Research article
Volume 9:1, 2020
DOI: 10.37421/JMS.2020.9.251

Journal of Metabolic Syndrome

ISSN: 2167-0943 Open Access

Aerobic Glycolysis Couples Metabolic Syndrome to Alzheimer's Disease

Delia Labatt, Cole Smith and Kelly Gibas*

Human Bioenergetics and Applied Health Science, Bethel University, Minnesota, United States

Abstract

Alzheimer's Disease (AD) is a global epidemic; every 3 seconds someone in the world develops dementia. An estimated 50 million people are living with a disease that cannot be prevented, treated or cured. Without novel breakthroughs, AD is predicted to exceed 130 million by 2050. Pharmaceuticals offer minimal relief with dismal evidence of reversing neurodegeneration. Research focuses on β-amyloid plaques and tau tangles; but, in a clinical trial, medications designed to sop-up toxic proteins in the brain fail to impede neural decline. Instead, plaques and tangles appear to be late-arrivers in the insidious progression of dementia. The recent explosion of comorbid metabolic pathologies (global prevalence of T2DM estimated @ 463 million) invites researchers into a deeper discussion of bioenergetics regulating cognitive impairment and metabolic dysregulation. Age-related energy deficits, driven by peripheral insulin resistance, exacerbate Aβ/tau accumulation, increase oxidative stress and impede mitochondrial function; work by Sergi et al. and Mastroeni et al. suggest that mitochondrial dysfunction with epigenetic impairment in oxidative respiration appear to be the earliest offenders in the progression of T2DM and AD [1,2]. This case report highlights a novel, integrated intervention with a 69-year-old male dually diagnosed with T2DM and Mild Cognitive Impairment (MCI). Physiological biomarkers were measured pre/mid/post-intervention; the MoCA (Montreal Cognitive Assessment) measured cognitive function, pre/post. Statistically significant results were observed in the metabolic risk biomarkers, memory was restored to normal ranges, and the HbA1c normalized out of the diabetic range @ <5.6%. Furthermore, the metabolic and cognitive improvements were sustained @ 3 months post-intervention. These promising results suggest that dietary ketogenesis restores peripheral insulin sensitivity, mitigates T2DM and improves cognition by circumventing neural starvation via the restoration of metabolic flexibility.

Keywords: Alzheimer's disease • Mild cognitive impairment • Metabolic syndrome • Type 2 diabetes mellitus • Hyperinsulinemia • Ketogenic diet • Photobiomodulation • Inverse warburg effect • β-amyloid plaque

Introduction

Deciphering genetic susceptibility is valuable for mitigating the risk of cognitive impairment; however, the regulation of peripheral and cerebral glucose metabolism may offer the deepest insight into the etiology of neurodegenerative disorders. Through the lens of metabolic pathology, hyperinsulinemia occupies a conjunctive role in body/brain starvation; sustained peripheral insulin resistance initiates whole-body glucose dependency coupled with metabolic inflexibility and a marked reduction in the cerebral metabolic rate of glucose (CMR_{glc}) [1]. Likewise, diminished metabolism has been shown to exceed/precede brain atrophy and neurodegeneration. Metabolic pathologies common to insulin dysregulation trigger epigenetic modifications in fuel partitioning and cell respiration. Chronic episodes of hypoglycemia, common to insulin resistance, alter gene expression, which may be responsible for reduced glucose uptake and dysregulation of GLUT1 transport at the Blood-Brain-Barrier (BBB) [3]. In addition, recent publications show that reduced glucose availability in the central nervous system is a direct trigger for behavior and motor deficits related to the progression of neuropathology; the observed deficits arise from hyperphosphorylated tau proteins made in response to diminishing CMR_{glc} [4,5]. Pere Llinàs-Arias et al. showed epigenetic dysregulation in the SVIP gene leads to metabolic inflexibility and systemic glucose dependency [6]. Sustained glucose cycles switch cell respiration away from oxidative phosphorylation toward aerobic glycolysis, a form of molecular fast food to ensure "cheap" energy. Research shows a robust, linear association between the progression of cognitive impairment and somatic energy deficits [3,7]. Chronic energy failure distorts the epigenome causing shifts in methylation marked by global hypo-methylation with local hyper-methylation of key proteins aimed at increasing the flux of aerobic glycolysis while blunting oxidative respiration [8]. The shift allows for an expedited flux of glucose, but cheap energy comes at the expense of metabolic inflexibility [6]. In glucose-dependent states, aerobic glycolysis and fermentation become the primary biochemical processes to sustain energy [9]. However, peripheral glucose dependency can have dire consequences on the brain.

Cerebral starvation is accelerated by impaired glucose transit across the BBB; however, reduced CMR_{glc} shows clinical distinctions from peripheral starvation. Neurons are primarily oxidative; they do not synthesize a full range of glycolytic enzymes for flux into aerobic glycolysis, like peripheral cells. Instead, astrocytes receive glucose directly from the BBB and go through the cycle of glycolysis yielding lactate. The lactate can be shuttled to neighboring neurons via MCT transport where it is converted back to pyruvate by LDH-B for oxidative phosphorylation (OXPHOS) in the neuron. Thus, declining energy supplies in the brain have been shown to activate compensatory mechanisms in neurons that up-regulate oxidative enzymes increasing mitochondrial respiration [10]. The epigenetic shift ensures a hypermetabolic flux of electrons during low energy states [2]. At first glance, this hyper-metabolic, compensation appears to be more advantageous than glycolysis, as it offers a greater potential for ATP. However, the increased flux through an already fragile inner membrane is uncoupled by ATP production, which results in increased oxidative stress in the matrix [2]. Mastroeni et al.

***Address for correspondence:** Gibas K, Human Bioenergetics and Applied Health Science, Bethel University, Minnesota, United States, Tel: +7639134387, E-mail: kelly-gibas@bethel.edu*

Received: 12 March, 2020; **Accepted:** 19 March, 2020; **Published:** 30 March, 2020

and Pere Llinàs-Arias et al. suggest that these epigenetic signatures regulate gene expression via metabolic reprogramming in critical nutrient-sensing pathways including PGC-1a, AMPK, ERAD, HIF-1 and mTOR [2,6]. Aberrant respiration is fuel adaptive; stress-induced reprogramming of cellular respiration appears to accelerate the onset of chronic disease [6]. Whole-body metabolic shifts ensure glucose for the brain, but hyperinsulinemia and impaired GLUT1 transport impede its delivery across the BBB [7].

This case highlights the powerful role of endogenously produced ketones as an alternative fuel. The synthesis/oxidation of ketones can circumvent energy stress, blunt hepatic de novo lipogenesis, restore metabolic flexibility and normalize the flux of regulatory hormones in the fed/fasted cycle. Nutritional ketosis accelerates beta-oxidation allowing the liver to strategically convert acetyl CoA into ketone bodies rather than saturated fat. Ketones are immediate fuel during states of low insulin. Paradoxically, the oxidation of ketone bodies also blunts the endogenous synthesis of liver fat, thereby reducing VLDL and mitigating the progression of NAFLD (Non-Alcoholic Fatty Liver Disease) [11]. Aberrant activation of de novo lipogenesis, with the elevated synthesis of VLDL, is common in insulin resistance and T2DM. The accretion of palmitate from hepatic lipid synthesis compromises cell function; saturated fatty acids accumulate into solid "chunks" that stiffen phospholipid membranes and accumulate as visceral fat around organs in the thoracic cavity [11]. Visceral fat amplifies the secretion of dangerous inflammatory cytokines. Ketone bodies are rich, lipid substrates that readily cross the blood-brain barrier delivering carbon/energy to the brain independent of GLUT1 transport. Likewise, ketones provide immediate fuel for peripheral tissues through beta-oxidation, thereby circumventing the bottleneck of glycolysis to help restore metabolic flexibility.

Methods

A 69-year old male with a twenty-year history of T2DM was referred by his Optometrist to participate in a Service Learning Program hosted at Bethel University in Saint Paul, MN. The patient was previously diagnosed with T2DM by his primary care physician, as measured by HbA1c>6.5%. He adhered to the clinical standard of care for diabetes including daily doses of: Metformin, Glimeperide and Lipitor. Despite compliance to protocol, the patient's pre-intervention EAG (Estimated Average Glucose) was @ 183 mg/dL and HbA1c @ 8.0%. Lipitor appeared to normalize Total Cholesterol and LDL, but his fasting triglycerides remained elevated @ 178 mg/dL and VLDL @ 36 mg/dL suggesting hepatic de novo lipogenesis and metabolic inflexibility despite normal LDL [12]. The patient presented with comorbid Mild Cognitive Impairment (MCI), assessed by a licensed mental health profession (LPCC) based on the MoCA (21/30). After physician referral, the patient elected to self-register for the 6-week Service-Learning Program offered by the Human Kinetics and 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. As part of the educational experience, volunteers signed HIPAA educational releases allowing academic access to their health history, laboratory values, and test results.

Guided by the professor, student clinicians assessed metabolic risk for each volunteer using the following international biomarkers of metabolic risk: HOMA-IR (homeostatic model assessment of insulin resistance), TRI/HDL ratio, WHtR (waist-to-height ratio) and the results of a comprehensive metabolic panel. For 6 weeks, the patient volunteers followed bio-individualized lifestyle interventions based on their level of stratified risk. The interventions for the volunteers were designed by student clinicians with oversight from the professor. Volunteers were supported by weekly, student-led educational sessions utilizing a patient-centered model of medical illustration designed to empower the volunteers with a deeper, more comprehensive understanding of physiology and the progression of the disease, thereby building self-efficacy and strengthening self-advocacy. Common to each intervention was a 6-week, clinically prescribed ketogenic meal plan designed specifically for each volunteer by licensed Functional Medicine Practitioners (CFMP). The macronutrient breakdowns were calculated using the patient's stratified risk scores and body compositional analyses (lean body mass/fat mass/body fat%). Post-intervention goals included: normalization of peripheral insulin resistance (measured via HOMA-IR), reduction in cardiovascular risk (measured via TRI/HDL ratio) and mitigation of metabolic pathology (including T2DM, pre-diabetes and MetS assessed via HbA1c) through restoration of whole-body, metabolic flexibility. Likewise, improvements in cognitive function were hypothesized to be a step-function of increased cerebral metabolic rate for glucose (CMR_{glc}) [6]. A functional reduction in glucose transport (GLUT1) at the blood-brain-barrier is known to precede the onset of MCI/AD symptoms; likewise, PET of [F]fluoro-2-deoxyglucose ([F]FDG)-derived radioactivity in the brain reveals that a similar progressive reduction in cerebral metabolism occurs before the detection of clinical symptoms in individuals with AD. The preclinical symptoms occur in the temporal region of the brain where early diminishment of glucose mimics a hyper-metabolic state eventually leading to brain atrophy and neurodegeneration [13].

Unique to the metabolic intervention for this patient was: regular use of a far-infrared sauna to initiate heat shock proteins (160 degrees F for 20 minutes/4-5 days per week), daily use of a Respiratory Training Device (RTD) to simulate hypoxia with hypercapnic rebreathing for vasodilation (approximately 10 minutes/day) and photobiomodulation (PBM) red light therapy to mediate optimal circulation/blood flow (approximately 12 minutes, every other day). The clinically prescribed ketogenic diet was designed using the patient's body composition; the macronutrient ratios for the 6-week intervention included: 75% fat, 15% protein and 10% carbohydrate (% of caloric expenditure was based on his Metabolic Rate as measured by indirect calorimetry). Protein was allocated @ 15% of his total caloric load calculated using the formula lean body mass × .8 grams of protein (moderate activity level). In addition, a time-restricted feeding window of 6-8 hours was encouraged for 3-5 days per week; time-restricted feeding has been shown to reduce fasting insulin and restore the circadian rhythm. MetS biomarkers were collected via blood serum during three stages of the intervention: pre/mid/post. Fasting insulin, fasting blood lipid panel (VLDL, LDL, HDL, triglycerides, total cholesterol), blood ketones, HOMA-IR and TRI/HDL ratio were calculated at each stage. The patient's Waist to Height Ratio (WHtR), Body Fat Mass (BFM), body fat %, Lean Body Mass (LBM), Body Mass Index (BMI) and weight were calculated and recorded every week. Cognitive changes were assessed weekly during the on-campus visits using clinically valid/reliable cognitive screening tools to measure change in the various centers of the brain: language, memory and focus, mental agility and problem-solving in the frontal/prefrontal cortex, parietal, occipital/temporal lobes, angular gyrus, posterior cingulate cortex and hippocampus [14]. 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

The patient, a 69-year old male presented with T2DM and distinct features of MCI; recently retired after a productive career in Information Technology (IT). He volunteered at a local nursing home and enjoyed staying active outdoors by riding his bike. For regular aerobic exercise, he consistently cycled during tepid months and exercised regularly at a local gym throughout the year. Despite his active lifestyle, the patient had a 20-year history of erratically controlled T2DM with a strong family history of diabetes, hyperlipidemia, and cardiovascular disease. His signs of cognitive decline emerged within the past 12-months. His Optometrist noticed changes in cognition and referred the patient to the Service Learning Program at Bethel

University. The patient self-reported the cognitive deficits and said they were most apparent during activities of daily life, like remembering a grocery list or recalling where he put his keys. Before the intervention, the patient did not explore remedies to improve his cognition. Throughout the 6-week intervention, he remained under the supervisory care of his physician. The patient was confounded by the progression of his diabetes (HbA1c>8.0%) as he religiously adhered to the medical protocol, exercised regularly, attempted to eat a balanced diet and maintained normal body weight and normal BMI. Otherwise, the patient was in good health; he had no family history of AD and tested negative for the APOE4 genetic variant; he was heterozygous for APOE3.

Results

After the aforementioned 6-week Service Learning Program, the patient achieved notable results. After only three weeks of adherence to protocol, he achieved physiological ketosis with blood ketones registering @ 0.7 mmol/L as measured by the Abbott Precision Xtra ketone meter (Nutritional Ketosis=0.5-2.0 mmol/L). At 6 weeks, significant reductions were achieved in each of the primary metabolic risk biomarkers and he experienced marked cognitive improvement supported by his post-intervention MoCA score moving into the normal range (28/30); in addition, he continued his cognitive improvement @ the 3-month screening, (29/30). Other notable changes at post-intervention included: 45% decrease in fasting triglycerides and VLDL signifying restoration of metabolic flexibility; 80% reduction in HOMA-IR moving the patient from severely insulin resistant (6.1) to insulin-sensitive (1.2). And most notably, he achieved normalization of his HbA1c (5.6%) moving him out of the diabetic range for the first time in over twenty years.

Statistical analyses were completed using SPSS (Versions 25.0). Regression analysis demonstrated a significant linear correlation between fasting insulin and HOMA-IR (R^2=0.99, p=0.046), the Tri/HDL ratio and Triglycerides (R^2=0.940) and the Tri/HDL ratio and fasting insulin (R^2=0.943). In addition, a significant negative correlation was observed between HOMA-IR and blood ketones (R^2=0.954). See Table 1 below for a summary of the results.

Table 1. Percent change in MetS biomarkers and MoCA score following the 6-week intervention.

Variable	Percent Improvement
HOMA-IR	80.3% decrease
Triglycerides	45% decrease
Triglyceride/HDL ratio	43.5% decrease
VLDL	45% decrease
Fasting insulin	58% decrease
Fasting glucose	53.6% decrease
MoCA (cognitive/memory assessment)	33% increase into the normal range

Data

Statistically significant positive correlations were observed between: decreased HOMA-IR and decreased fasting insulin; decreased HOMA-IR and falling Triglyceride/HDL ratio; and, reduced fasting insulin and reduced triglycerides. In addition, a significant negative correlation was observed between decreased HOMA-IR and increased endogenous ketone production. This supports previous research showing that HOMA-IR has a significant negative association with healthy glucose metabolism in the brain; in MCI, early deficits in glucose cause a hyper-metabolic shift in the medial temporal regions of the brain (Inverse Warburg Effect) followed by oxidative damage and global hypo-metabolism [2,10] (Figures 1-5).

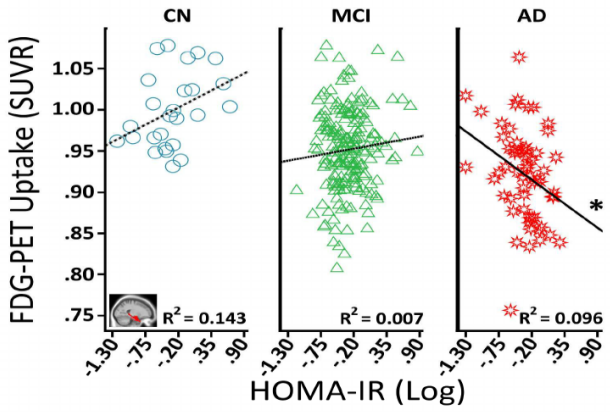

Figure 1. Willette et al. showed elevated HOMA-IR (predicted dysregulated, hyper-metabolism in MCI patients and hypo-metabolism in AD in the medial temporal regions reflecting the early epigenetic shifts toward "cheap energy" that precede the onset of AD. This supports Mastroeni et al. conclusions that showed significant downregulation in OXPHOS genes in AD, particularly those encoded in the nucleus, but in contrast, there was up-regulation of the same gene(s) in MCI subjects compared to AD and controls [2,10].

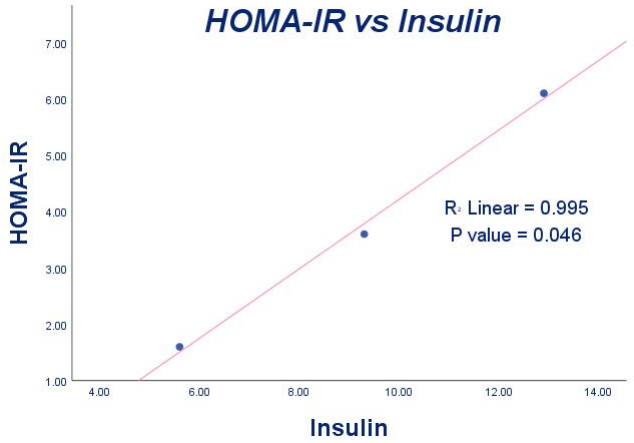

Figure 2. The patient's HOMA-IR was positively correlated with reduced insulin levels, showing an adjusted R^2 value of 0.995 and a p-value of 0.046, indicating statistical significance.

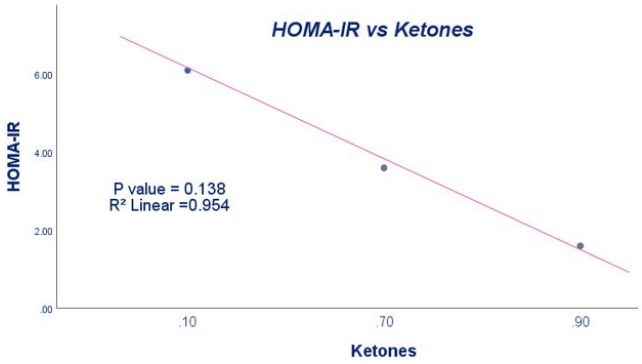

Figure 3. The patient's HOMA-IR was inversely correlated with endogenous ketone production, showing an adjusted R^2 value of 0.954, reflecting statistical significance.

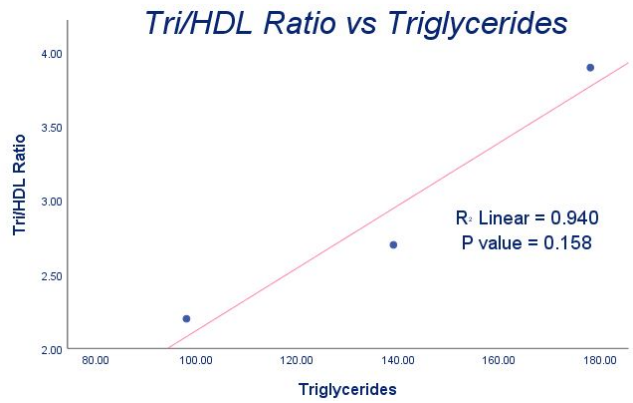

Figure 4. The patient's Tri/HDL ratio was positively correlated with a decrease in triglycerides, showing an adjusted R^2 value of 0.94, indicating statistical significance.

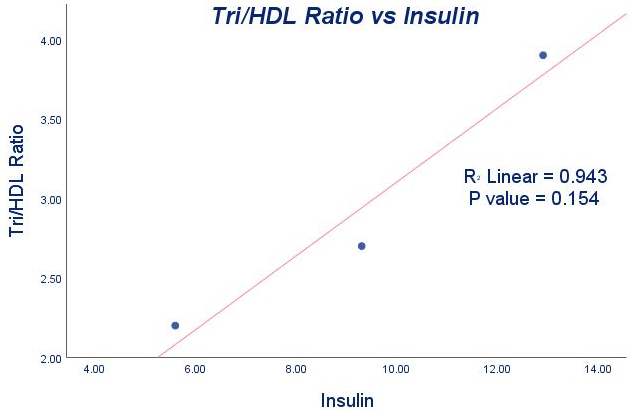

Figure 5. The patient's Tri/HDL ratio was positively correlated with decreased insulin levels, showing an adjusted R^2 value of 0.943, demonstrating statistical significance.

Discussion

Research shows the progression of T2DM and AD starts years before patients notice symptoms of glucose instability or cognitive decline. This is not a discovery. Key papers published in 1975 by Dr. Joseph R. Kraft observed hyperinsulinemia to be etiological in numerous disease states hypertension, obesity, atherosclerosis, micro-vascular disease, neurodegenerative disorders, idiopathic peripheral neuropathy, and certain cancers; likewise, Dr. Joseph R. kraft discovered an association between elevated insulin and idiopathic tinnitus, vertigo and hearing loss [15]. Early-onset of MetS and neurodegenerative disorders appear to originate from what Dr. Joseph R. Kraft referred to as diabetes in-situ or occult diabetes: elevated fasting insulin, acute/transient swings in blood glucose and retrograde diversion of oxidative respiration in the peripheral tissues to aerobic glycolysis [15]. The progression of each disease will be exacerbated by the duration and intensity of the preclinical metabolic pathologies and subsequent epigenetic shifts to mitigate the energy deficits [16].

Peripheral hyperinsulinemia results in an overfed/undernourished phenotype; cells express resistance to insulin to defend against a toxic extracellular matrix. A stress-related shift in gene regulation allows the cells immediate access to "cheap" fuel; however, an enduring pattern of aerobic glycolysis changes signaling in the master nutrient-sensing pathways leading to the secondary pathologies described by Kraft [15]. Likewise, energy deficits in the brain trigger similar epigenetic shifts in fuel partitioning via the up-regulation of the nuclear-encoded mitochondrial enzymes in the neuron to amplify oxidative respiration. However, increased enzyme expression in the matrix of 'hungry' neurons increases the proton gradient across their fragile inner membranes without a coupled increase in ATP synthesis; 'hypermetabolic' uncoupling increases oxidative stress and damages cell membranes [2]. Likewise, epigenetic shifts in the brain create secondary vulnerabilities to apoptotic, degenerative diseases including dementia, AD and Parkinson's disease [17,18].

The statistically significant results in this case report reflect a robust, inverse relationship between peripheral insulin resistance (measured by HOMA-IR) and endogenous blood ketone levels. Chronic insulin resistance inhibits hepatic ketone synthesis/utilization via the blunting of beta-oxidation and repression of the AMPK nutrient-sensing pathway associated with the flux to the fasted state. Physiologically, excess insulin impedes the oxidation of fat resulting in a state of glucose-dependent, metabolic inflexibility [6]. Modulation of serum insulin through nutritional ketogenesis allows the liver to shunt acetyl-CoA toward ketone synthesis and away from de novo lipogenesis. Ketone bodies readily cross the blood-brain barrier using MCT transport serving as a carbon source and direct energy supply for oxidative respiration in the CNS.

Conclusion

Increased ketone production/oxidation achieved through nutritional ketogenesis appears to promote life-changing, epigenetic effects in the body and the brain consequent to the restoration of metabolic flexibility. Dietary ketosis is known to mitigate insulin resistance, inhibit the synthesis of liver fat, reverse long-term T2DM, restore normal cognition and provide an alternative fuel for the brain. The bio-individualized intervention outlined in this case report highlights the importance of establishing self-efficacy through patient-centered biological education, especially in populations struggling with chronic disease. As patients are empowered to understand the etiology of disease, their self-advocacy and adherence/compliance to protocol improves. This bio-individualized program implements three distinct arms of horizontal, patient-centered care: identification of individualized risk stratification, delivery of patient-centered education specific to the disease process and implementation of personalized, lifestyle coaching. A horizontally delivered, bio-individualized standard of care holds great promise in slowing the worldwide trajectory of MetS/T2DM and MCI/AD by empowering patients to find their voice one person, one family, one community, one nation at a time.

Acknowledgments

We are thankful to Joovv, Inc. for the donation of red/NIR light therapy devices for the case study.

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 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

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 the treatment of AD; (b): the potential reversibility of neuronal damage in the AD brain.

References

1. Sergi, Domenico, Nenad Naumovski, Leonie Heilbronn Kaye Heilbronn, and Mahinda Abeywardena, et al. "Mitochondrial Function and Insulin Resistance: From Pathophysiological Molecular Mechanisms to the Impact of Diet." *Front Physiol* 10 (2019): 532.
2. Mastroeni, Diego, Jennifer Nolz, Shobana Sekar, and Elaine Delvaux, et al. "Laser-Captured Microglia in the Alzheimer's and Parkinson's Brain Reveal Unique Regional sssssExpression Profiles and Suggest a Potential Role for Hepatitis B in the Alzheimer's Brain." *Neurobiol Aging* 63 (2018): 12-21.
3. Patching, Simon G. "Glucose Transporters at the Blood-Brain Barrier: Function, Regulation and Gateways for Drug Delivery." *Mol Neurobiol* 54 (2017): 1046-1077.
4. Lauretti, E, JG Li, Adi Meco, and D Pratico. "Glucose Deficit Triggers Tau Pathology and Synaptic Dysfunction in a Tauopathy Mouse Model." *Transl Psychiatry* 7 (2017): 1020-1020.
5. Lauretti, Elisabetta, and Domenico Praticò. "Novel Key Players in the Development of Tau Neuropathology: Focus on the 5-Lipoxygenase." *J Alzheimers Dis* 64 (2018): 481-489.
6. Llinàs Arias, Pere, Margalida Rosselló Tortella, Paula López Serra, and Montserrat Pérez Salvia, et al. "Epigenetic Loss of the Endoplasmic Reticulum-Associated Degradation Inhibitor SVIP Induces Cancer cell Metabolic Reprogramming." *JCI Insight* 4 (2019).
7. Cunnane, Stephen C, Alexandre Courchesne Loyer, Camille Vandenberghe, and Valérie St Pierre, et al. "Can ketones help Rescue Brain Fuel Supply in Later Life? Implications for Cognitive Health During Aging and the Treatment of Alzheimer's Disease." *Front Mol Neurosci* 9 (2016): 53.
8. Zhao, Na, Chia Chen Liu, Alexandra J VanIngelgom, and Yuka A Martens, et al. "Apolipoprotein E4 Impairs Neuronal Insulin Signaling by Trapping Insulin Receptor in the Endosomes." *Neuron* 96 (2017): 115-129.
9. Seyfried, Thomas N, and Laura M Shelton. "Cancer as a Metabolic Disease." *Nutr Metab* 7 (2010): 7.
10. Willette, Auriel A, Barbara B Bendlin, Erika J Starks, and Alex C Birdsill, et al. "Association of Insulin Resistance with Cerebral Glucose Uptake in Late Middle–Aged Adults at Risk for Alzheimer Disease." *JAMA Neurology* 72 (2015): 1013-1020.
11. Mato, José M, Cristina Alonso, Mazen Noureddin, and Shelly Clu. "Biomarkers and Subtypes of Deranged Lipid Metabolism in Non-Alcoholic Fatty Liver Disease." *World J Gastroenterol* 25 (2019): 3009.
12. Sanders, Francis WB, and Julian LGriffin. "De Novo Lipogenesis in the Liver in Health and Disease: more than Just a Shunting Yard for Glucose." *Biol Rev* 91 (2016): 452-468.
13. Gejl, Michael, Birgitte Brock, Lærke Egefjord, and Kim Vang, et al. "Blood-Brain Glucose Transfer in Alzheimer's Disease: Effect of GLP-1 Analog Treatment." *Sci Rep* 7 (2017): 1-10.
14. Rowsey, Kyle E, Jordan Belisle, and Mark RDixon. "Principal Component Analysis of the PEAK Relational Training System." *J Dev Phys Disabil* 27 (2015): 15-23.
15. Kraft, Joseph R. "Detection of Diabetes Mellitus in Situ (occult diabetes)." *Lab Med* 6 (1975): 10-22.
16. Demetrius, Lloyd A, Pierre J Magistretti, and Luc Pellerin. "Alzheimer's Disease: the Amyloid Hypothesis and the Inverse Warburg Effect." *Front Physiol* 5 (2015): 522.
17. Zilberter, Yuri, and Misha Zilberter. "The Vicious Circle of Hypometabolism in Neurodegenerative Diseases: Ways and Mechanisms of Metabolic Correction." *J Neurosci Res* 95 (2017): 2217-2235.
18. Sonntag, Kai C, Wooln Ryu, Kristopher M Amirault, and Ryan A Healy, et al. "Late-onset Alzheimer's Disease is Associated with Inherent Changes in Bioenergetics Profiles." *Sci Rep* 7 (2017): 1-13.

How to cite this article: Labatt D, Cole Smith and Kelly Gibas. "Aerobic Glycolysis Couples Metabolic Syndrome to Alzheimer's Disease". J Metabolic Synd 9 (2020): 251. doi: 10.37421/JMS.2020.9.251