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Case Report

The Ketogenic Diet as a Prospective Intervention to Remit Mild Alzheimer's Disease in Apoe4+ Patient: A Case Report -

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ABSTRACT

Throughout the years, scientists have conducted extensive research on the Apolipoprotein E4 (ApoE4) genetic variant in regard to its correlation with Alzheimer's Disease (AD). Although it has been established that carriers of the ApoE4 allele variant, which is also termed as the Alzheimer's disease gene, have an increased risk for developing cognitive impairment, the exact metabolic mechanisms for this connection still remains inconclusive. However, there is evidence that ApoE4 directly impacts AD pathology due to impaired lipid transportation to the astrocytes, resulting in neuronal starvation and degradation. There especially appears to be a gap between ApoE4 and its association with Metabolic Syndrome (MetS), insulin resistance, and hyperlipidemia. This case study analyzes the effects of a 6- week clinically prescribed Ketogenic Diet (KD) on a 67-year old female, heterozygous ApoE4 carrier, with a 20 year history of insulin dependent Type 2 Diabetes (T2DM), hyperlipidemia and comorbid Mild Cognitive Impairment (MCI) as indicated via the Montreal Cognitive Assessment (MoCA) with a score of 21/30. The intervention goal was to improve cognitive function with the hope of long term diabetic remission. The results from this case study may suggest that a ketogenic diet in conjunction with red light therapy and hypercapnic breathing could be a prospective intervention for reversing cognitive impairment in ApoE4+ patients with mild AD.

Keywords: Alzheimer's Disease; ApoE4; Type 2 Diabetes Mellitus; Mild Cognitive Impairment; Metabolic Syndrome; Hyperinsulinemia; Hyperlipidemia; Ketogenesis; Photobiomodulation

INTRODUCTION

Alzheimer's Disease (AD) is an incapacitating neurodegenerative disorder associated with cognitive decline, which affects over five million Americans [1,2]. Alzheimer's disease is difficult to predict due to limited etiological understanding of the disease. However, it is well known that individuals with the ApoE4 allele have the strongest risk for developing AD. Further exploration associating the ApoE4 allele in individuals with a comorbidity of Metabolic Syndrome (MetS) and cognitive impairment could help uncover preventative interventions that decrease an ApoE4+ individual's susceptibility to AD [3]. Apolipoprotein E (ApoE) is the most prevalent lipoprotein found in the brain and is responsible for the transport and recycling of cholesterol and lipids between cells [4]. Due to the brain's high lipid profile, it is imperative to maintain homeostasis between lipoproteins, cholesterol, and lipids in order to maintain normal brain function [5]. ApoE is polymorphic and each of its variants expresses a different lipid and receptor binding efficiency [5]. The ApoE4 variant contributes to poor lipid transport capabilities as well as impaired cerebral insulin signalling and glucose metabolism [5,6]. Because of these defects, the ApoE4 variant has been shown to exacerbate cerebral metabolic problems found in patients with MetS, insulin resistance, and T2DM. Neurons do not depend on insulin; however, they do respond to it [7]. Peripheral production of insulin crosses the Blood Brain Barrier (BBB) and signals a fed state [8]. This allows for the uptake of glucose at the BBB primarily by the astrocytes' GLUT1 transporters [8]. Furthermore, when insulin is low as with the fasted state, astrocytic GLUT1 receptors are inhibited and astrocytes begin to synthesize glycogen and eventually lactate for metabolic coupling to the neurons [8]. However, when elevated insulin continuously crosses the BBB due to peripheral insulin resistance, signalling errors occur in the nutrient sensing, hypothalamic GLUT4 receptors [8]. The error in nutrient sensing causes a reduction in the rate of cerebral glucose metabolism; with reduced glucose availability, the astrocyte shuttling of lactate to the neurons declines causing energy deprivation [9,10]. Research has shown that ketone bodies are able to cross the BBB, enter the neuronal mitochondria via the MCT lactate transporter, and circumvent starvation and stop cognitive decline [10,11]. As Cunnane, et al. showed in brain imaging, ketone delivery to the brain occurs even when the peripheral tissue is highly insulin resistant [12].

Research has shown that red light therapy can also play a role in the reduction and elimination of oxidative stress and the increased production of ATP in the mitochondria. Red light enhances the creation of ATP by eliminating excess nitric oxide in the 4th protein chamber where oxygen becomes the final electron acceptor [13]. Nitrous oxide competes with oxygen at the 4th chamber, which impedes the production of ATP and increases oxidative stress via Reactive Oxygen Species (ROS) in the matrix. Oxidative stress damages in the inner mitochondrial membrane and compromises neural functioning leading to pathologies of cognitive decline such as lewy body syndrome [14]. The photons in the red light aid to break-up the accumulated nitric oxide bonds in the 4th chamber, which increases the hydrogen ion gradient moving through the inner membrane and increases efficiency of electron transport to increase ATP synthesis in the 5th chamber [13].

Although carriers of the ApoE4 genetic variant and those with comorbidities of MetS are at an increased risk for neurodegeneration, the ability to produce ketones for brain metabolism and increasing ATP production via red light could potentially help reduce the risk of future cognitive impairment. A clinically prescribed Ketogenic Diet (KD), with periods of time restricted feeding, along with daily red light therapy and the hormetic effect of intermittent hypoxic breathing with hypercapnic rebreathing, provide a remedial "cocktail" to mediate mitochondrial dysfunction and rescue neurons from degradation.

METHODS

This case report outlines the protocol of a 67- year old female with mild Alzheimer's disease, T2DM and morbid obesity and who is heterozygous for the ApoE4 gene variant. At physician referral, the patient elected to self-register for a 6-week Service-Learning Program offered by the Human Kinetics & Applied Health Science Department at Bethel University in St. Paul, MN. Student clinicians, completing Science Degrees in pursuit of graduate programs in Healthcare/Medicine, were matched with community volunteers. To qualify for the program, the volunteers were previously diagnosed with a chronic metabolic disorder including: Metabolic Syndrome (MetS), insulin resistance, pre-diabetes and/or Type 2 Diabetes (T2DM) and comorbid selective memory complaints (SMC) or Mild Cognitive Impairment (MCI) as determined through cognitive screening by licensed mental health professionals (LPCC). As part of the educational experience, volunteers signed HIPAA educational releases allowing academic access to their health history, laboratory values and test results. During the 6- week intervention, ten physiological biomarkers for metabolic syndrome were measured by healthcare professionals through serum blood draws at baseline, mid

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and post intervention. These biomarkers included: HgA1c, fasting triglycerides, fasting insulin, total cholesterol, LDL, VLDL, HDL, HOMA-IR, Triglyceride/ HDL ratio, and fasting glucose. Weight and body fat % were also measured throughout the intervention. The Montreal Cognitive Assessment (MoCA) was administered by a Licensed Professional Clinical Counselor (LPCC) and was used to assess cognitive function pre/post intervention and 3 months post-intervention. The patient's blood ketones were measured daily using the Abbott Precision Xtra blood glucose/ketone monitor to ensure blood ketones were kept in the 0.5-2.0 mmol/L range. The ApoE4 genetic test was administered by a healthcare professional via buccal swab and was processed by an independent lab service.

The 6- week intervention included a clinically prescribed ketogenic diet, a time restricted feeding window, red light therapy twice daily for 10 minute sessions each using Joovv Solo red light therapy device (660nm/820nm wavelengths), hypoxic breathing with hypercapnic rebreathing, twice daily for 10 minutes sessions using Expand- A- Lung Breathing Exerciser, and weekly in-person meetings with health care professionals and the student researchers. The meetings included patient centered education which focused on nutritional biochemistry and the restoration of insulin sensitivity and metabolic flexibility. Specifically, the educational materials were aimed at increasing health literacy in the patient; the educational topics included: cholesterol synthesis, brain metabolism, HPA stress response pathway regulation, insulin/glucagon negative feedback loop, ketone synthesis/utilization, COMT/MTHFR genetic testing, ApoE4 genetics, and the benefits of intermittent fasting. The MoCA was administered pre/post and 3 months post-intervention by the same Licensed Mental Health Professional (LPCC) to maintain testing consistency.

CASE REPORT

A 67- year old female, heterozygous ApoE4 carrier, presented with T2DM and mild AD. The patient was retired, but remained highly involved with her community, family and grandchildren. She was highly motivated to participate in the wellness intervention with the hope of losing weight and reversing her diabetes. Prior to the intervention, the patient had an extensive history of uncontrolled appetite regulation with weight fluctuations, increased visceral fat accumulation, chronic fatigue, shortness of breath and sleep problems. She also struggled with cycles of anxiety/depression and complained of forgetfulness. She was very concerned about her history of familial heart disease.

RESULTS

A 67- year old female was prescribed a 6-week, clinically formulated ketogenic diet with a 10 hour time restricted feeding window, together with lifestyle interventions aimed at restoring peripheral and cerebral metabolic flexibility. MetS biomarkers were measured at baseline, mid- and post intervention. The MoCA assessment was measured pre and post-intervention and at 3 months post-intervention. The patient was able to achieve marked improvement in insulin sensitivity and decrease her cardiovascular risk as seen in her 64.8% reduction in HOMA-IR and 71.2% reduction in fasting insulin. She also reduced her TRI/HDL ratio, HgA1c, triglycerides, total cholesterol, VLDL, total weight, and normalized her C-reactive protein. These reductions show marked improvement in her metabolic flexibility evidenced by the changing lipid panel. Although, the patient was unable to get her diabetic biomarkers (HgA1c & fasting glucose) back in the normal range within the 6-week period, she still experienced significant metabolic improvement despite elevated blood sugar throughout the program. The inability of her peripheral tissues to metabolize ketones efficiently may be related to the patient's long-term diabetes and down-regulation of fatty acid/ketone transport. This could indicate an epigenetic shift in cellular respiration due to chronic insulin resistance sustaining a Crabtree-like Effect in the peripheral cells - the use of the less efficient fermentation pathway as a precautionary default in the presence of elevated glucose [15]. Epigenetic shifts in cellular respiration ensure the immediacy of glucose during the energy stress of metabolic inflexibility; the shifts occur and stabilize following decades of glucose dependent insulin resistance and T2DM. Aerobic glycolysis, or cellular fermentation, becomes the energy default to sustain glucose dependency in the overfed/undernourished phenotype [16]. Recent work by Pere Llinas-Arias et al. showed epigenetic dysregulation in the methylation pattern of the SVIP gene leads to metabolic inflexibility and a bypass of oxidative respiration; the cell's maladaptive attempt to sustain the glucose dependent state [16].

However, despite the resistant hyperglycemia, the patient's cognitive scores improved from 21 (mild-Alzheimer's) to 28 (normal) suggesting a strong correlation between nutrition intervention and cognition, despite the sluggishness observed peripherally. Additionally, she continued her cognitive improvement @ the 3 month screening, (30/30). The subject noticed clearer skin and stronger mental clarity by the end of the intervention (see Table 1 for biomarker summary and Table 2 for cognitive summary). Figures 1-3 reflect linear regression correlating the improvements of the HOMA-IR with VLDL and triglycerides, as well as the HgA1c with the fasting insulin.

DISCUSSION

This case report examines the prospect of a clinically prescribed KD, red light therapy and life style interventions delivered in a community based wellness platform aimed at weekly education to increase health literacy and empower patients with chronic, non-communicable diseases to understand the etiology and management of symptoms. The guided implementation of a clinically prescribed KD improved biomarkers for T2DM and provided an alternate fuel source for the brain to increase cognition and reverse mild Alzheimer's disease in a heterozygous ApoE4+ patient. The ApoE4 gene variant is known to increase a patient's risk for Alzheimer's disease and amplifies metabolic dysregulation associated with MetS due to its negative effects on cholesterol and lipid transport in the body and the brain, impairment of insulin signalling and glucose metabolism [3,5,6]. Elevated insulin dysregulates nutrient sensing in the hypothalamus; when the cerebral rate of glucose metabolism drops due to impaired signaling, endogenous or exogenous ketone bodies can be used as a fuel source to prevent neuronal starvation [8-11]. This alternate fuel allows the brain to receive ample oxidative energy thereby preventing apoptosis and cognitive decline, even in the presence of peripheral insulin resistance and metabolic inflexibility [8-12]. Red light therapy, time restricted feeding and hypoxic breathing/hypercapnic rebreathing are hermetic lifestyle interventional tools that work by creating small metabolic stressors in energy production with remedial compensatory shifts in cellular metabolism that increase mitochondrial efficiency and amplify ATP production [14].

CONCLUSION

The results of this case report provide compelling support for

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Table 1: Summary of MetS biomarker improvements for pre-/mid-/post intervention.

Biomarker	Pre-intervention	Mid-Intervention	Post Intervention	Percent Change
C-Reactive Protein (< 0.3)	0.7	n/a	0.5	-28.6%
Chol/HDL ratio (0.0-4.9)	6.1	5.2	4.6	-24.6%
Cholesterol (< 200)	269	232	212	-21.2%
EAG-Average (< 117 mg/dL)	192	n/a	243	+26.6%
Glucose (70-90 mg/dL)	199	263	262	+31.7%
HgA1C (< 5.7%)	8.3%	8.0%	7.6%	-8.43%
HDL (> 40)	44	45	46	+4.5%
Insulin (2.6-11.1)	39.2	30.7	11.3	-71.2%
Homocysteine (< 7)	8.0	n/a	6.9	-13.8%
LDH total (87-241 IU/L)	170	151	139	-18.2%
LDL Chol (< 100)	193	139	119	-38.3%
VLDL (9-13)	32.4	31.2	22.4	-30.9%
Triglycerides (< 150< 100)	162	156	112	-28.4%
Tri/HDL (< 2.0)	3.7	3.5	2.4	-35.1%
Body Fat % (< 30%)	48.0	47.4	46.7	-2.7%
BMI (< 25)	41.4	38.3	37.7	-8.9%
HOMA-IR (< 1.0)	19.3	n/a	6.8	-64.8%
Weight	249	230.2	226.6	-9.0%
Blood Ketones (.5 – 2.0)	0.1	3.9	6.6	+6,500%

Table 2: Summary of cognitive/memory improvements for pre/post/3 months post-intervention.

MoCA Scores			
Memory Assessment	**Pre- Intervention**	**Post- Intervention**	**3 months post-intervention**
MoCA (26-30)	21	28	30

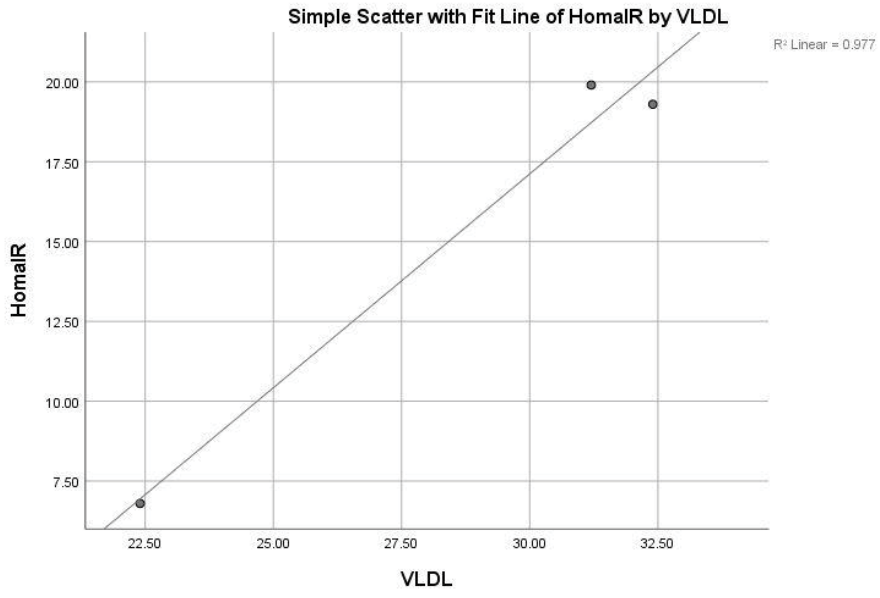

Figure 1: The patient's HOMA-IR was positively correlated with reduced VLDL, showing an adjusted R2 value of 0.977, indicating statistical significance.

cost-effective, community based educational support and lifestyle interventional programs aimed at increasing health literacy in patients with chronic, non-communicable diseases. The clinically prescribed ketogenic diet, time restricted feeding, and at-home, hermetic lifestyle modifications together with weekly education aimed at increasing patient literacy/self-efficacy regarding disease etiology and management may be beneficial in the prevention and remission of the worldwide epidemic of T2DM and comorbid Mild Cognitive Impairment (MCI). Patients with T2DM and mild AD who are carriers of ApoE4 gene variant seem to benefit peripherally and cognitively from a clinically prescribed KD as the nutritional protocol provides an alternate fuel for the brain (ketones) and increases ATP production in the mitochondria. Previous studies have shown the efficacy of ketones to provide an alternate fuel in times of starvation, leading to cellular restoration and rescue from apoptosis [7-11]. This case study provides a prospective, community based intervention that could easily be replicated with groups of individuals who are suffering from T2DM and comorbid cognitive impairment as well

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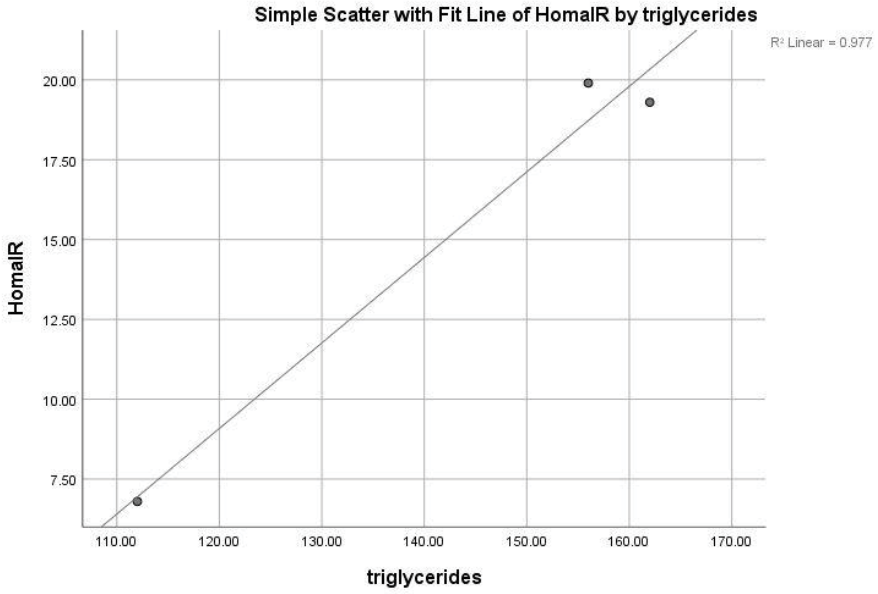

Figure 2: The patient's HOMA-IR was positively correlated with reduced triglycerides, showing an adjusted R2 value of 0.977, indicating statistical significance.

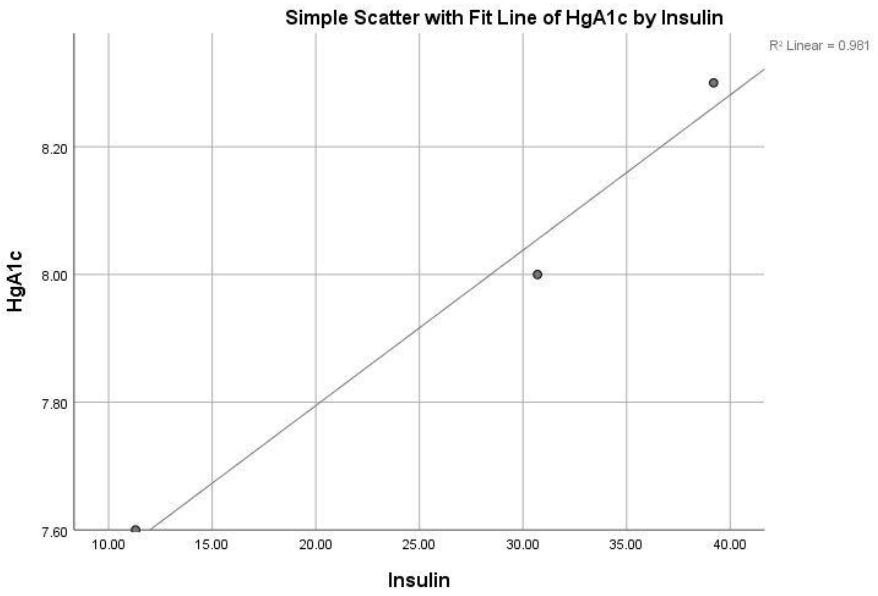

Figure 3: The patient's HgA1c was positively correlated with reduced fasting insulin, showing an adjusted R2 value of 0.981, indicating statistical significance.

as other non-communicable, chronic diseases. However, community based, nutritional interventions and their empowerment of patients with MetS, T2DM and/or cognitive impairment warrants further investigation.

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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.

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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