Diabetes & Metabolic Syndrome: Clinical Research & Reviews 12 (2018) 1141–1146

Contents lists available at ScienceDirect

Diabetes & Metabolic Syndrome: Clinical Research & Reviews

journal homepage: www.elsevier.com/locate/dsx

Case Report

AMPK induced memory improvements in the diabetic population: A case study

Alicia Halikas[b], Kelly J. Gibas[a,*]

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

ARTICLE INFO

Keywords:
Type 2 diabetes (T2D)
Alzheimer's disease (AD)
Mild cognitive impairment (MCI)
Ketogenic diet
High intensity interval training (HIIT)
AMPK
mTOR

ABSTRACT

Diabetics in mid-life carry a 1.5 times higher risk of developing Alzheimer's disease than those diagnosed with diabetes (T2D) later in life [1]. Recent research points to accelerated cognitive decline within a range of 20%–50% for middle-aged diabetics as compared to non-diabetic populations [2,3]. Metabolic syndrome (MetS), a type 2 diabetes (T2D) precursor, is also linked to MCI and AD pathologies via hypo-metabolic brain circuitry that inhibits glucose metabolism and attenuates cognitive function [4]. Dysregulation of intracellular and extracellular signaling as mediated by the mTOR and AMPK pathways is the result. These critical nutrient sensing pathways modulate epigenetic shifts in the genome by channeling fuel substrates either towards mitochondrial fatty acid oxidation (AMPK) or cytosolic glycolysis and substrate level phosphorylation (mTOR) [5]. This case study was designed to examine the link between peripheral insulin resistance and early stage memory loss in a type 2 diabetic male. Reactivating the AMPK pathway via induced and controlled nutritional ketosis combined with high intensity interval training (HIIT) (in order to inhibit mTOR signaling) were primary features of the 10 week intervention. Post intervention results revealed statistically significant reductions in HgA1c, fasting insulin and HOMA-IR (homeostatic model assessment of insulin resistance). Restoring peripheral and hypothalamic insulin sensitivity by way of AMPK activation may restore memory function, improve neuroplasticity, and normalize MetS biomarkers (Demetrius and Driver, 2014; [4,6]).

© 2018 Diabetes India. Published by Elsevier Ltd. All rights reserved.

1. Introduction

The hypothesis that cerebral plaques of beta-amyloid (Aβ) and hyperphosphorylated tau contributing to neurofibrillary tangles are the primary causes of MCI and AD is well established. This amyloid cascade model posits that the imbalance of production versus clearance of beta-amyloid is foundational to sporadic forms of AD [1]. The hypothesis is based the assumption that nuclear-genomic defects allow excess accumulation of Aβ and tau, which eventually becomes toxic to neurons [2,3]. Conventional treatment based on this model has been ineffective at slowing and/or reversing symptoms of MCI and AD. However, as science progresses researchers are discovering that the neuropathological basis of cognitive decline may be more likely due to dysregulated mitochondria induced by hyperinsulinemia and hyperglycemia. This bioenergetics model posits that mitochondrial defects and metabolic alterations ultimately lead to the development of two types of neurons-some that are intact and others that are impaired due to reprogramming, causing the latter to behave erratically [2,4]. This erratic neuronal behavior stems primarily from lifestyle factors including a high carbohydrate diet and lack of sufficient exercise. Excess carbohydrate intake over time results in hyperglycemia and hyperinsulinemia, ultimately causing insulin resistance in the brain. This process of glucose transporter downregulation begins to have a spiral effect that eventually deteriorates neurons due to malnourishment. The resulting hypo-metabolic state causes complications in memory and may develop into Alzheimer's disease ([4,6]). Studies show that a reduction in carbohydrate intake with increased fat consumption can significantly alter the way cells are interact in the brain [2,4,7]. Ketone bodies are produced in the absence of carbohydrate as an alternate fuel substrate. Ketone bodies cross the BBB (blood brain barrier) and can be utilized by the brain. Henderson

* Corresponding author.
E-mail addresses: info@bristleconemedical.com (A. Halikas), Kelly-gibas@bethel.edu (K.J. Gibas).

https://doi.org/10.1016/j.dsx.2018.04.033
1871-4021/© 2018 Diabetes India. Published by Elsevier Ltd. All rights reserved.

Table 1
Results summary of MetS biomarker and memory assessment after 10-week intervention.

	Pre-Intervention	Post Intervention	Adjusted R-squared	p-value
HgA1c	6.90%	4.90%	0.884	0.16
Triglycerides	109	87	0.996	0.03
Fasting insulin	15.1	4.8	0.997	0.02
Glucose	168	97	0.884	0.03
VLDL	21.8	17.4	0.996	0.03
Weight	253	227.6	0.921	0.01
HOMA-IR	5.4	1.4	0.965	0.85
MoCA	21	29	0.996	0.03

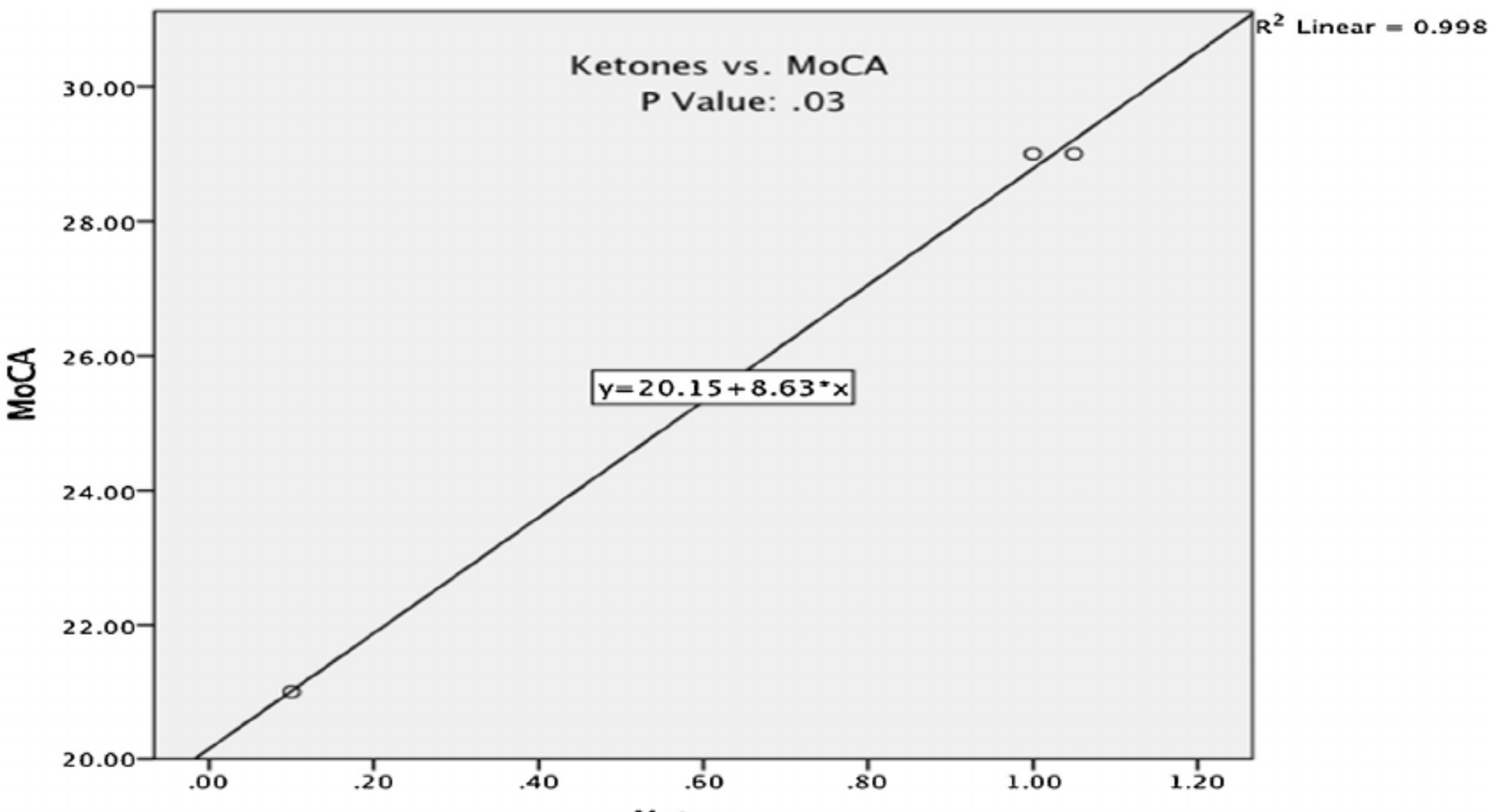
et al. demonstrated that patients with moderate AD who took exogenous ketones for 45 days experienced a statistically significant improvement in their ADAS-Cog scores [9]. The results suggest improved neurological function as a result of ketone delivery to the brain. Likewise, Doody's research revealed that delivering ketones to malnourished neurons resulted in increased neuroplasticity and improved memory capacity in AD patients regardless of age [10]. As an antecedent to endogenous ketone production, AMPK pathway activation serves to feed the starving brain [4].

2. Case study

The patient, a 70-year-old male with an extensive history of heart disease, myocardial infarction and diabetes (T2D) since age 55, was recently diagnosed with MCI. The retired executive complained of subjective memory problems and multiple health risk factors that interfered with his quality of life. After being diagnosed with MCI, he wanted to implement a lifestyle change approach to control his blood sugar and improve memory function. The patient was taking two statin medications and blood pressure medication at the beginning of the 10-week intervention. High risk MetS biomarkers included elevated HgA1c (6.9%), HOMA-IR (5.4), fasting insulin (15.1 mU/L), triglycerides (109 mg/dL) and VLDL (21.8 mg/dL). The MoCA (Montreal Cognitive Assessment) for memory function was administered by a licensed clinical counselor (LPCC). The patient's score was 21 out of 30, confirming the diagnosis of MCI (normal range: 26–30). Although the patient was facing a severe family hardship during the 10-week intervention, he continued to persevere making clinically significant improvements in blood biomarkers as well as memory function.

3. Method

A ketogenic diet was prescribed to the patient designed to sustain physiological ketosis (0.5–2.0 mg/dL) as measured by the Abbott Precision Xtra blood ketone meter. The patient's blood ketones and fasting glucose were monitored weekly by healthcare professionals. A high intensity interval training program was administered by the student researcher each week during the 10-week intervention. The patient was instructed to use the PEAK brain training application five times per week. The PEAK app utilizes games in the following domains: language, memory, focus, mental agility and problem solving designed to improve neuroplasticity. MetS biomarkers were assessed pre/post intervention including HgA1c, fasting insulin, fasting glucose, triglycerides, HDL, LDL, and VLDL.



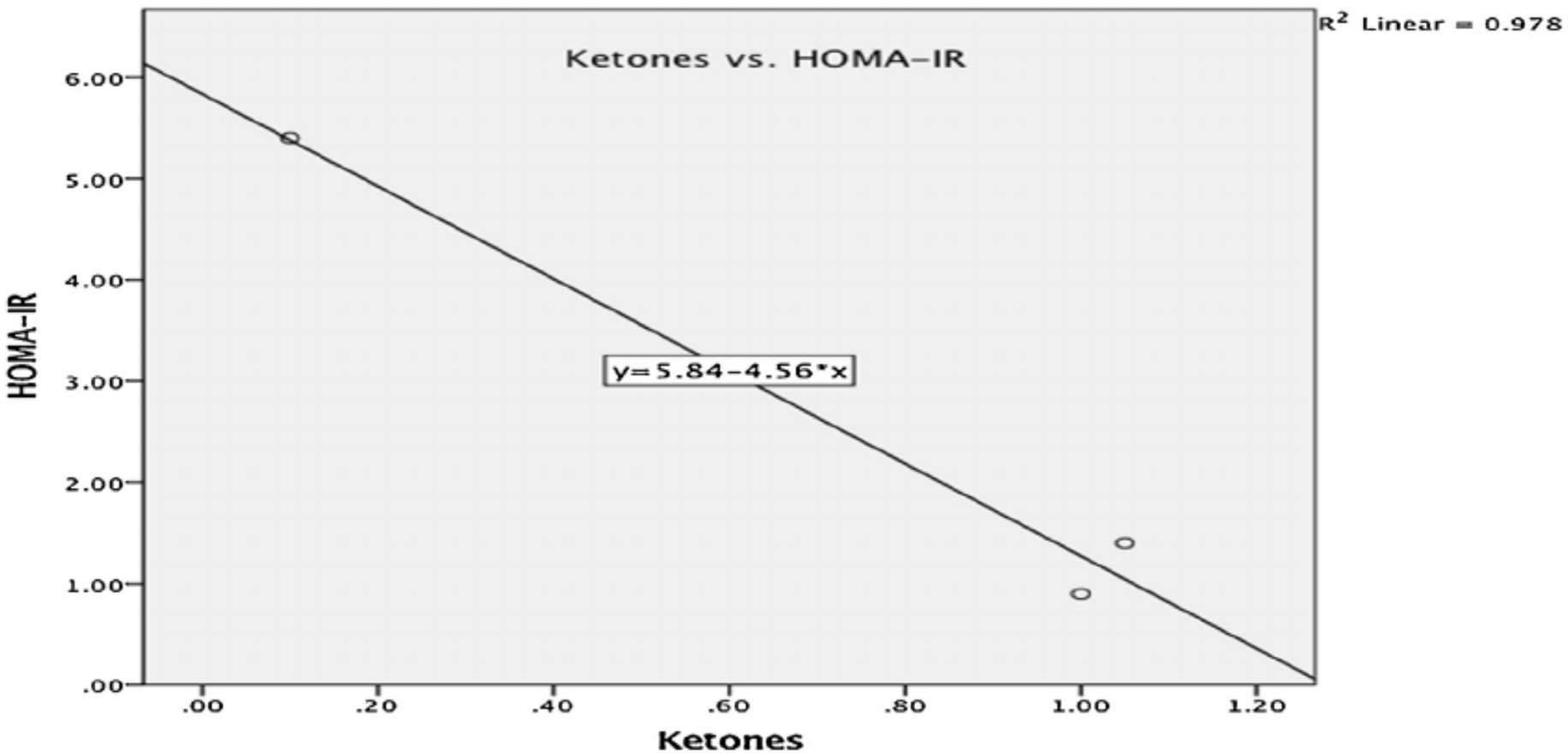


Fig. 2. The patient's HOMA-IR score reflected a linear relationship to ketone production with an R^2 of 0.978 reflecting statistical significance.

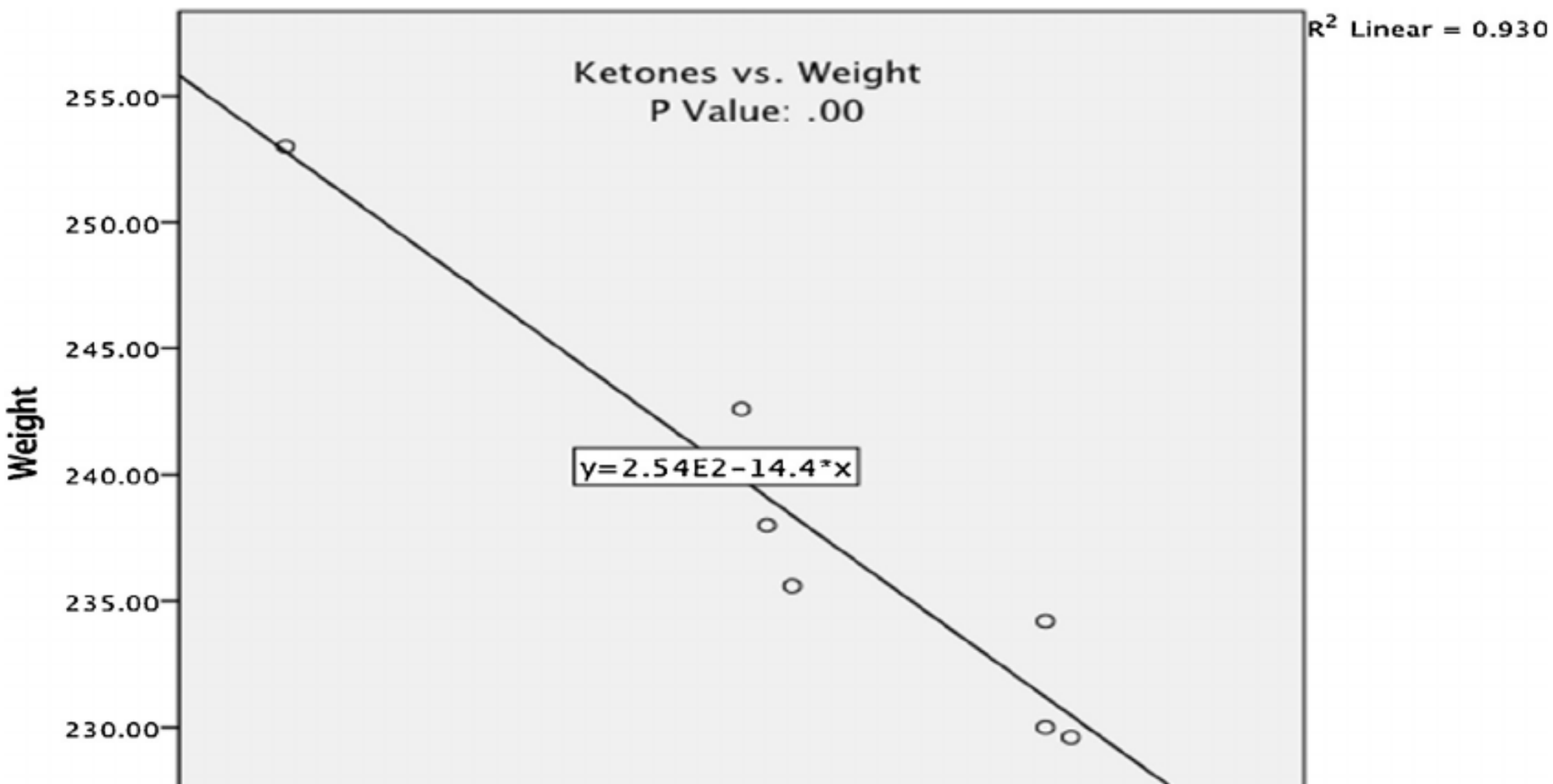
Memory function was assessed pre/post intervention using the MoCA assessment.

4. Results

One adult diabetic male with comorbid MCI was enrolled in the 10-week intervention. Within the first two weeks of the ketogenic nutrition protocol, the patient as able to sustain physiological ketosis (0.5–2.0 mg/dL) as measured by the Abbott Precision Xtra blood ketone meter. By the fourth week the patient's HgA1c had decreased into the normal range of 5.5%. Additionally, observed improvements in spatial awareness and self-efficacy were evident each week. Improved PEAK brain training scores were consistently achieved. Memory function improved significantly as measured by the MoCA; the baseline score of 22 increased to 29 (normal range = 26–30). MetS biomarker improvement was statistically significant for the HgA1c, fasting insulin, triglycerides, weight and HOMA-IR. The intervention outcome measures are clinically relevant as they reflect diabetes (T2D) and MCI reversal. See Table 1 for results summary.

5. Data

The data reflects a robust linear correlation between sustained physiological ketosis (0.5–2.0 mg/dL) and memory function



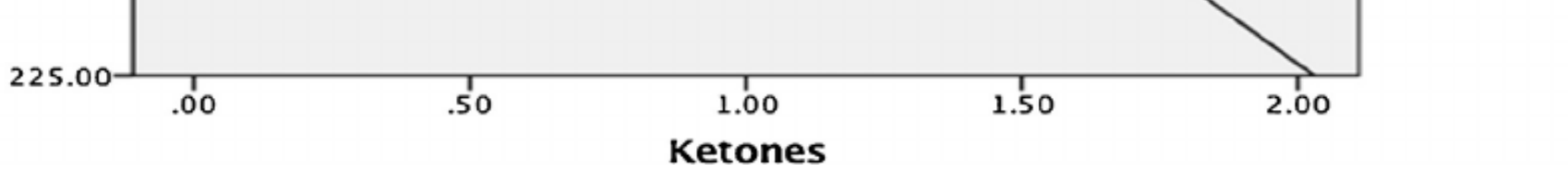


Fig. 3. The patient's weight revealed a linear relationship with increased ketone levels with a p-value <.05 reflecting statistical significance.

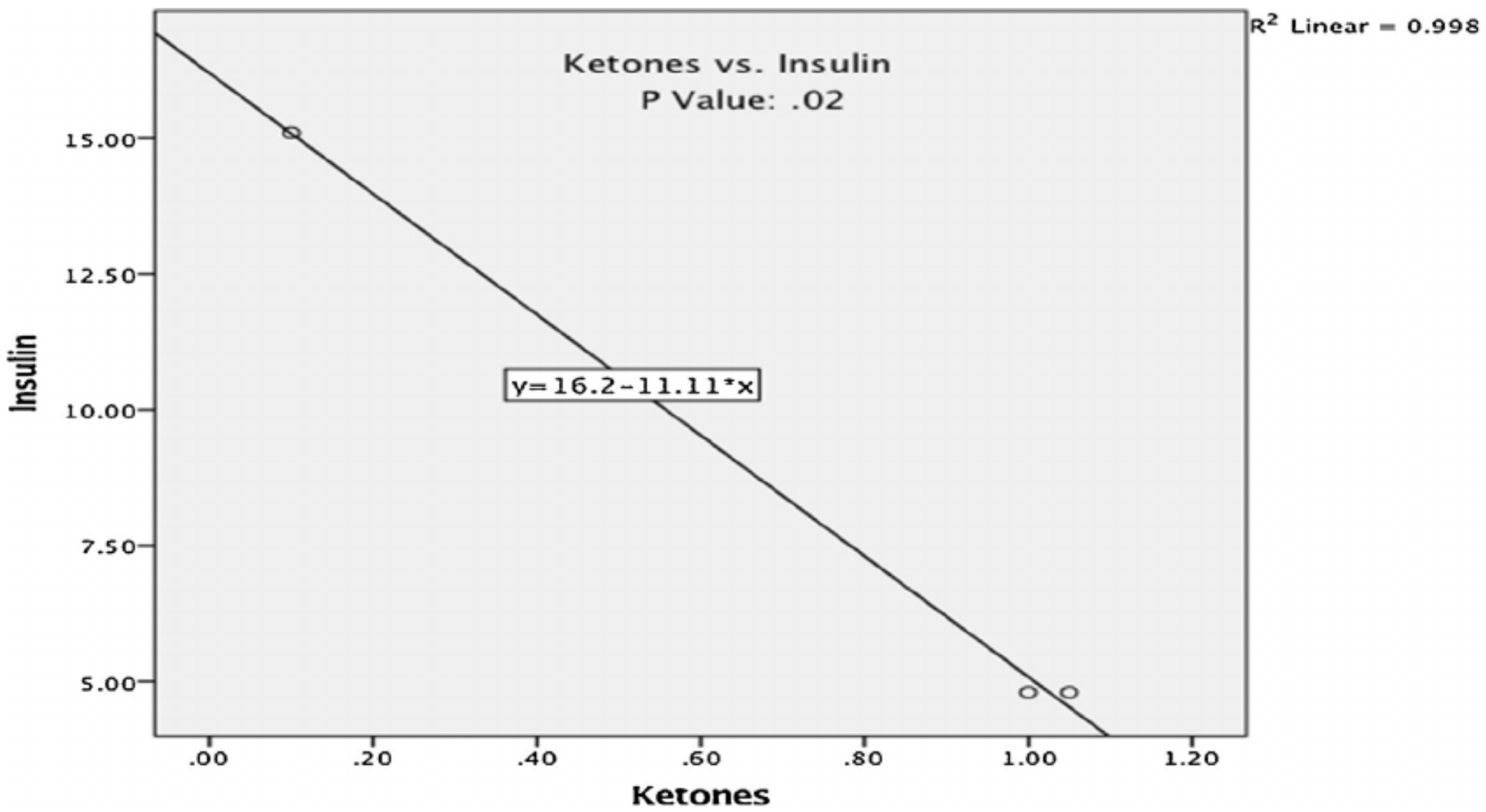
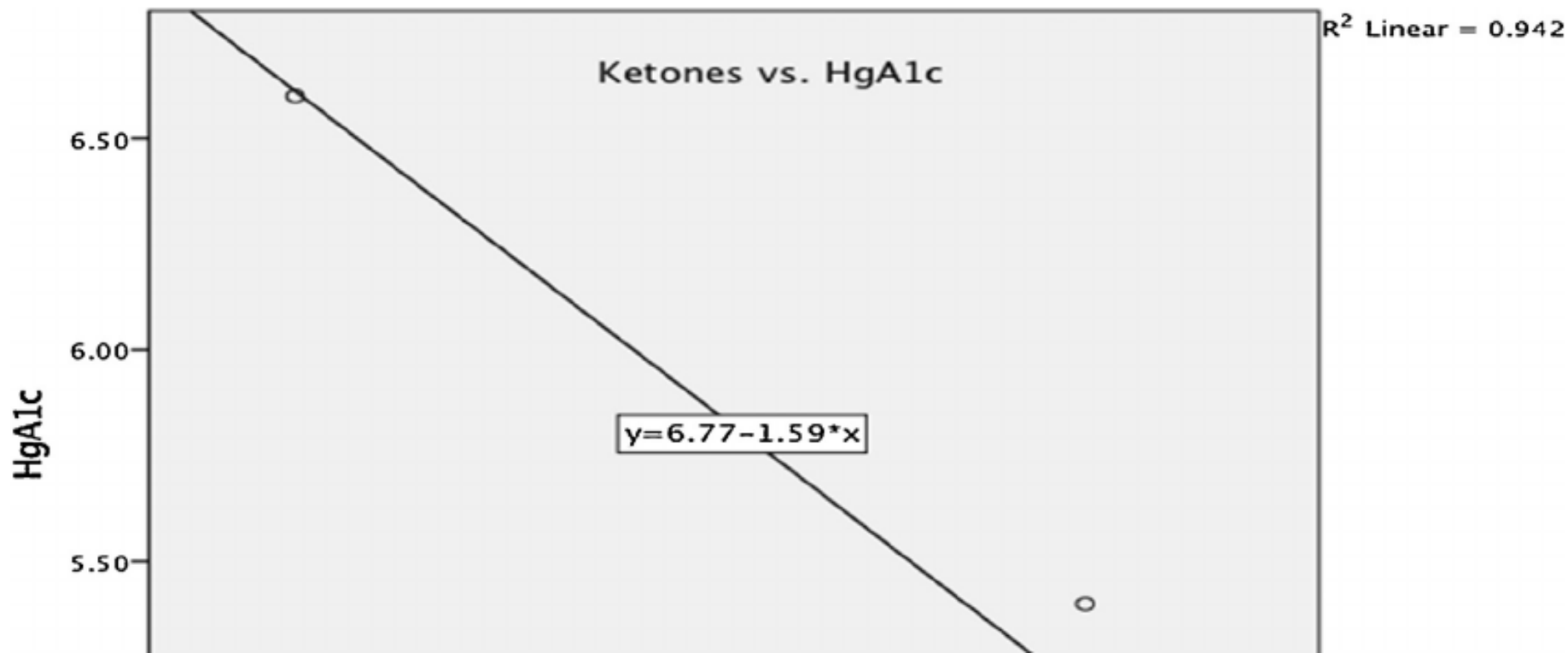


Fig. 4. The patient's fasting insulin revealed a linear relationship with increased ketone levels with a p-value <.05 reflecting statistical significance.

(MoCA), HOMA-IR, weight, fasting insulin, HgA1c and triglycerides. See Figs. 1–6 for a summary of the data.

6. Discussion

The efficiency of biochemical processes in AD and MCI is governed by the dynamics of the mitochondria in neurons. The nonlinear, age-dependent progression of AD triggered by mitochondrial dysfunction creates a crisis in neurons of impaired energy production [7]. Restoring dysregulated mitochondrial function via AMPK pathway activation through a ketogenic protocol and HIIT offers promising trends for future neurological and metabolic research. Nutrition status has the potential to epigenetically modify the genome by activing either the AMPK or mTOR nutrient sensing pathways [4]. This case study effectively demonstrated the role of nutrition status on MetS biomarkers and memory function. Statistically significant improvements were observed in fasting insulin, HgA1c, triglycerides, VLDL, HOMA-IR, weight and the MoCA. Interestingly, the patient's HDL also increased substantially from 52 mg/dL to 70 mg/dL during the



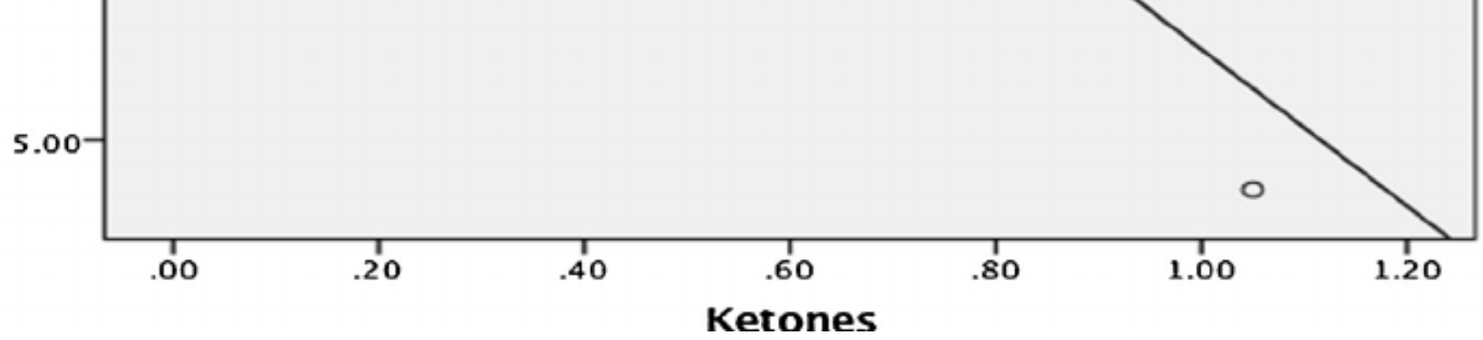


Fig. 5. The patient's HgA1c revealed a linear relationship with increased ketone levels with an R^2 of 0.942 reflecting statistical significance.

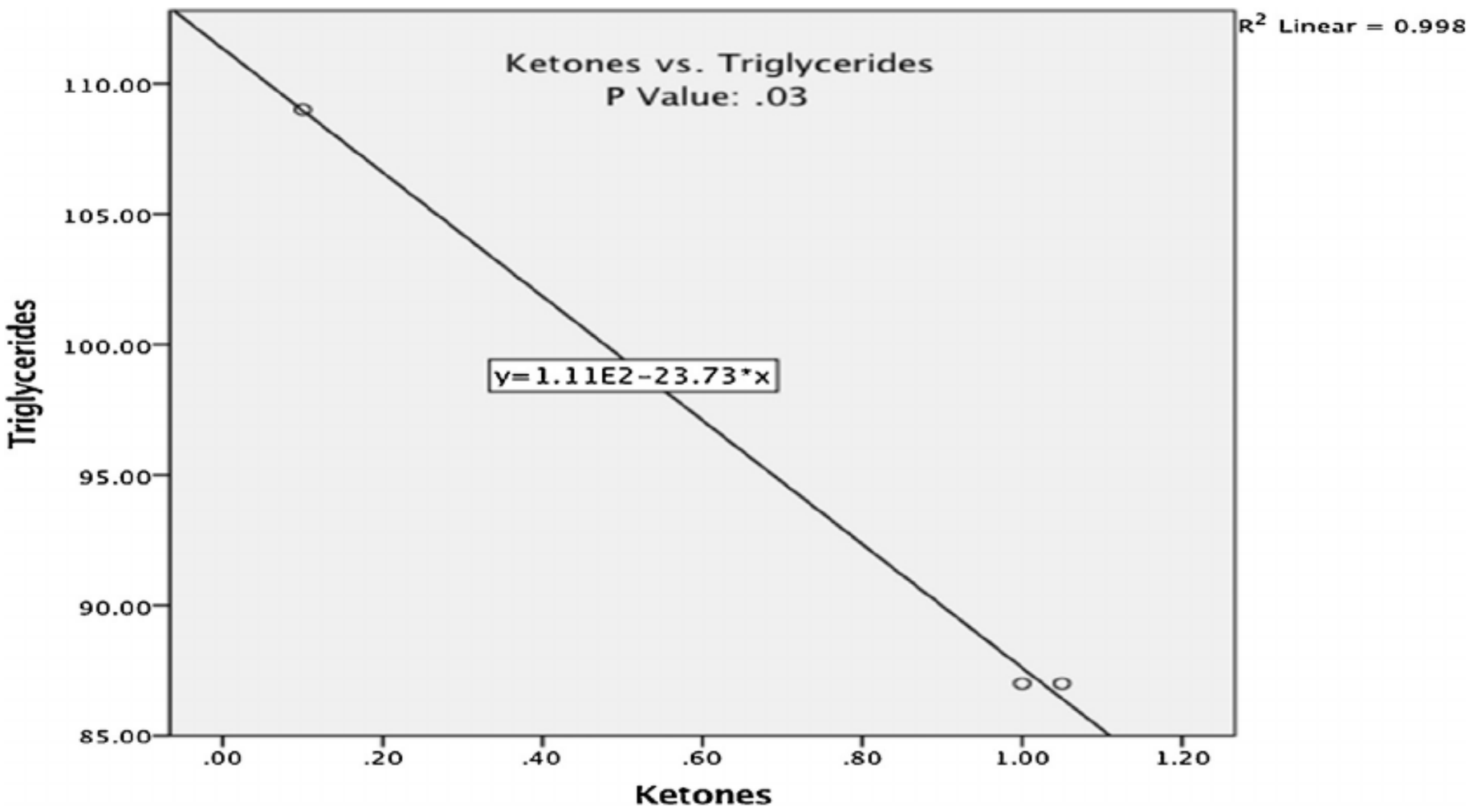


Fig. 6. The patient's triglycerides revealed a linear relationship with increased ketone levels with a p-value <.05 reflecting statistical significance.

intervention reflecting improved cerebral vascular health. Recent research has demonstrated that ketogenic energy production and beta-oxidation effectively restore impaired signaling pathways in peripheral tissues and the brain via AMPK activation ([11,6,12,13]).

Limitations to this design include small sample size and single gender. In future studies, it would be beneficial to expand sample to include an equal number of men and women of varying ages.

7. Conclusion

Impaired brain insulin sensing, diabetes and MetS are associated with the pathogenesis of Alzheimer's disease, MCI and other neurological disorders. Focused treatment on AMPK induction and mTOR suppression through ketogenic protocol and high intensity interval training (HIIT) designed to restore GLUT3 and GLUT4 translocase in the brain and peripheral tissues, respectively, may functionally halt neurological disease progression and restore early stage memory loss.

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.

Con ict of interest

Research in context

1 Systematic review: The authors reviewed the literature using traditional (e.g., PubMed) sources and meeting abstracts and presentations. While the effect of ketogenic diet and Alzheimer's disease is not widely studied form of treatment, there have been several recent publications describing the clinical implications of improvement in cognition when using this form of treatment. These relevant citations are appropriately cited.

2 Our findings led to an integrated hypothesis describing the effects of the ketogenic diet as a form of treatment for mild cognitive impairment (MCI) and Alzheimer's disease. This hypothesis is consistent with nonclinical and clinical findings currently in the public domain.

3 The manuscript proposes a framework for the generation of new hypotheses and the conduct of additional studies. Examples include further understanding the role of a ketogenic diet in patients with genetic predispositions to Alzheimer's disease and the long-term effect of this form of treatment.

References

[1] Ronnemaa E., Zethelius B, SundelofJ, et al. Impaired insulin secretion increases the risk of Alzheimer disease. Neurology 2008;71(14):1065–71, doi:http://dx.doi.org/10.1212/01.wnl.0000310646.32212.3a.

[2] Feinkohl I, Price JF, Strachan MW, Frier BM. The impact of diabetes on cognitive decline: potential vascular, metabolic, and psychosocial risk factors. Alzheimers Res Ther 20157(1), doi:http://dx.doi.org/10.1186/s13195-015-0130-5.

[3] Winkler A, Dlugaj M, Weimar C, Jo ckel K-H, Erbel R, Dragano N, et al. Association of diabetes mellitus and mild cognitive impairment in middle-

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.

aged men and women. J Alzheimers Dis 2014;42:1269–77.
[4] Gibas KJ. The starving brain: overfed meets undernourished in the pathology of mild cognitive impairment (MCI) and Alzheimers disease (AD). Neurochem Int 2017;110:57–68, doi:http://dx.doi.org/10.1016/j.neuint.2017.09.004.
[5] Felice FGD, Ferreira ST. Inflammation, defective insulin signaling, and mitochondrial dysfunction as common molecular denominators connecting type 2 diabetes to Alzheimer disease. Diabetes 2014;63(7):2262–72, doi:http://dx.doi.org/10.2337/db13-1954.
[6] Paoli A, Bosco G, Camporesi EM, Mangar D. Ketosis, ketogenic diet and food intake control: a complex relationship. Front Psychol 20156:, doi:http://dx.doi.org/10.3389/fpsyg.2015.00027.
[7] Demetrius LA, Driver JA. Preventing Alzheimer's disease by means of natural selection. J R Soc Interface 201412(102), doi:http://dx.doi.org/10.1098/rsif.2014.0919 20140919-20140919.
[9] Henderson ST, Vogel JL, Barr LJ, Garvin F, Jones JJ, Costantini LC. Study of the ketogenic agent AC-1202 in mild to moderate Alzheimers disease: a

randomized, double-blind, placebo-controlled, multicenter trial. Nutr Metab 2009;6(1):31, doi:http://dx.doi.org/10.1186/1743-7075-6-31.
[10] Doody RS. Therapeutic standards in Alzheimer disease. Alzheimer Dis Assoc Dis 1999;13, doi:http://dx.doi.org/10.1097/00002093-199911001-00004.
[11] Feinman RD, Volek JS, Westman EC. Dietary carbohydrate restriction in the treatment of diabetes and metabolic syndrome. Clin Nutr INSIGHT 2008;34 (12):1–5, doi:http://dx.doi.org/10.1097/01.nmd.0000342337.87297.9c.
[12] Gibas MK, Gibas KJ. Induced and controlled dietary ketosis as a regulator of obesity and metabolic syndrome pathologies. Diabetes & metabolic syndrome. Clin Res Rev 201711:, doi:http://dx.doi.org/10.1016/j.dsx.2017.03.022.
[13] Seyfried TN. Cancer as a metabolic disease August. , doi:http://dx.doi.org/10.1002/9781118310311.

Further reading

[8] Craft S. The role of metabolic disorders in Alzheimer disease and vascular dementia. Arch Neurol 200966(3), doi:http://dx.doi.org/10.1001/archneurol.2009.27.