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Case Report

Ketogenic diets potentially reverse Type II diabetes and ameliorate clinical depression: A case study

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ABSTRACT

Efficacious adherence to treatment protocol predicts metabolic control among Type 2 diabetics (T2DM) [1–4]; however, few healthcare systems employ individualized strategies to mediate the comorbidity of T2DM with other chronic disease states. A clinically prescribed ketogenic diet, patient-centered nutritional education and high intensity interval training (HIIT), girded by solution-focused psychotherapy, modulate significant improvements in the clinical biomarkers associated with concurring T2DM and clinical depression [5–15]. Relevant metabolic change was noted in the following measures: HOMA-IR, triglyceride/HDL ratio, HgA1c, fasting insulin, fasting glucose, fasting triglycerides, LDL, VLDL, HDL, total cholesterol and C-reactive protein. The Patient Health Questionnaire 9 (PHQ-9) along with clinical interview and the mental status exam showed notable change in the patient's depressive symptoms; likewise, her self-efficacy score normalized, as measured by the General Self-Efficacy Questionnaire (GSE) and the Metabolic Syndrome Compliance Questionnaire (MSC). The case study highlights a 65-year old female who presented with a 26-year history of dually-diagnosed Type 2 diabetes (T2DM) and major depressive disorder (MDD). The patient was prescribed a ketogenic diet (KD), clinically formulated from her resting metabolic rate, body fat percentage and lean body mass, together with weekly nutrition education, high intensity interval training (matched to her cardiovascular conditioning), and eight 45-minute solution-focused psychotherapy sessions. Intervention goals included improved insulin sensitivity evaluated by the HOMA-IR, sustained glycemic control measured via HgA1c, reduced cardiovascular risk via the triglyceride/HDL ratio, and improved depressive symptoms with increased self-efficacy monitored by the PHQ-9 and GSE/MSC. The results of the 12-week intervention were statistically significant. The patient's HgA1c dropped out of diabetic range (8.0%) and normalized at 5.4%. Her average daily glucose measurements declined from 216 mg/dL to 96 mg/dL; the HOMA-IR and triglyceride/HDL ratios improved by 75%. Her marker for clinical depression and measurement of self-efficacy normalized. The 12-week individualized treatment intervention served to functionally reverse 26 years of T2DM, ameliorate two and half decades of chronic depressive disorder and empower/equip the patient with a new experience of hope and success.

1. Introduction

The diabetes epidemic in the United States continues to overburden applied health solutions in primary care settings. While Type II diabetes is largely preventable and reversible, the rate of new diagnoses far surpasses the rate of disease reversal. According to the Centers for Disease Control and Prevention from 1980 through 2014, the number of Americans with diagnosed Type II diabetes has increased fourfold [6]; p. 3). Diabetes is considered *the* major health burden of the day [16]. Diabetes and its precursor, metabolic syndrome (MetS), are engulfing America. Medical doctors have the basic knowledge and they understand the pathological physiology, but the current medical system fails to apply this knowledge effectively [16]. Additionally, adherence to medical regimen is essential to the proper management of chronic disease; few diabetic patients are compliant with physician-recommended pharmacological guidelines and/or lifestyle modifications including a change in diet and exercise habits [2,17]). The proper management of chronic disease necessitates patient self-efficacy.

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A staggering 26% increase in diabetes related medical expenses occurred between 2012 and 2017 [10]; this substantial shift in disease related expenses has staggering implications for the exponential rise in the cost of diabetes-associated diseases. Cardiovascular disease, stroke, heart attack, neurodegenerative disorders and cancerous proliferations are among the most common diseases that can be traced backed to poor glycemic control. The per/person increase in medical expense is substantially higher among people 65 years and older. Likewise, the remarkably high rate of mortality in Type II diabetics is primarily due to poor metabolic control, or more specifically, poor glycemic control [17]. Surprisingly, poor glycemic control is also associated with other key non-patient factors, including lack of integrated care in the healthcare system and sluggish clinical inertia among health care providers [17]. Likewise, diabetes distress is a diagnosed affective disorder characterized by a complexity of factors, which significantly contribute to patient non-compliance [8].

Worry, frustration, conflict and discouragement characterize the experience of many diabetics; likewise, Type II diabetes is closely associated with clinical depression. Diabetes distress negatively impacts individual problem-solving skills required for adequate self-care, which may ultimately result in substandard glycemic control. Self-efficacy, a personal belief in one's innate ability to effectively deal with prospective stressful situations, is commonly influenced by diabetes and diabetes distress. Recent studies demonstrate that higher levels of self-efficacy with stronger compliance to medically prescribed protocols is associated with superior self-care practices and effective glycemic control among Type II diabetics [8].

1.1. Case report

The case involved a 65-year old female patient with a 26-year history of uncontrolled, Type 2 diabetes (T2DM) and persistent major depressive disorder. The patient's medical history included comorbid hypertension, hyperlipidemia and clinically diagnosed major depressive disorder. Since her diagnosis with T2DM in 1992, the patient refused injectable insulin, however she was prescribed Glipizide, Lisinopril and an SSRI (selective serotonin reuptake inhibitor). Previous to the intensive lifestyle intervention, the patient lived a sedentary lifestyle; she has worked full-time at a desk job for the past 18 years. The patient entered the program with the personal goal of reversing her diagnosis of T2DM in order to live longer and improve her quality of life (including the capacity to travel during the retirement years). Before the intervention program, the patient self-reported foggy thinking, ruminating fears of incompetency, irrational fear of abandonment with chronic and sustained bouts of clinical depression.

Table 1
Descriptive statistics of study outcome variables via multiple regression analyses.

Independent Variable	Dependent Variable	Adjusted R^2	*P*-value
HgA1c	HOMA-IR	.95	.03
HgA1c	PHQ-9	.88	.04
HOMA-IR	PHQ-9	.97	.01
HOMA-IR	GSE	.88	.04
HgA1c	Weight	.97	.01

2. Methods

The patient, a 65-year old female with comorbid T2DM and major depressive disorder, completed a 12-week program designed to reverse her glucose dependent, T2DM via metabolic fuel flux facilitated by the endogenous, hepatic production of ketone bodies. She was treated at Bristlecone Medical, Inc., an integrated care clinic located in Maple Grove, Minnesota. The 12-week intervention was delivered at Bristlecone Health, Inc. and included a clinically prescribed ketogenic diet along with patient centered education focusing on nutritional biochemistry and guided HIIT (high intensity interval training) with weekly, 60 min face-to-face health coaching sessions. The 45 min educational sessions encompassed a broad range of applied health science principles including the NMR lipoprofile as it relates to T2D and cholesterol synthesis; protein metabolism (transamination/deamination), carbohydrate and fatty acid metabolism; serotonin uptake deficiencies associated with

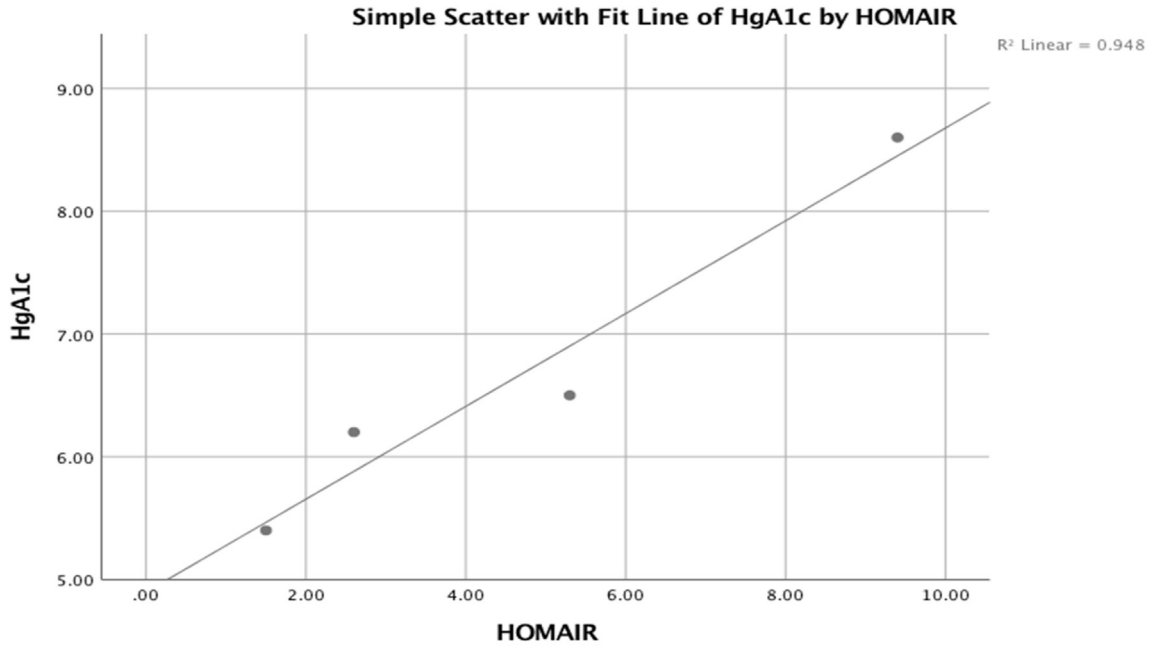

Fig. 1. The patient's HgA1c reduction was positively correlated with the decreased HOMA-IR and reflects statistical significance, adjusted $R^2 = 0.95$, $p = 0.03$.

T2DM and depression; HPA axis regulation; insulin/glucagon negative feedback loop; ketone synthesis/utilization; and Omega-3 cellular signaling pathways; and the therapeutic benefits of intermittent fasting. The bio-individualized nutritional protocol included a clinically prescribed low carbohydrate/high fat ketogenic diet with a time restricted feeding window [9]. The protocol was administered and supervised by licensed mental health and medical professionals for 12 consecutive weeks. The patient's daily macronutrient ratios were based on her metabolic rate/daily calorie expenditure, body fat mass/lean mass ratio, level of insulin resistance as measured by the HOMA-IR: 65% fat, 25% protein, and 10% carbohydrate. Pertinent biomarkers for metabolic flexibility included blood glucose and blood ketones using the Precision Xtra Meter (0.5–2.0 mmol/L goal range for blood ketones), the NMR lipoprofile, fasting blood lipid panel, HgA1c, fasting insulin and the following risk ratio assessments: HOMA-IR, triglyceride/HDL ratio and WHtR (waist-to-height ratio as proxy for visceral fat). The Patient Health Questionnaire 9 (PHQ-9), General Self Efficacy scale (GSE) and MetS Compliance Questionnaire (MSC) were administered pre/post intervention to assess the influence of the clinical protocol on both physiological and behavioral outcomes.

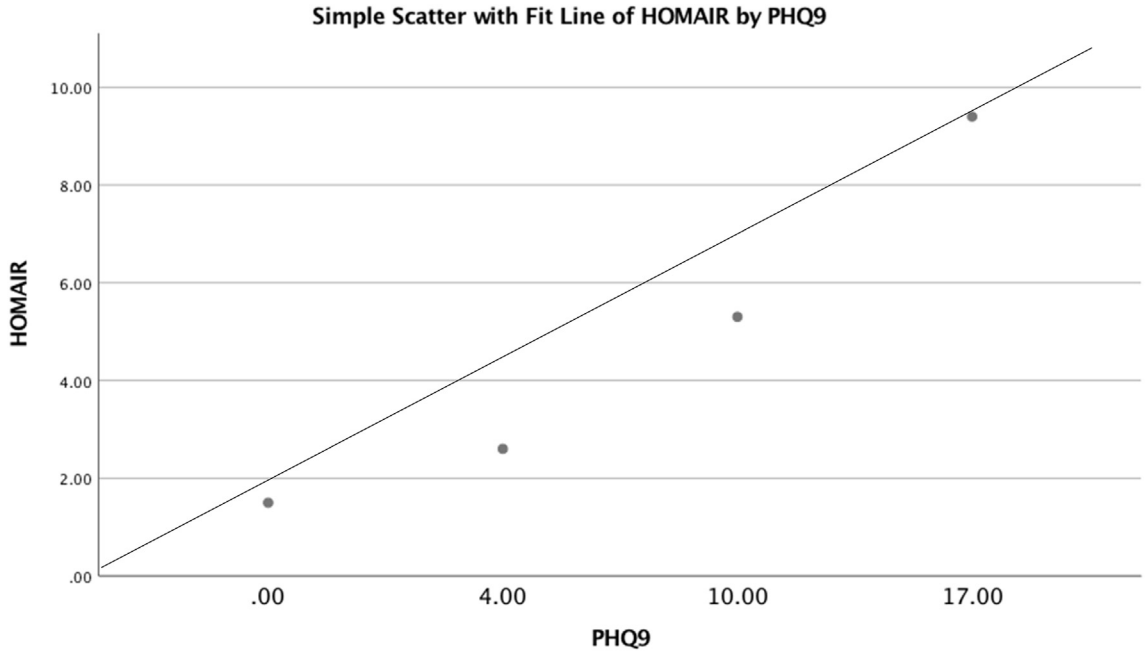

Fig. 2. The patient's HOMA-IR reduction was positively correlated with the PHQ-9 depression inventory score and reflects statistical significance, adjusted $R^2 = 0.97$, $p = 0.01$.

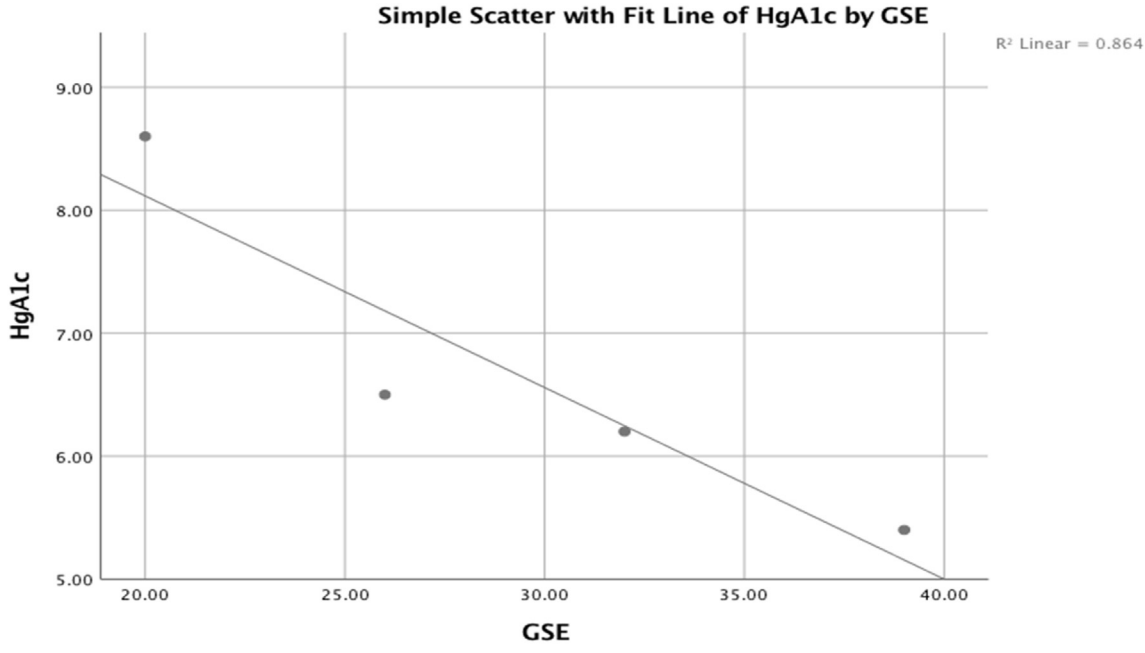

Fig. 3. The patient's HgA1c reduction was positively correlated with the increased general self-efficacy (GSE) and reflects statistical significance, adjusted $R^2 = 0.96$, $p = 0.02$.

3. Results

Upon completion of the 12-week intervention, statistically significant results were achieved in both physiological and psychological domains. The HgA1C, the Gold Standard for blood glucose control, decreased from the diabetic range of 8.0% to the normal range of 5.4%, reversing the patient's 26-year history of T2DM. Her estimated average glucose decreased from 216 mg/dL to 96 mg/dL by week 12 and her blood ketones averaged 1.5 mmol/L. The HOMA-IR (the Gold Standard to assess tissue insulin resistance) improved by 75% (9.4 pre-intervention: 2.3 post intervention); the triglyceride/HDL cardiac risk ratio improved by 75% (4.7 pre-intervention; 1.2 post intervention). Psychological domains also yielded significant change. The Patient Health Questionnaire 9 (PHQ-9) score was substantially decreased from 17 (moderately severe depression) to 0 (minimal depression). The General Self-Efficacy Scale (GSE) also improved from 20 to 39, reflecting increased confidence in the patient's self-management of diabetes. Finally, the MetS Compliance Questionnaire (MSC) improved from 7 to 24 indicating increased levels of compliance with diabetes management. At the conclusion of the 12-week intervention, the patient's physician decreased her overall medications by 75%. The patient self-reported a heightened self-confidence, increased self-efficacy, increased energy, improved sleep and stability in her

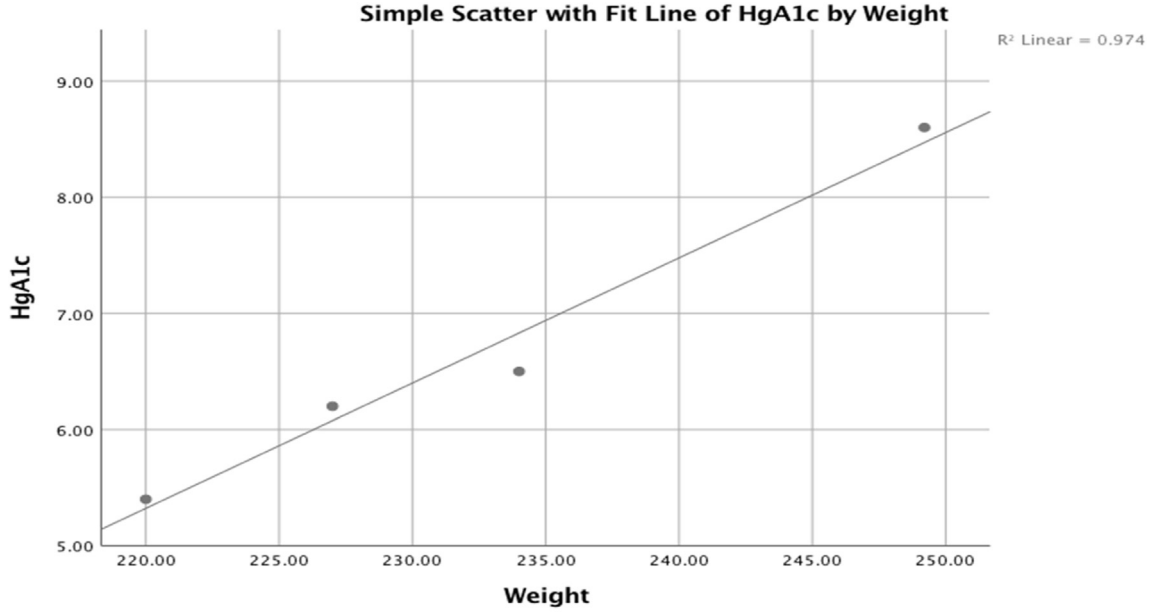

Fig. 4. The patient's HgA1c reduction was positively correlated with the decreased weight and reflects statistical significance, adjusted $R^2 = 0.97$, $p = 0.01$.

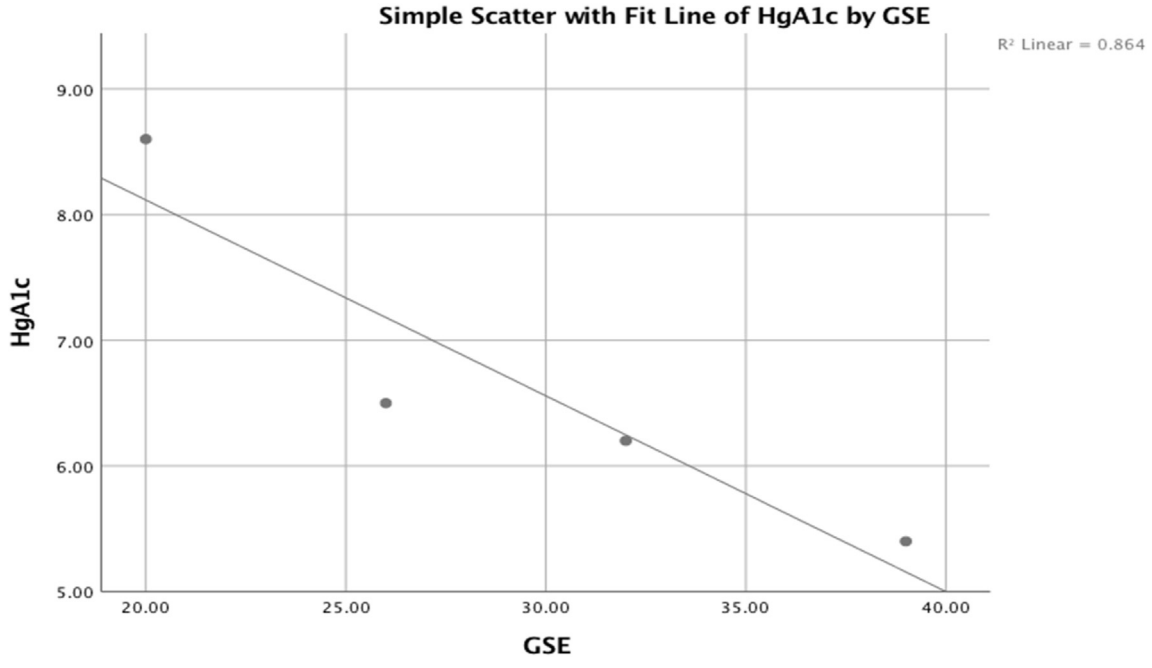

Fig. 5. The patient's HgA1c reduction was positively correlated with increased general self-efficacy and reflects statistical significance, adjusted $R^2 = 0.97$, $p = 0.01$.

mood with clearer cognition.

Significant correlations were observed between reduced HgA1c and HOMA-IR, depressive symptoms, generalized self-efficacy and weight via regression analyses. See Table 1 below.

Linear correlation between HgA1c, HOMA-IR, GSE, PHQ-9 and weight are reflected in Figs. 1–5 below.

4. Discussion

This study reveals a strong correlation between a clinically prescribed ketogenic diet aimed at endogenous, hepatic ketone production, improved symptoms of clinical depression (based on the PHQ-9), and increased self-efficacy associated with compliance to the protocol of diabetes care measured by the General Self-Efficacy Scale (GSE) and MetS Compliance Questionnaire (MSC). The statistically significant results suggest that the 12-week intervention had a substantial impact on reversing Type II diabetes, ameliorating clinical depression, and improving compliance to medical protocol via increased self-efficacy. Research strongly supports the thoughtful integration of clinically prescribed lifestyle interventions, such as a clinically prescribed ketogenic diet, to reverse Type II diabetes and ameliorate treatment resistant clinical depression, while sustaining physiological and psychological improvements [1,5,7,11,12,13,14,15,18,19].

Statement of ethics

This study was approved by an ethics committee. All the participants gave their written informed consent before taking part of the study.

Conflicts of interest

The authors declare that there is no conflict of interest.

Disclosure statement

Sources of support (funding): No funding was required.

Author contributions

All persons who meet the 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 and APOE4 has not yet been widely studied as other aspects of AD physiology, there have been several recent publications describing the clinical aspects of a ketogenic diet and ketone supplementation. These relevant citations are appropriately cited.
- Interpretation: Our findings led to an integrated hypothesis describing the role of a ketogenic diet and insulin levels, MetS biomarkers, and memory function. The hypothesis is consistent with 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 neuroprotective properties of MCT (ketone) oils and their defense against MCI and AD. (b) universal routine insulin level screenings to identify cerebral hypometabolism before the detrimental neurodegenerative cascade begins.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.dsx.2019.01.055.

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