Case Report

Metabolic syndrome marks early risk for cognitive decline with APOE4 gene variation: A case study

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\textbf{ABSTRACT}

A vast amount of research has been done on the APOE4 genetic marker for Alzheimer’s disease (AD), but its connection to metabolic processes associated with peripheral insulin resistance and cerebral glucose metabolism is still relatively unknown. The APOE4 allele is the strongest genetic risk factor for developing late-onset Alzheimer's disease, particularly in individuals who have inherited two copies of the gene (Zhao et al., 2017). In this case study, a 38 year old male with metabolic syndrome (MetS), the APOE4 gene, early stage memory problems and a family history of Alzheimer’s Disease (AD) was placed on a ketogenic diet combined with high intensity interval training (HIIT) for 10 weeks. The primary intervention goal was to reduce insulin defect, impaired cerebral and peripheral insulin signaling, associated with metabolic syndrome. Recent research demonstrates that insulin defect competes for space with APOE4 in brain cells, thus exacerbating amyloid pathology (Zhao et al., 2017). Primary biomarkers for metabolic syndrome were measured at baseline and after 10 weeks. The MoCA (Montreal Cognitive Assessment) was administered at baseline and after 10 weeks. The results were statistically significant. The HOMA-IR (homeostatic measure of insulin resistance) decreased by 59% from 4.3 to 1.8. The triglyceride/HDL ratio decreased by 77% from 14.7 to 3.4. Fasting triglycerides were reduced from 573 mg/dl to 167 mg/dl (71% reduction); VLDL decreased from 114 mg/dl to 33.4 mg/dl (71% decrease); and fasting insulin was reduced by 55% from 15.6 mU/L to 7.1 mU/L. The baseline MoCA score was 22/30; post treatment score was 30/30. If APOE4 is the strongest genetic risk factor for developing late-onset Alzheimer’s Disease, then implementing a ketogenic diet and high intensity exercise could essentially turn “off” the effects of this APOE4 gene earlier in life for prevention of future neurodegeneration.

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1. Introduction

APOE4 has been of great interest in the field of Alzheimer’s for many years, but recent research correlating APOE4 with metabolic syndrome offers the exciting possibility of inactivating the gene’s potential for neural decline by reversing peripheral and cerebral insulin resistance [1–3]. Alzheimer’s disease has long been the most common form of dementia for the elderly. It is usually accompanied by memory loss, language troubles, and cognitive depletion [4]. Alzheimer’s is difficult to predict and can be troublesome to treat once it has progressed, however the discovery of the APOE genetic marker has contributed to the ability to discern risk before onset occurs. The APOE4 gene has many single-nucleotide polymorphisms. Each of these (SNPs) come with different amounts of amino-acids at residue 112 and 118. These slight variations can cause contrast in function of the APOE4 gene. These slight variations allow for medical professionals to accurately assess risk of developing early onset dementia [5]. Scientists at the Mayo clinic in Jacksonville, Florida discovered that APOE4 seems to be in conflict with insulin for space on the GLUT4 insulin-dependent glucose transporter. This leads to insulin resistance which is primary to metabolic syndrome. Not only does APOE4 compete for space on the GLUT4 transporter, but it also encapsulates endosomes. The encapsulating of these endosomes decreases proper insulin signaling in the brain [3]. Sustained peripheral insulin resistance creates a flux of insulin across the blood brain barrier (BBB), leading to gradual impairment in hypothalamic glucose/insulin sensing with reduced expression of GLUT4 transport. This loss of cerebral cellular sensitivity is known to be an early biomarker for dysregulation of glucose homeostasis and defects in neuro-cognition [2]. Restoring peripheral and hypothalamic insulin signaling pathways through a ketogenic diet and high intensity...
exercise may play a key role in negating the effects of the APOE4 gene polymorphism later in life.

2. Methods

Fifteen physiological biomarker tests for metabolic syndrome (MetS) were administered by healthcare professionals on a 38 year old male patient. The patient was overweight with a BMI of 31.2, waist/hip ratio (WHR) of 0.97, and waist/height (WHR) of 0.58. The family medical history included Alzheimer's disease, type 2 diabetes (T2D) and stroke. The MetS biomarker measures were taken in three different stages: baseline, mid-intervention and post intervention. Three serum blood tests were administered during the 10 week intervention which measured the patient’s HOMA-IR, Tri/HDL ratio, fasting insulin, fasting glucose, LDL, VLDL, HDL and fasting triglycerides. The final seven tests performed were WHR, WHR, body fat mass (BFM), body fat %, lean body mass (LBM), BMI (body mass index) and weight. The 10 week intervention incorporated a ketogenic diet with three days per week of high intensity interval training (HIIT). The HIIT was paired with 2 days of heavy lifting per week for a total of 5 days of exercise per week.

Under the supervision of healthcare professionals, the ketogenic diet was prescribed and monitored. The patient’s blood glucose and ketones were monitored daily using the Abbott Precision Xtra blood glucose/ketone meter to ensure sustained fasting glucose below 100 mg/dL and blood ketones in the physiological range of 0.5–2.0 mg/dL. The MoCA cognitive assessment was administered by a licensed professional clinical counselor (LPCC) pre/mid/post intervention. The ApoE4 genetic test was administered via buccal swab prior to the intervention by a healthcare professional. The patient met with health care professionals once per week to monitor blood glucose/ketone levels and the student researcher a total of five times throughout the program in order to guide workouts and adjust the nutrition intervention as needed.

3. Case report

The patient, a 38-year-old male presenting with signs of mild cognitive impairment (MCI) and metabolic syndrome, is employed as a children's pastor and manager of ACR Homes for people with disabilities. The patient also stays active at home with a wife and four daughters. Regarding exercise, he consistently finds time to run 2–3 days per week but is unhappy with the results in terms of physical and mental health. Prior to the intervention, the patient had not previously sought treatment for the memory problems but had been diagnosed with MetS by his primary care physician. The patient has been concerned about the early subjective memory complaints due to his familial history of cognitive impairment including AD and dementia.

$R^2 = 0.994$
Fig. 1. The patient’s HOMA-IR was positively correlated with reduced insulin levels with an adjusted $R^2$ of 0.994 reflecting statistical significance.

Fig. 2. The patient's Tri/HDL ratio was positively correlated with reduced insulin levels with an adjusted $R^2$ of 0.939 reflecting statistical significance.

Fig. 3. The patient’s triglycerides were positively correlated with reduced insulin levels with an adjusted $R^2$ of 0.976 reflecting statistical significance.

4. Results

One adult male was enrolled in the 10 week intervention. A ketogenic diet was combined with HIIT for the duration of the program. Weekly monitoring of blood ketones and body composition analysis were implemented. The patient’s primary biomarkers for MetS and memory scores improved significantly demonstrating a robust correlation with a ketogenic diet combined with HIIT. More specifically, the results reveal a strong association between lowered fasting insulin levels and improved memory function and MetS biomarkers. The results are consistent with the research 58% reduction in the HOMA-IR from 4.3 to 1.8; 71% decrease in VLDL from 114.6 mg/dL to 33.4 mg/dL; and a fasting insulin reduction of 55% from 15.6 mU/L to 7.1 mU/L. The patient decreased his body weight by 14%, as he lost 30.9 pounds, and reduced his BMI by 15%. See Table 1 for MetS biomarker results.

The patient’s memory scores improved significantly during the 10 week intervention. The normal range for MoCA scoring is $>26$. The patient scored 22/30 at baseline and 30/30 at the conclusion of the intervention. See Table 2 for MoCA scores pre/mid/post intervention.
conducted by Zhao et al., which demonstrates the correlations between APOE4, insulin resistance and poor memory features [3]. The patient’s primary biomarkers for MetS decreased significantly. The results reflected a 71% reduction in triglycerides from 573 mg/dL to 167 mg/dL: 77% decrease in Tri/HDL ratio from 14.7 to 3.4.

5. Data

The correlations between lowered insulin and increased ketone levels with MetS biomarkers and memory scores were statistically significant. See Figs. 1–5 below.

![Graph](image1.png)

**Fig. 4.** The patient’s VLDL was positively correlated with reduced insulin levels with an adjusted $R^2$ of 0.976 reflecting statistical significance.

![Graph](image2.png)

**Fig. 5.** The patient’s MoCA score was positively associated with increased ketone levels with an adjusted $R^2$ of 0.945 reflecting statistical significance.

The data from this case study is consistent with previous research demonstrating correlative properties between insulin signaling defects on memory [1,6], on neurodegeneration [7–10]. Early onset dementia is memory impairment. The 38-year old patient’s baseline MoCA score of 22, fasting triglycerides of 573 mg/dL, and family history of AD suggest a rapid trajectory toward neurodegeneration. However, the significant improvement
6. Discussion

The statistically significant results suggest that implementing a ketogenic diet allows for proper GLUT4 translocate on the cell despite APOE4 competition for space on the insulin-dependent receptor. In essence, the APOE4 gene is essentially turned off. Research has shown that the APOE4 gene mutation is the strongest risk factor for late-onset AD [3]. Early onset AD and dementia are highly correlated with metabolic syndrome [11]. One of the signs of late-onset AD is the 6.4% increase in post intervention MetS biomarkers and memory seems to demonstrate that a ketogenic diet and HIIT turns off the APOE4 gene, thus eliminating competition for space on the GLUT4 insulin-dependent transporter. The resulting increase in insulin sensitivity promotes decreased MetS biomarkers and increased memory function [1,12].

The primary limitation to this case study is the small sample size. Future studies should attempt to increase sample size and equalize the number of men and women involved in research.

7. Conclusion

Increased ketone production and high intensity exercise not only improve MetS biomarkers [13] and memory function [1], but also seem to turn off the effects of the APOE4 gene mutation as evidenced by normal insulin signaling [3]. Early testing for APOE4 with patients with MetS may serve to pioneer robust intervention strategies designed to increase peripheral and cerebral GLUT4 translocate in order to prevent future neurodegeneration.

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.

Conflicts of interest

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

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 the APOE4 gene and metabolic syndrome 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 combined with high intensity interval training (HIIT). These relevant citations are appropriately cited.

2 Interpretation: Our findings led to an integrated hypothesis describing the role of a ketogenic diet and HIIT on MetS biomarkers and memory function. 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 hypotheses and the conduct of additional studies regarding this area of study. Examples include further understanding: (a) the role of sustained normalized MetS biomarkers on the genesis of AD for patients with APOE4; (b) the potential of APOE4 testing for all adults over the age of 21 in order to prevent future neurodegeneration.

References
