related primarily to tasks of daily living such as remembering a grocery list or people’s names. She also experienced problems with staying focused on the task at hand or forgetting why she entered a room. The patient was previously diagnosed with MetS and MCI. Although she is a breast cancer survivor and taking thyroid medication, the patient is in good health. There is no family history of Alzheimer’s disease.

4. Results

One adult female was enrolled in the 12-week intervention program. Within three weeks, the patient entered into physiological ketosis at 1.1 mg/dL, as measured by the Abbott Precision Xtra ketone meter (normal range 0.5–2.0 mg/dL). Triglycerides decreased by nearly 50% by the fourth week of the intervention. The MoCA score increased by 26% from baseline: 22/30 to 30/30 (normal range 26–30). The improvement in memory is statistically significant and clinically relevant to this case. The significant MetS biomarker improvements are also pertinent, as the triglyceride/HDL ratio and VLDL are directly correlated with increased cerebral metabolism and marked reductions in cognitive decline [4]. See Table 1 below for results summary.

The patient experienced a corollary increase in all domains of the PEAK brain training application suggesting improved brain metabolism. See Table 2 below.

5. Data

Statistically significant results were recorded in all aspects of the intervention including memory, MetS biomarkers and PEAK brain training domains relevant to brain metabolism. See Figs. 1–4 below.

6. Discussion

Early stages of AD induce region-specific declines in brain glucose metabolism [1]. A vicious cycle ensues ultimately leading to AD and dementia. Brain hypo-metabolism leads to chronic brain energy deprivation, deteriorating neuronal mitochondrial function, further decline in glucose demand and finally progression of cognitive impairment [8]. According to the bioenergetic model, AD is governed by the dynamics of the mitochondria in neurons [2,3]. Ketone bodies have neuroprotective features that not only feed the starving brain but also favor cell growth and regeneration [8]. Several clinical studies demonstrate that nutritional treatments designed raise plasma ketones improve brain metabolism and restore mitochondrial integrity [4,8–13].

This case study of a patient with comorbid MCI and MetS suggests that a ketogenic diet, high intensity interval exercise, and memory training may reverse early stage memory loss (MCI) and improve/normalize MetS biomarkers. The results of this case

<table>
<thead>
<tr>
<th>Variable</th>
<th>Percent Improvement</th>
</tr>
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<tbody>
<tr>
<td>Triglycerides</td>
<td>56%</td>
</tr>
<tr>
<td>HDL</td>
<td>29%</td>
</tr>
</tbody>
</table>

Table 2

Improvement in PEAK brain training scores.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Percent Improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Problem Solving</td>
<td>114%</td>
</tr>
<tr>
<td>Focus</td>
<td>115%</td>
</tr>
<tr>
<td>Memory</td>
<td>27%</td>
</tr>
<tr>
<td>Mental Agility</td>
<td>105%</td>
</tr>
<tr>
<td>Language</td>
<td>30%</td>
</tr>
</tbody>
</table>

![Weeks on Ketogenic Diet Compared with HDL Levels](image-url)
Fig. 2. The patient’s PEAK brain training overall total score increased by 83 points after the 12-week intervention with an adjusted R-squared of 0.96 reflecting statistical significance.

Fig. 3. The patient’s PEAK brain training score in the area of FOCUS increased by 115% after the 12-week intervention with an adjusted R-squared of 0.93 reflecting statistical significance.

Fig. 4. The patient’s MoCA score increased 26% after the 12-week intervention with an adjusted R-squared of 0.89 reflecting statistical significance.

stage memory loss warrants further clinical investigations based on the promising results produced in this case study and recent clinical trials.

Statement of ethics

The study was approved by an ethics committee. All the participants gave their written informed consent before taking part in the study.

Conflict of interest

The authors declare that there is no conflict of interest.

Disclosure statement

Sources of support (funding): No funding was required.

Author contributions

All persons who meet authorship criteria are listed as authors, and all authors certify that they have participated sufficiently in the work to take public responsibility for the content, including participation in the concept.

Research in context

1 Systematic Review: The authors reviewed the literature using traditional (e.g., google scholar) sources. While the role of a ketogenic diet applied to Alzheimer’s disease is not yet as widely studied as other aspects of AD physiology, there have been several recent publications describing the clinical aspects of a ketogenic diet. These relevant citations are appropriately cited.

2 Interpretation: Our findings led to an integrated hypothesis describing the role of the high fat ketogenic diet. This hypothesis is consistent with nonclinical and clinical findings currently in
References


