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Case Report

Nutritional Ketosis and Photobiomodulation Remediate Mitochondria Warding off Alzheimer's Disease in a Diabetic, Apoe4+ Patient with Mild Cognitive Impairment: A Case Report

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Abstract

Alzheimer's Disease (AD) is a neurodegenerative progressive disorder for which there is currently no cure. Recently, there has been a robust correlation between Type-2 Diabetes Mellitus (T2DM) and the development of MCI and AD, which is now referred to as type-3 diabetes. This is extremely important in recognizing both AD and T2DM as metabolic pathologies, which can be traced to the level of mitochondrial function. Although glucose is known to be the deferred source of fuel for cells, ketone bodies have been observed to be able to provide metabolically compromised brain cells with an alternative fuel source, bypassing deficiencies in GLUT transport due to increased insulin resistance. By keeping glucose and insulin levels low to allow for the production of ketones, there is evidence that mitochondrial function will be restored, which treats the underlying problems of T2DM and MCI. Further, visible red or Near-Infrared (NIR) light has been shown to heal and stimulate damaged tissue by interacting with the mitochondria to restore function. This case study evaluates the effects of a 10-week clinically prescribed ketogenic nutrition protocol combined with transcranial Photobiomodulation (PBM) with a 59-year-old male, heterozygous ApoE4 carrier, with a dual diagnosis of mild AD and an 11 year history of insulin dependent Type 2 Diabetes (T2DM). Statistically significant results reflect an 83% reduction in HOMA-IR; 64% decrease in the triglyceride/HDL ratio; HgA1c reduction from 9.44% to 6.4%; a 57% decrease in VLDL and triglycerides; and normalized cognition as measured via the MoCA (Montreal Cognitive Assessment), 26/30 post intervention.

Keywords: Alzheimer's disease; T2DM; ApoE4; mTOR; Lactate dehydrogenase; Inverse warburg effect; Astrocyte-neuron lactate shuttle; Ketogenic diet; Photobiomodulation

Introduction

Alzheimer's Disease (AD) is a neurodegenerative disorder which is characterized by neuronal loss and progressive cognitive decline. According to the Alzheimer's Association, AD is responsible for roughly 290 billion in annual expenditures in the US and is the sixth leading cause of death [1]. Currently, there is no cure for a diagnosis of AD. The available treatments are devoted to methods of reducing or targeting several of the phenotypic hallmarks of the disease, which include Neurofibrillary Tangles (NFTs) of hyperphosphorylated tau protein, as well as the accumulation of beta-amyloid plaques. Pharmacological agents which have attempted to target these biological compounds have been woefully ineffective at relieving symptoms associated with AD [2,3]. According to the commonly acknowledged amyloid hypothesis, the accumulation of beta-amyloid plaque between neuron cells in the brain is seen as the cause of disease. This gene centered hypothesis proposes that a mutation for the Amyloid-Precursor Protein (APP) is partly responsible for the development of plaque [4]. However, there are several major discrepancies which the amyloid hypothesis is not able to account for. First, the rapid progression in disease prevalence over the last half decade is not reflective of a gene mutation model. Rather, disease that reflects a genetic mutation would be expected to consistently rise over a long time period. Additionally, if beta-amyloid plaques were responsible for cognitive decline, it would be expected that unaffected individuals lacked these plaques. However, it is commonly noted that patients of normal cognitive capacity have beta-amyloid plaques, and there is no observed dose-response relationship between amount of plaque and cognitive function [3]. It is important to note that gene variants, such as ApoE4, increase the genetic predisposition for AD [5]. However, because the presence of allele variants is not sufficient for the onset of AD, they can be seen merely as a risk factor. Now, it is widely observed that prior to cognitive decline there is a dramatic decrease in Cerebral Metabolic Rate of glucose (CMRglu) [6]. Interestingly, it has been recognized that cerebral hypometabolism can occur years before symptoms of AD are present. This metabolic hypothesis suggests that the cause of AD may be rooted in mitochondrial dysfunction accompanied by fuel shortages to the brain. In fact, the connection between glucose handling, insulin signaling, and AD is so strong, that many researchers now refer to AD as 'diabetes of the brain' [7].

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If AD truly is analogous to type 3 diabetes mellitus, insulin resistance can be targeted as the primary issue for the onset of disease. High levels of blood glucose and insulin are common to both peripheral insulin resistance and a state of insulin resistance in the hypothalamus. Although the brain is not known as an insulin dependent organ, research suggests that the brain is able to perceive and integrate signals from peripheral hormones. Specific neuronal populations within the arcuate nucleus of the hypothalamus contain insulin sensitive receptors, including GLUT4, and communicate with multiple regions of the brain to perform coordinated responses [9]. Because of the connection that the hypothalamus has to regions of the brain, insulin resistance in this region could have major implications in cerebral glucose metabolism. It is plausible that this insulin resistant state of the hypothalamus would result in diminished availability of glucose circulation in the brain. This is of considerable importance when examining astrocyte glial cells, which are known to provide a vital role for neuronal function. As astrocytes breakdown glucose to produce lactate, this can be transferred to neurons and act as a fuel substrate to generate ATP. This relationship is known as the Astrocyte-Neuron Lactate Shuttle (ANLS) [10]. Now, if the amount of glucose available to astrocytes is compromised due to an insulin resistant state the hypothalamus, the viability of neurons to function and survive would be compromised.

A clinically-prescribed ketogenic diet has been shown to restore flexibility in utilizing metabolic substrates, as well as an increase in cellular sensitivity to insulin [11]. Ketone bodies are synthesized in the liver and are able to be used as a fuel substrate in the brain as an alternative to glucose and without the need for insulin. In addition, Photobiomodulation (PBM) with radiant visible red and Near-Infrared Light (NIR) has shown to provide several positive effects for neuron and mitochondrial function, including stimulation of metabolic activities and even neurogenesis. As light passes via a transcranial and intranasal pathway to the brain, it interacts with Cytochrome C Oxidase in complex IV of the Electron Transport Chain (ETC), and is thought to stimulate mitochondrial activity [12,13]. Thus, a clinically prescribed ketogenic diet in conjunction with PBM visible red and NIR light therapy would be expected to reduce insulin resistance, restore mitochondrial function, and improve cognition.

Methods

The 59 year-old male with comorbid T2DM, diabetic neuropathy, and mild AD had an 11+ year history of insulin dependency. Biomarkers for MetS (HgA1c, fasting insulin, lipid panel and glucose) were tested pre/mid/post intervention. ApoE4 genetic testing was administered via buccal swab prior to the intervention by a health care professional and processed by an independent laboratory service. The MoCA assessment was administered pre/post intervention by a Licensed Professional Clinical Counselor (LPCC). The patient completed a 10-week lifestyle intervention, which incorporated PBM 3 times/week (20 minutes per session) and a clinically prescribed Ketogenic Diet (KD) designed to reverse T2DM via homeostatic restoration of peripheral and cerebral insulin sensitivity. The prescribed nutrition protocol utilized moderate protein (based on lean mass and activity level) designed to reduce fasting insulin levels facilitated the endogenous production of blood ketones (beta-hydroxybutyrate) as measured by the Precision Xtra Abbott Blood Ketone Meter (>0.5 mmol/L). A time-restricted feeding window of 5-6 hours combined with moderate intensity exercise was integrated into the lifestyle intervention; the patient exercised approximately 3 days per week. Real time monitoring was provided weekly by licensed healthcare providers as well as the student researchers.

The patient's MoCA (Montreal Cognitive Assessment) score of 20 reflected deficits in delayed recall (frontal lobe; posterior cingulate hypometabolism; hippocampal-parieto-frontal network); clock drawing (parietal lobe); serial 7 subtractions (prefrontal cortex; left inferior frontal lobe; angular gyrus); and letter 'F' fluency (frontal lobe). Hypometabolism is a key feature of each aforementioned cognitive deficits. Transcranial PBM was administered using the 'Vielight Neuro Gamma' device. (The device is not labeled for treating dementia or AD but is described as a "low risk general wellness product" by the Food and Drug Administration.).

The Vielight Neuro Gamma consists of a nasal applicator, controller, and head set with Five Emitting Diode (LED) modules. Painless, non-invasive, non-thermal, non-laser pulsed (40Hz; 50% duty cycle), Near Infrared (NIR) light (810nm wavelength) is transmitted through five non-laser LED's on the headset for 20 minutes. The LED lights are strategically positioned to deliver NIR to the subdivisions of the Default Mode Network (DMN). The subdivisions include the dorsal lateral medial Prefrontal Cortex (dmPFC); ventral medial Prefrontal Cortex (vmPFC); the Posterior Cingulate (PCC); Lateral Parietal Cortex (LPC); adjacent Precuneus (PCu); and the Entorhinal Cortex (EC). The nasal applicator transmits NIR light to the ventral section of the brain, which includes the vmPFC and the olfactory bulb, directly activating projection to the EC and para hippocampal area. The LED's positioned on the dmPFC and intranasally pulse in synchrony (in-phased) and the rest of the LED's on the PCu and left and right LPC's also pulse in synchrony (in-phased) within its group [12].

The power density output of the nasal applicator is 25mW/cm^2, three posterior LEDs are 100mW/cm^2, and the anterior LED is 75mW/cm^2. During the 20-minute session, the energy dose to the brain via headset and nasal applicator equals 240 J/cm^2. Detailed parameters and specifications are listed in the table below.

Case Report

The case involved a 59-year-old morbidly obese male patient with a dual diagnosis of Type 2 Diabetes (T2DM) and mild AD. The patient reported an 11+year history of T2DM. The patient, a heterozygous carrier of the ApoE4 allele, was given the diagnosis of mild AD after a cognitive assessment via the Montreal Cognitive Assessment (MoCA). The MoCA was chosen for evaluating cognition due to its clinically accepted validity and sensitivity to cognitive changes [13]. The patient scored a 20/30 before the 10-week intervention. He also reported complaints of peripheral neuropathy in the left lower extremity. The patient was prescribed a 10-week ketogenic nutritional intervention protocol targeted at endogenous hepatic production of ketones to restore peripheral and cerebral metabolic flexibility as well as reduce cerebral hypometabolism. Prior to the intervention, the subject reported reduced memory at work; he also presented no family history of cognitive decline or T2DM.

Table 1: Vielight Neuro Gamma Parameters.

Source	LED
Wavelength (nm)	810
Power output of LED on the anterior band (mW)	75(transcranial)
Power output of each LED on the posterior band (mW)	25(intranasal)
Power density of LED on the anterior band (mW/cm2)	100(transcranial)
Power density of each LED on the posterior band (mW/cm2)	25(intranasal)
Pulse frequency (Hz)	40
Pulse duty cycle, percentage	50
Duration of each treatment session (min)	20
Beam spot size (cm2)	≈1
Total energy delivered per session (Joules)	240
Total energy density per session (Joules/cm2)	240

Results

The results of this case report suggest the utilized protocol provided therapeutic effects towards relieving symptoms of T2DM and mild AD. In order to confirm patient adherence to the prescribed protocol, blood ketone levels were monitored weekly in clinic and via self-report. The patient's primary risk markers for MetS were measured before, during and after intervention while cognitive assessments were tested pre-/post-treatment. The patient's HgA1C, the gold standard for blood glucose control, decreased from the diabetic range of 9.4% to the prediabetic range of 6.4%. This signifies a reversal of the patient's diagnosis of T2DM to a clinically pre-diabetic level. It is interesting to note that after the patient continued following the protocol for a 15-week period, his HgA1c decreased to completely normal level of 5.5%. His fasting insulin and blood lipids saw improvements toward normative values as seen in Table 1. He restored cellular insulin sensitivity and reduced his cardiovascular risk measured by an 83% reduction in HOMA-IR and a drop in Tri/HDL ratio by 64% [14]. Memory and cognition in the patient improved as measured by increases in MoCA and animal naming scores. The MoCA score improved from mild AD (20/30) before intervention to normal (26/30) after intervention while animal naming scores improved from 19 before intervention to 33 after intervention.

Discussion

This case investigated the potential of a clinically prescribed ketogenic diet coupled with PBM to improve cognitive impairment measured by markers for MetS and MoCA. The results of this study strongly suggest that the utilized protocol restored metabolic flexibility and may have significant potential in restoring cognition and increasing insulin sensitivity for ApoE4 heterozygous individuals. As mentioned previously, AD is beginning to be recognized as being analogous to type 3 diabetes. If this is true, it would be expected that there is an issue with insulin signaling and fuel substrate being delivered to the brain. The data presented suggest this relationship. One key relationship from the data is the decrease in serum insulin due to a ketogenic diet correlated with a decrease in HOMA-IR, which is the measure for insulin resistance. This decrease in insulin resistance likely allowed for the restoration of fuel substrate to enter the brain, and a restoration of cognitive ability as a result. If the relationship between AD and diabetes reflects the issue in glucose and insulin handling, an improvement in the patient's biomarkers for T2DM would be likely observed as well. The patient's HgA1c level, which is clinically used to diagnose prediabetes and T2DM, decreased to a level below the classification for T2DM. The relationship between reversed T2DM and improved cognition strongly suggests that the metabolic hypothesis for AD is correct.

Table 2: Biomarkers for MetS pre/mid/post intervention.

Results	Pre-intervention	Mid-intervention	Post intervention	% change
HOMA-IR (<1.0)	4.67	1.84	0.79	-83%
Tri/HDL ratio (<2.0)	3.36	1.21	1.22	-64%
Fasting insulin mU/L (3-5)	9.4	6.1	3.5	-63%
HgA1c (%)	9.4%	7.0%	6.40%	-32%
Triglycerides mg/dL (<150)	141	63	61	-57%
HDL mg/dL (>40)	43	54	50	14%
VLDL mg/dL (9-13)	28.2	12.6	12.2	-57%
Weight (lbs)	261	244	234	-10%
Body fat mass (lbs)	91	77	72.8	-20%
LDH Total IU/L	164	127	109	-34%

Table 3: Cognitive Assessments pre/post intervention.

Memory Assessment change	Pre-intervention	Post intervention	Percent
MoCA (≥ 26)	20 (MCI)	26 (normal)	30% improvement
Animal Naming (≥ 21)	19	33	74% improvement

Abbreviations: MoCA: Montreal Cognitive Assessment; MCI: Mild Cognitive Impairment (a.k.a. mild Alzheimer's disease)

At its core, this neuroenergetic model hinges on the ability of the mitochondria to function efficiently. In energy deficient neurons, an early and temporary hyper-metabolic response has been described especially in the temporal lobe [15,16]. Low fuel results in an epigenetic shift and nuclear upregulation of enzymes for Oxidative Phosphorylation (OXPHOS) in the mitochondria; consequently, the upregulation of OXPHOS increases oxidative stress and the production of reactive oxygen species that causing further damage to the matrix [17]. Neurons undergoing this epigenetic, hyper metabolic shift have an increased demand for fuel; this creates fuel shortages in neighboring neurons eventually leading to cell death. Peripheral up regulation of LDH(A) to facilitate anaerobic conversion of pyruvate to lactate and neural up regulation of LDH(B) for oxidative conversion of astrocytic lactate into pyruvate for entry into PDH complex for oxidative respiration, mark the earliest epigenetic shifts [18,19]. The treatment protocol with PBM sought to contribute to the restoration of metabolic functioning through stimulating mitochondrial function in the 4th chamber of electron transport chain where electrons meet oxygen as the final acceptor [20]. Lactate Dehydrogenase (LDH) levels can provide insight into this hyper metabolic shift. The up-regulation of oxidative phosphorylation in neurons promoting oxidative stress can be detected by an increase in peripheral LDH activity [21]. Therefore, decreases in peripheral LDH activity proxy more activity in the PDH complex and therefore more pyruvate conversion into acetyl CoA for oxidative respiration. It is hypothesized that this reduction in peripheral LDH translates into improvements in hypothalamic insulin sensitivity, thereby inhibiting

the hyper metabolic, epigenetic shift in the brain [16,19].

Acknowledgement

The study was designed by SH, LB and KG; data were collected and analyzed by SH, LB and KG; data interpretation and manuscript preparation were undertaken by SH, LB and KG. All authors approved the final version of the paper.

Declaration

This study was IRB approved (Project SP-23-18) and informed consent was obtained in writing from all participants.

Statement of Ethics

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

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

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.

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 the public domain.

Future Directions: The manuscript proposes a framework for the generation of new hypotheses and the conduct of additional studies regarding this area of study. Examples include further understanding: (a) the role of MCT oil in treatment of AD; (b) the potential reversibility of neuronal damage in the AD brain.

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