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Case Report

Ketogenic diet rescues cognition in ApoE4+ patient with mild Alzheimer's disease: A case study

Sarah J. Morrill [a], Kelly J. Gibas [b,*]

[a] Human Bioenergetics & Applied Health Science, Bethel University, MN, USA
[b] Behavioral Health Sciences, Human Bioenergetics & Applied Health Science, Bethel University, MN, USA

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ABSTRACT

It has been established that there is a correlation between Alzheimer's disease and apolipoprotein E, specifically the ApoE4 genetic variant. However, the correlation between Apoe4, insulin resistance and metabolic syndrome (MetS) pathologies still remains elusive. As apolipoprotein E has many important physiological functions, individuals with the ApoE4 allele variant, also known as the Alzheimer's disease gene, are primarily at a greater risk for physiological consequences, specifically cognitive impairment (Chan et al., 2016). In this case study, a 71-year old female, heterozygous for ApoE4 with a family history of Alzheimer's Disease (AD) and the dual diagnosis of mild AD/metabolic syndrome (MetS) was placed on a 10-week nutrition protocol purposed at raising plasma ketones through carbohyrdrate restricted, high fat ketogenic diet (KD), time- restricted eating and physical/cognitive exercise. Primary biomarkers for MetS were measured pre/mid-/post intervention. The MoCA (Montreal Cognitive Assessment) was administered pre/post intervention by a licensed clinical therapist. The results were statistically significant. The HOMA-IR decreased by 75% from 13.9 to 3.48. Triglycerides decreased by 50% from 170mg/dL to 85mg/dL. VLDL dropped by 50% from 34mg/dL to 17mg/dL, and HgA1c decreased from 5.7% to 4.9%. The baseline MoCA score was 21/30; post treatment score was 28/30. The significant results in both MetS biomarkers and the MoCA score suggest that a ketogenic diet may serve to rescue cognition in patients with mild AD. The results of this case study are particularly compelling for ApoE4 positive (ApoE4+) subjects as ketogenic protocols extend hope and promise for AD prevention.

1. Introduction

Apolipoprotein E (ApoE) is part of a class of proteins produced by astrocytes in the brain that help transport cholesterol to neurons. These receptors are associated with the low-density lipoprotein receptor gene family; ApoE acts as the principle carrier of cholesterol/lipids in the brain. Cholesterol is important to brain function, as it enhances the myelin sheath of the neurons allowing for signals to be passed quickly and efficiently [1,2]. ApoE is polymorphic with three major alleles, e2, e3, and e4, that differ from one another by the position of their amino acids. These differences alter the ApoE structure and function; each variant has differing physiological consequences. Individuals with the ApoE4 allele are at an increased risk for physiological consequences, specifically cognitive impairment [3,4]. The ApoE4 allele is a variant that prevents cholesterol from being efficiently transported in the brain, as ApoE4 interferes with signaling mechanisms [5]. This variant prevents the efficient clearance of amyloid plaque from the brain causing accumulation, which further interferes with the neurons' signaling capacity [4,5]. Insulin resistance has been hypothesized to be at the root of this problem, as insulin competes with amyloid for the insulin-degrading enzyme (IDE). With continually high levels of blood glucose and insulin common to peripheral insulin resistance and less degradation of amyloid, research suggests that the brain experiences an insulin resistant state [6]. Furthermore, astrocytes are significant in maintaining cerebral glucose homeostasis, as they are responsible for the paracrine metabolic coupling with neurons; astrocytes uptake glucose at the blood brain barrier (BBB) via the GLUT 1 receptor where they synthesize glucose to its storage forms, glycogen and lactate, for eventual delivery to the neurons. Although the brain is not an insulin dependent organ, research suggests that insulin signaling and nutrient sensing pathways are activated via the hypothalamus. Thus, the reduced expression of insulin in the brain, mediated by insulin sensitive GLUT4 receptors of the

* Corresponding author.
E-mail address: kelly-gibas@bethel.edu (K.J. Gibas).

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hypothalamus, blunt the nutrient signaling cascade; metabolic coupling between astrocytes and neurons becomes increasingly impaired. Insufficient fuel delivery to neurons modulates, down-regulates the most energy expensive neurobehaviors, like cognition [7]. Correspondingly, insulin resistance and the presence of the ApoE4 allele are significant risk factors for metabolic pathologies such as MetS and type II diabetes. The ApoE4 carriers are located on the surface of LDL and VLDL cholesterol particles circulating in the cardiovasular system; the E4 variant is associated with impaired fat transort and delayed lipid clearance from the liver and blood. Likewise, ApoE4 alleles correspond with a repressed expression of HDL cholesterol and reverse cholesterol transport, leading to increased risk for atherosclerosis, heart attack and stroke. Thus, the clustering of irregular blood lipids common to most metabolic pathologies increases cardiovascular risk, reduces overall quality of life and elevates risk for cognitive impairment. [8]. Although carriers of ApoE4 have increased risk for neurodegeneration, the E4 variant does not predict cognitive decline, rather the variant increases likelihood; however, diet, exercise and lifestyle interventions have been shown as modulators of potential risk for cognitive impairment in E4+ patients with comorbidities of MetS. Research suggests the mediation/normalization of blood lipids in ApoE4 carriers may be a proxy for cognitive prevention; as shown in previously published case study reports, clinically prescribed dietary ketogenesis modulates cerebral metabolic flexibilty by regulating nutrient sensing pathways via the heptatic production of ketone bodies supplying fuel to dysregulated neurons [9]. A clinically prescribed, ketogenic diet (KD), with periods of time restricted eating, has been shown to restore systemic fuel flux and increase cellular sensitivity to insulin. Ketone bodies are synthesized in the liver and move across the BBB as supplemental fuel as well as an available carbon substrate for neuroplasticity. As the energy demands of the hypo-metabolic circuitry are satisfied via ketone synthesis, physical exercise and cogntive training (PEAK Brain APP) initiate building/repair of neural networks, thereby restoring cognition by ameliorating consequences of neuronal dormancy.

2. Methods

The case study focused on a 71-year-old female with MetS, mild Alzheimer's disease (a.k.a. mild cognitive impairment [MCI]) who was heterozygous for the APOE4 gene variant. Nine physiological biomarkers for metabolic pathology were administered by healthcare professionals through serum blood draws: HgA1c, fasting triglycerides, fasting insulin, total cholesterol, LDL, VLDL, HDL, fasting glucose and C-reactive protein. Cardiac/metabolic and neurodegenerative risk ratios were calculated from anthropometric and serum biomarkers including:HOMA-IR, Triglyceride/HDL ratio and Waist/Height ratio (WHtR). The MoCA was the primary cognitive assessment utilized for the study due to its clinical accuracy as a diagnostic tool for mild Alzheimer's disease. Daily cognitive training was incorporated into the intervention and recorded through the PEAK Brain Training Mobile Application. Recent longitudinal data suggests that brain-training applications, like PEAK, designed to improve cognition and prevent neurodegeneration are dismal failures [10]. The PEAK training modality was selected in this case study to illustrate the centrality of restoring metabolic flexibility and nutrient sensing in the brain *prior* to cognitive stimulation. Guided, low-impact exercises were provided throughout the 10-week intervention; the patient performed the guided exercise 3-days per week for approximately 30 minutes.

More specifically, the 10-week intervention incorporated a nutrition based intervention purposed at restoring systemic metabolic flexibility by sustaining plasma ketones within a normal physiological range (.5 - 2.0 mg/dL) via a low carbohydrate/high fat diet together with time restricted eating, weekly low-impact exercise and daily cognitive training. This aforementioned protocol was prescribed by licensed health care professionals and monitored by the student researcher under direct clinical supervision. The patient's blood ketone levels were measured weekly via the Abbott Lab's Blood Ketone Meter as well as daily measurements using Reli-On Urine Ketone strips. The ApoE4 genetic test was administered via buccal swab prior to the intervention by a healthcare professional and processed by an independent lab service. The MoCA cognitive assessment was administered pre/post intervention by a licensed professional clinical counselor (LPCC). The patient was instructed to utilize the PEAK Brain Training Application on her mobile device daily; the PEAK results were recorded in the application and sent to the student researcher at the end of each week. The PEAK brain training domains included: language, problem solving, mental agility, memory, and focus designed to strengthen the frontal, parietal, occipital, prefrontal cortex, temporal, and hippocampus respectively[11.] Additionally, the patient integrated low-impact exercise by walking on a treadmill, 3-5 days per week for 30 minutes using light hand weights. The patient met with health care professionals and the student researcher once per week throughout the intervention period to monitor blood ketones/blood glucose levels, assess anthropometric biomarkers and perform a guided low-impact workout session guided by the student researcher.

3. Case presentation

The 71-year-old female presented for therapeutic intervention after experiencing progressive cognitive decline and compounding

Table 1
Biomarkers for MetS pre/mid/post intervention.

RESULTS	Pre-Intervention	Mid-Intervention	Post-Intervention	Percent Change
HOMA-IR (<1.0)	13.9	4.48	3.48	75% reduction
Tri/HDL ratio (<2.0)	2.7	1.51	1.18	56% reduction
WHtR (<0.5)	0.66	0.63	0.59	11% reduction
Fasting Insulin mg/dL (3–5)	48.7	19.5	16.2	67% reduction
Fasting Glucose mg/dL (70–90)	116	93	87	25% reduction
HgA1c (%)	5.7	5.4	4.9	15% reduction
Triglycerides mg/dL (<150)	170	103	85	50% reduction
HDL mg/dL (>50)	64	68	72	13% increase
LDL mg/dL (<100)	118	70	68	42% reduction
VLDL mg/dL (9–13)	34	20.6	17	50% reduction
Weight (lbs)	227	224	221	3% reduction
BMI (<25)	41.5	40.8	40.4	3% reduction
Body Fat % (<30%)	50	49	47	6% reduction

Table 2
MOCA scores pre/post intervention.

Memory Assessment	Pre-Intervention	Post-Intervention
MOCA (>26)	21	28

symptoms of MetS. The impairment of cognition was described as forgetfulness, delayed word recall and frequent misplacement of objects. The participant's cognitive deterioration was confirmed after administration of the MoCA; she was classified as mild Alzheimer's disease based on her baseline score (21/30). Her comorbidity of MetS and cognitive decline developed gradually over the course of several years. However, she self-reported cognitive deficits as marked increase over the past year. Her diagnosis of MetS was determined by centroid obesity and serum values, including but limited to: fasting insulin, fasting triglycerides, fasting glucose, HOMA-IR and TRI/HDL ratio. The patient was morbidly obese as determined by her BMI of 41.5, waist/height ratio (WHtR) at 0.66, and body fat mass at 50%. The participant otherwise reported good health and had not sought treatment. The participant is a retired female who is single with no children. She had an immediate family history of progressive cognitive decline, including one diagnosis of AD.

4. Results

A morbidly obese, 71-year old female, who was a heterozygous ApoE4 carrier, was enrolled in a 10-week lifestyle/nutrition intervention aimed at restoring systemic metabolic flexibility. A clinically prescribed, ketogenic diet with time restricted eating was was combined with daily brain training via a mobile App and low-impact exercise (3-5 days per week/30 minute sessions) for the duration of the 10-week intervention. Weekly monitoring of blood ketones and anthropometric analysis were implemented. The patient's primary risk biomarkers for MetS as well as her cognitive domain scores improved significantly demonstrating a robust

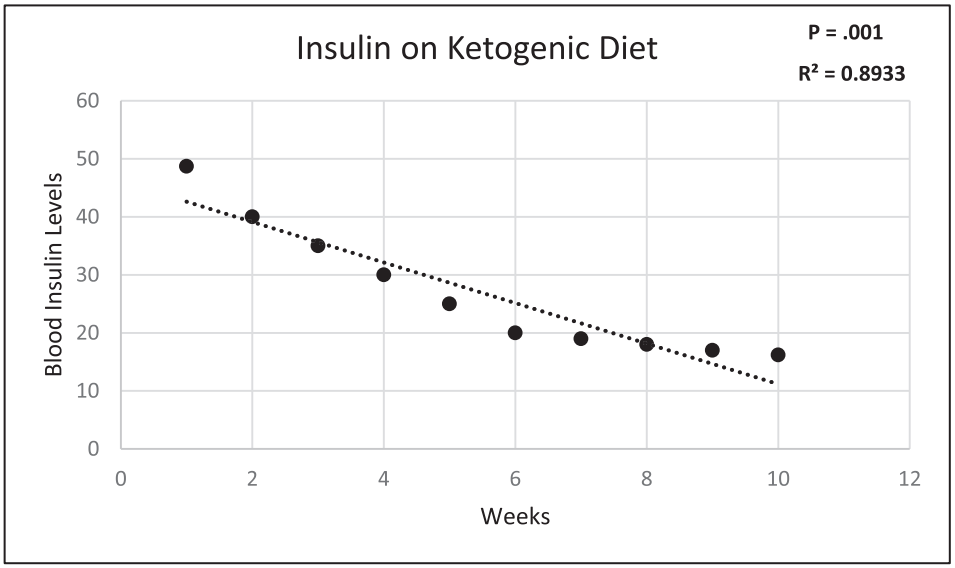

Fig. 1. The patient's insulin was positively correlated with effects of the ketogenic diet and reflects statistical significance, adjusted $R^2 = 0.880$, $p = .001$.

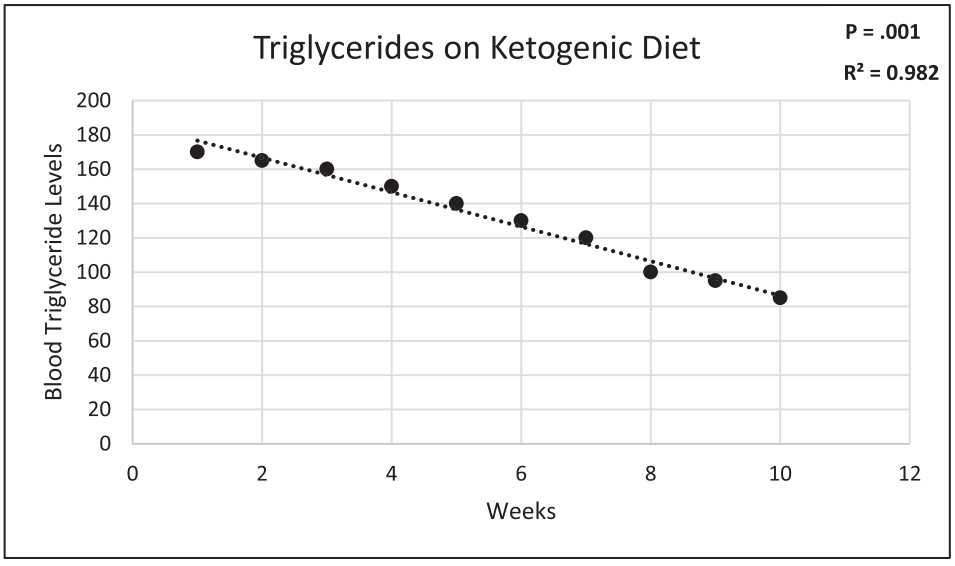

Fig. 2. The patient's triglycerides were positively correlated with effects of the ketogenic diet and reflect statistical significance, adjusted $R^2 = 0.980$, $p = .001$.

correlation with the nutritional/lifestyle intervention protocol as displayed in Tables 1 and 2. More specifically, the results reveal a strong association between reduced fasting insulin levels, improved memory function and normalization of MetS biomarkers.

5. Data

Statistically significant results were recorded in all aspects of the intervention and include, but are not limited to: insulin, triglycerides, glucose, and HgA1c. See Figs. 1–4 below.

6. Discussion

The statistically significant results suggest that implementing a nutrition protocol purposed at restoring metabolic flexibility through a ketogenic diet, time restricted feeding, low-impact exercise and daily brain training can ameliorate symptoms of insulin resistance and mediate inherent risk of the ApoE4 gene variant in a mild Alzheimer's disease patient. The apolipoprotein E carrier has many important physiological functions; individuals with one or two ApoE4 alleles are known to be at greater risk for physiological consequences, specifically neurodegeneration [3]. Although there is limited research on the interrelationship between the ApoE4 variant, insulin resistance/metabolic syndrome and eventual AD, this case study attempts to correlate the relationship between metabolic pathology and cognitive decline. The 71-year old, female patient started the intervention with a baseline MoCA score of 21/30, her fasting insulin was 48.7mU/L and she had a strong family history of AD suggesting a rapid trajectory toward neurodegeneration. Yet, the statistically significant improvements in her MoCA score and normalization of MetS biomarkers, signify the importance of nutrient sensing to overall systemic health and prevention of Alzheimer's disease for patients witht the ApoE4 gene variant comorbid with insulin signaling defects.

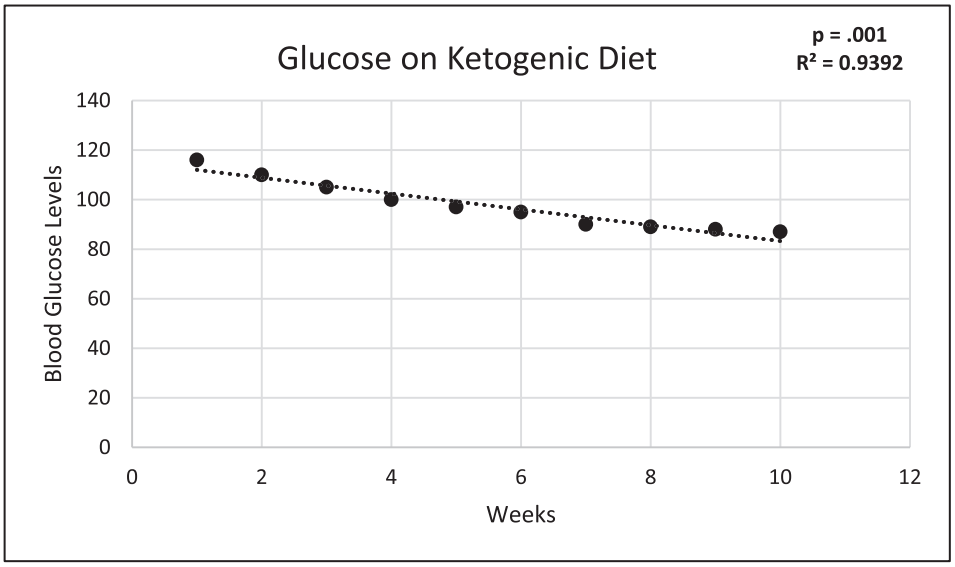

Fig. 3. The patient's glucose was positively correlated with effects of the ketogenic diet and reflect statistical significance, adjusted R^2 0.932, p = .001.

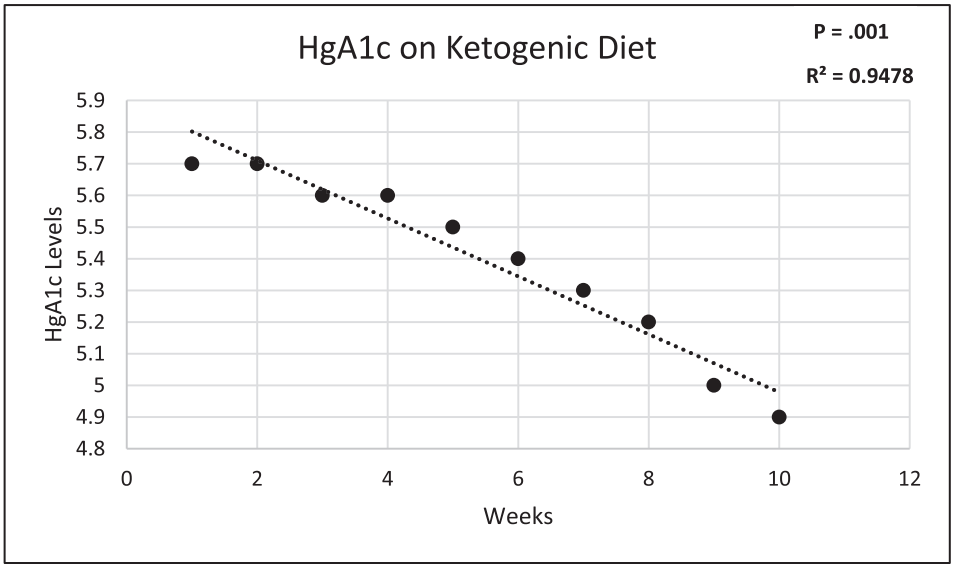

Fig. 4. The patient's HgA1c was positively correlated with effects of the ketogenic diet and reflects statistical significance, adjusted $R^2 = 0.941$, p = .001.

This case study is limited by the small sample size. Future studies should expand on the number, sex, and age of the sample.

7. Conclusion

Patients diagnosed with mild AD who are carriers of the ApoE4 gene variant can yield significant improvement in cognition and overall metabolic health through a clinically prescribed, nutrtitional ketogenic approach aimed at restoring metabolic flexibilty to both peripheral tissues and the brain. As shown by previous clinical research, dietary ketosis is known to restore metabolic flexibility by regulating the kinase nutrient signaling pathways of mTOR/AMPK through the heptatic production of ketone bodies. Ketones provide a subsequent fuel substrate to the starving brain and carry the potential to restore the metabolic pathology in dysregulated neurons [9]. This case study together with previously published reports, provide clinically significant data using reputable and clinical measurements to sustain hope for the prevention and eventual cure of AD. Further clincal investigation is warranted.

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.

Conflicts of interest

The authors declare that there is no conflict of interest associated with this manuscript.

Disclosure statement

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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. Systemic Review: The authors reviewed the literature using traditional (e.g., google scholar) sources. While the role of ApoE4 gene in correlation to insulin resistance and metabolic syndrome is not yet 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: The hypothesis of this case study describing a multifaceted nutritional protocol centered around the KD was proved through the results obtained throughout the intervention. This hypothesis is consistent with nonclinical and clinical findings currently in the public domain.
3. Future Directions: The manuscript proposes a framework for the generation of new hypothesis 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 reversal of neuronal damage in the AD brain; (c) the potential of ApoE4 testing for all adults over the age of 21 in order to prevent future neurodegeneration; (d) the role of sustained normalized MetS biomarkers on the genesis of AD for patients with ApoE4

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.dsx.2019.01.035.

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