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Induced and controlled dietary ketosis as a regulator of obesity and metabolic syndrome pathologies

Madeline K. Gibas, Kelly J. Gibas*

Bethel University, MN, United States

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ABSTRACT

A worsening epidemic of diabetes and its precursor, metabolic syndrome (MetS) is engulfing America. A healthy individual, with proper glucose regulation has an ability to switch between burning fat and carbohydrates. It has been suggested that signaling errors within this homeostatic system, characterized by impaired switching of substrate oxidation from glucose to fat in response to insulin, can contribute to the etiology of metabolic syndrome and occurs before the development of type II diabetes.

Glucose regulation with restored insulin sensitivity facilitated through clinically regulated, benign dietary ketosis (BDK), may significantly reduce, regulate and reverse the adverse pathologies common to MetS and obesity. The study assessed if prolonged maintenance of induced and controlled physiological, dietary ketosis, would reverse pathological processes induced by MetS including a reduction in fasting triglycerides, BMI (body mass index) and body fat mass (BFM), weight, a significant decrease and/or normalization of hemoglobin A1c (HgA1c) and an increase in resting metabolic rate (RMR) and blood ketones. A group of 30 adults, previously diagnosed with MetS by their primary care physician, were randomly prescribed to one of three groups: a sustained ketogenic diet with no exercise, standard American diet (SAD) with no exercise or SAD with 3–5 days per week of exercise (30 min.). The results demonstrated that the change over time from week 0 to week 10 was significant ($p=0.001$) in the ketogenic group for weight, body fat percentage, BMI, HgA1c and ketones. All variables for the ketogenic group out-performed those of the exercise and non-exercise groups, with five of the seven demonstrating statistical significance.

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1. Introduction

Metabolic syndrome and the etiology of deranged metabolic pathways dramatically increase the risk factors for obesity, pre-diabetes, diabetes and numerous degenerative diseases [1]. The annual cost of pharmaceutical treatment for this cluster of metabolic pathology is US \$750 billion [2]. Very low carbohydrate diets, or ketogenic diets, have been used since the 1920s as a therapy for epilepsy; ketosis can completely remove the need for epileptic medications by modulating the central nervous system (CNS). In addition, since the 1960s, ketogenic diets have become widely known as one of the most effective methods of obesity treatment and weight management. Ketogenic diets are characterized by a reduction in carbohydrates (usually less than 50 g/day) with a relative increase in the physiological proportion of dietary

fat with adequate protein to feed individual lean body mass. Ketosis is an alternative energy state when glucose availability is low; the production of ketones by the liver is a natural process during a fasting state and /or prolonged exercise. Recent research provides substantial evidence for the therapeutic potential of ketogenic diets in numerous chronic pathological conditions such as diabetes, polycystic ovary syndrome (PCOS), neurological degeneration, cancer as well as marked improvement of respiratory and cardiovascular disease risk factors [3].

Several landmark studies on MetS report significant weight and fat mass loss in type II diabetic (T2D) who were given a controlled, ketogenic diet. In the 2006 Dashti et al. study, obese individuals with MetS and/or T2D were prescribed a controlled ketosis diet for 56 weeks; significant improvements in both weight/fat loss and metabolic parameters were evidenced at 10 weeks and continued throughout the entire 56 weeks as evidenced by vast improvements in fasting levels of glucose/HgA1c (–51%) and lipid markers (most specifically) triglycerides (–41%). In addition, Dashti et al. [4] reported the withdrawal of insulin and other anti-glycemic medications, which occurred prior to the significant weight and fat mass loss,

* Corresponding author.

E-mail addresses: info@bristlecconefitness.com (M.K. Gibas), kelly-gibas@bethel.edu (K.J. Gibas).

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supporting the role of restorative endocrine signaling with a ketogenic energy state. “Moreover, in isocaloric experiments, individuals showed dramatic improvements in markers of metabolic syndrome more than with [other] diets lower in fat” [2], p. 5).

Recently, Feinman et al., conducted a 2015 critical review of several studies comparing carbohydrate restriction to traditional low-fat diets as a first line of treatment for diabetes. The researchers posit, “The inability of current recommendations to control the epidemic of diabetes, the specific failure of the prevailing low-fat diets to improve obesity, cardiovascular risk, or general health and the persistent reports of some serious side effects of commonly prescribed diabetic medications, in combination with the continued success of low-carbohydrate diets in the treatment of diabetes and metabolic syndrome without significant side effects, point to the need for a reappraisal of dietary guidelines” [5], p. 2). Twelve points of clinical evidence derived from 26 researchers concluded: (1) carbohydrate restriction has the greatest impact on decreasing blood glucose values, (2) the benefits of carbohydrate restriction do not require weight loss, (3) total dietary and saturated fat do not correlate with risk for cardiovascular disease, and (4) dietary carbohydrate restriction is the most effective method of reducing serum triglycerides and increasing HDL [5]. The researchers postulate that the benefits of carbohydrate-restriction are immediate and well documented. The traditional concerns about safety and efficacy of low carbohydrate diets are conjectural rather than data driven, according to Feinman et al. (2015) [5].

Scientific studies continue to demonstrate the effectiveness of a low carbohydrate diet to combat the adverse metabolic pathologies of obesity, T2D and metabolic syndrome. The study was purposed at investigating how a ketogenic diet can modulate and/or reverse five primary biomarkers for MetS which include elevated triglycerides, BFM, and HgA1c as well as decreased RMR. In addition, blood ketones were assessed to measure the steady state of ketosis in the experimental group. The study also explored any significant differences between patients' biomarkers who were prescribed a 10 week ketogenic diet and patients placed on a 10 week exercise program with an SAD. The possibility of modulating dietary fuel substrates and reversing pathological diagnoses to eliminate pharmaceutical modalities of treatment, for impaired glucose tolerance are usually pervasive with chronic,

detrimental side effects, as evidenced by normative degeneration, warrants serious investigation. If corrective nutritional interventions can be shown to reduce the reliance on pharmaceutical treatments, while improving health biomarkers and disease prevention outcomes, these results will yield significant benefits both economically and socially as well as create a clinical protocol for standard of care. Based on the robust outcome measures outlined in Figure 1, the clinical utility of a standard of care protocol warrants further consideration (Fig. 1).

2. Participants

Research participants were patients who exercised regularly and were previously diagnosed with MetS, pre-diabetes or T2D. Subjects had a BMI ≥ 25 and/or WC (waist circumference) >37 (male), >31.5 (female), body fat percentage $> 30\%$ (men/women). All subjects were between the ages of 18 and 65. Each participant elected to self-register for a 10-week study and was randomly assigned to either an experimental group using a benign dietary ketogenic protocol ($<30\text{g}$ CHO/day), a control group using the SAD with no exercise or a control group using the SAD with 120–150 minutes per week of exercise. Physiological ketosis is defined as blood ketone levels of 0.5–2.0 mmol/L. This is in contrast to diabetic ketoacidosis, a concern for type I diabetics, where blood ketone levels are > 10 mmol/L. Participants were referred by their primary care practitioners and were sequentially assigned to three groups in the order of the referral. For example, the first patient was assigned to the experimental ketogenic group in the order of referral. The second patient was assigned to the control SAD group with no exercise. The third patient was assigned to the control SAD group with 3–5 days of exercise per week (30 min.).

3. Procedure

Within the three protocols, patients met in small groups modeled after the Cleveland Clinic's Shared Medical Appointment (SMA) format, to facilitate a horizontal delivery of care. Medical direction was provided by Kelly Kruschke FNP, DNP and clinical facilitation occurred at Bristlecone Health, Inc. by Kelly J. Gibas MA, LPCC, DBH (May 2017), Julie A. Gomer MA, LPCC, DBH (May 2017) and Madeline K. Gibas. Baseline triglycerides, HgA1c, BMI, RMR,

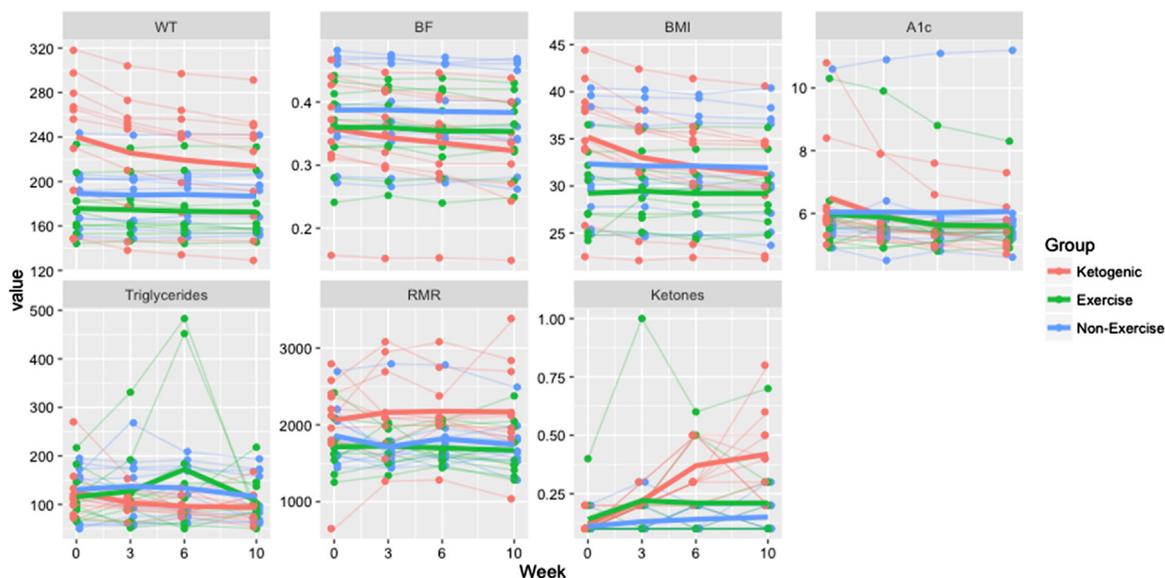


Fig. 1. Illustrates data for all individuals, and groups. Individual data is represented by thin lines; group averages are demonstrated by thick lines. The ketogenic group reflects greater reductions than the exercise and non-exercise groups in weight, BFM, BMI, HgA1c, triglycerides and greater increases in the RMR and ketones, as predicted.

blood ketone levels and BFM measurements were assessed for all three groups at week 0 and week 3, 6 and 10. Physiological ketosis is defined as blood ketone levels between 0.5–2.0 mmol/L. Blood ketones were measured using Smith Abbott Labs' Precision Xtra glucose/ketone monitor system. The portable meter is CLIA waived and has met the United Nations' multi-sector standard for efficiency and accuracy (UNSPSC: 41116201, 41116106). The measurement of baseline triglycerides was conducted using the *CardioChek P-A System and PTS Panels Test Strips*, which are manufactured by Polymer Technology Systems, Inc. The *CardioChek P-A* is a portable, Point-of-Care whole blood analyzer utilizing reflectance photometry. The hand-held device is used with PTS Panels Test Strips – disposable, single-use test strips formulated to analyze specific blood chemistries including triglycerides, total cholesterol, HDL and LDL [23]. Hemoglobin A1c (HgA1c) measurements were also taken for participants using the *A1cNow SELF-CHECK* by Bayer Laboratories [12]; HgA1c measurements evaluate the average blood sugar levels over the previous 3 month period. Body mass index (BMI) and body fat percentage were both calculated using a handheld Omron body composition analyzer, that utilizes weight, height, age and sex to compute precise measurements [22]. Finally, resting metabolic rate (RMR) was assessed using the *Metacheck* by Korr Medical an instrument designed to use indirect calorimetry (a measurement of heat exchange) to calculate metabolic rate from the measured amount of oxygen consumed by the body [20].

4. Data analysis

To test for a difference between the three groups at week 0 and week 10, an Analysis of Variance (ANOVA) for each variable was calculated at each time point separately, followed by tests of the pairwise differences using Tukey's HSD correction. To test for differences over time, a similar ANOVA was utilized to demonstrate the difference between week 0 and week 10, and reported both individual tests for a non-zero difference for each group. Tests of the pairwise differences were analyzed using Tukey's HSD correction, a post hoc test that is used to analyze statistically significant differences that may have occurred within the data set.

Additionally, to analyze all the time points, a longitudinal mixed model for each variable was constructed with treatment, week and their interaction as predictors. A random intercept and slope were calculated for each individual; the average slope was reported for each group. All results were reported using 95% confidence intervals; a significance level of 0.05 was considered statistically significant. When the assumption of normality was in question, pairwise Wilcoxon tests with the Bonferroni-Holm correction were also performed. All computing was performed in R version 3.3.1 (2016-06-21). Fig. 2 demonstrates the robust rate of change among the experimental ketogenic and control SAD groups.

5. Results

Statistical evaluation of the data focused primarily on the differences across the primary biomarkers including triglycerides, BMI, BFM, HgA1c and RMR as well as blood ketones from week 0 to week 10. A one-way ANOVA using Tukey's HSD comparison was utilized to find the pairwise comparison differences between the variables in each of the groups. All of the results reflect 95% confidence intervals and a significance level of 0.05 were considered statistically significant. The average slope for each group, representative of the change for each variable per time period, was also reported after week ten.

The results demonstrate that the change over time was significant ($p=0.001$) in the experimental ketogenic group for weight, body fat percentage, BMI, HgA1c and ketones. Moreover, the change in triglycerides for the experimental ketogenic group is clinically relevant as the magnitude of the slope is twice that of the control SAD exercise group and three times that of the control SAD non-exercise group; this reflects a large degree of change for the ketogenic group data for this biomarkers, despite a larger p-value. Likewise, the resting metabolic rate in the experimental ketogenic group also produced sizable change in the magnitude of the slope, more than ten times the other two control SAD groups. All variables for the experimental ketogenic group out-performed those of the exercise and non-exercise control groups, with five of the seven demonstrating statistical significance. Based on the results produced by the statistical data, the null hypotheses that a

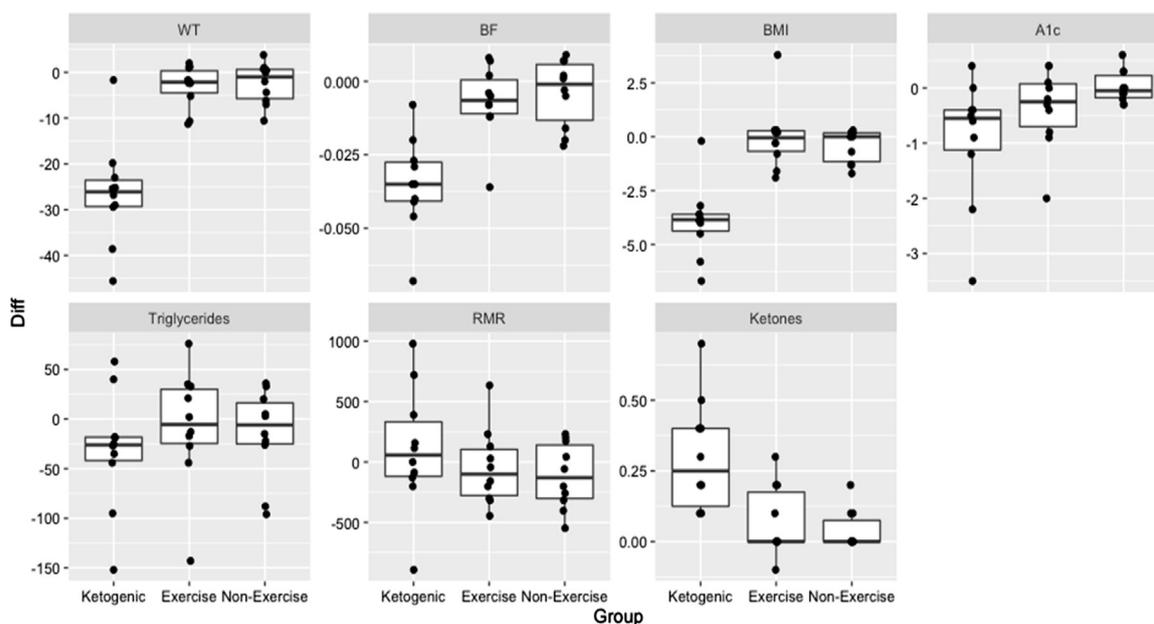


Fig. 2. Box plots in Fig. 2 demonstrate a significant degree of change in weight, BFM, BMI, HgA1c, triglycerides, RMR and ketones after ten weeks. As predicted, the weight, BFM, BMI, HgA1c and triglycerides in the experimental ketogenic group decreased significantly more than the control SAD exercise and non-exercise groups. The RMR and ketones in the experimental ketogenic group increased significantly more than the control groups, as predicted.

ketogenic diet has no effect on the five principle biomarkers of metabolic syndrome can be rejected.

Perhaps the most compelling data can be found below in Table 1. The difference over time, using all time points reveal statistical significance in the ketogenic group with p-values well below 0.05 for weight, body fat, BMI, HgA1c and ketones ($p=0.001$). The magnitude of the slope for every variable in the experimental ketogenic group far exceeds the magnitude of the slope in the control SAD exercise and non-exercise groups.

6. Discussion

The null hypothesis infers that nutritional ketosis, as compared to the standard America diet (SAD) or SAD with regular exercise, has no significant impact on the five principle biomarkers of MetS. An analysis of the differences in data between week 0 and week 10, within the ketogenic group participants, is sufficient to reject the null hypothesis. All variables for the experimental group showed greater degree of positive change at the end of the study compared to the SAD and SAD with exercise groups; furthermore, within the nutritional ketosis group, five of the seven MetS outcome variables showed a statistically significant difference between data points from week 0 and week 10.

The observed reductions in HgA1c, body fat mass, weight, BMI and increase in resting metabolic rate, have clinical relevance for the treatment and prevention of impaired homeostatic glucose regulation and resultant degenerative disease states [1]. Research supports that mitochondrial mass, structure and function, are altered in MetS leading to impairments in cellular respiration/ATP production, and beta-oxidation occurring within the mitochondrial TCA cycle and Electron Transport Chain. However, it has been postulated that these metabolic impairments are initiated by an underlying mitochondrial disorder rather than consequential to peripheral metabolic inflexibility caused by impaired homeostatic glucose control. The findings of this study show that through the induction of nutritional ketosis (<50g CHO), MetS can be successfully treated and many of the pathologies reversed through the restoration of beta oxidation. The study demonstrates that an increased ability to oxidize fat through modulation/regulation of insulin secretion is foundational to mediating the pandemic public health crisis of MetS, pre-diabetes and T2D [6]. Proper metabolic flexibility, evidenced by shifts in fuel substrate oxidation between

glucose and fatty acids, can be achieved through a sustained, nutritional ketosis protocol. Once the tissues become fat adapted, utilizing fatty acids and ketone bodies as primary fuel sources, profound health benefits naturally emerge in coordination with restored cellular signaling; the most prominent homeostatic restoration occurs with insulin signaling. In conjunction with flexibility of fatty acid oxidation, insulin levels normalize resulting in increased tissue/receptor sensitivity. In addition, the homeostatic negative feedback loop regulating blood glucose gains receptivity to pancreatic signals of insulin and glucagon resulting in significant drops in HgA1c, body fat mass, weight, triglycerides and BMI [6,13,15,25].

Neither control group, SAD or SAD with regular exercise, showed significant differences in their biomarker data between week 0 and week 10. While ample evidence supports the cardiovascular benefits of regular exercise, the results of the study show a sustained ketogenic protocol out-performed regular exercise in the modulation of metabolic pathologies over the course of a ten-week period [7]. Recent studies support these conclusions showing the improvement of MetS biomarkers accompany a ketogenic diet compared to a SAD. In a 2016 study, Hall et al. postulated that chronic consumption of a high-carbohydrate diet sequesters triglycerides within adipose tissues due to hyperinsulinemia, chronically elevated serum insulin levels, which leads to a suppression of energy expenditure (EE) via tissue insulin resistance (down-regulation of insulin receptors). Energy expenditure is defined as the total calories of dietary fuel substrate partitioned for ATP production within the mitochondria. Researchers hypothesized that an isocaloric exchange (retaining similar caloric values) of CHO for dietary fat would increase EE and the rate of fat oxidation resulting in a loss of body fat mass consequential of reduced insulin secretion. Hall et al. measured energy expenditure (EE), respiratory quotient (RQ) and sleeping energy expenditure (SEE) in overweight or obese men for eight weeks. Respiratory quotient assessed substrate utilization of the tissue by measuring carbon dioxide expired compared to oxygen consumed; pure fat oxidation is .7 (fat yields less expired CO₂), while pure glucose respiration is 1.0 (equal amounts of CO₂ and O₂). The RQ was an outcome variable for metabolic flexibility in the tissue. During the first four weeks, the men consumed a high-carbohydrate diet followed by a four-week, isocaloric ketogenic diet [7]. The results of the Hall et al. study demonstrate that ketosis, compared to a CHO

Table 1
Demonstrates the difference over time for the data using a longitudinal mixed model. The average change per day is reflected for each group. Statistical significance is measured by p-value < 0.05.

Variable	term	Estimate	conf.low	conf.high	p.value
WT	GroupKetogenic:Week	-2.547352	-3.0091939	-2.0855093	0.00000000
WT	GroupExercise:Week	-0.322329	-0.7841711	0.1395136	0.18262220
WT	GroupNon-Exercise:Week	-0.208311	-0.6701528	0.2535318	0.38448610
BF	GroupKetogenic:Week	-0.003411	-0.0042467	-0.0025761	0.00000000
BF	GroupExercise:Week	-0.000763	-0.0015983	0.0000723	0.08462000
BF	GroupNon-Exercise:Week	-0.000446	-0.001281	0.0003896	0.30496950
BMI	GroupKetogenic:Week	-0.378037	-0.4599824	-0.2960907	0.00000000
BMI	GroupExercise:Week	-0.009087	-0.0910326	0.0728591	0.82958110
BMI	GroupNon-Exercise:Week	-0.038402	-0.1203477	0.043544	0.36649670
A1c	GroupKetogenic:Week	-0.090411	-0.1380733	-0.0427486	0.00092900
A1c	GroupExercise:Week	-0.040365	-0.0880276	0.007297	0.10850740
A1c	GroupNon-Exercise:Week	0.0014612	-0.0462011	0.0491235	0.95252910
Triglycerides	GroupKetogenic:Week	-2.990868	-7.4277288	1.4459936	0.19056380
Triglycerides	GroupExercise:Week	0.1799087	-4.2569525	4.6167699	0.93687340
Triglycerides	GroupNon-Exercise:Week	-1.574429	-6.0112904	2.862432	0.48895390
RMR	GroupKetogenic:Week	9.4552511	-12.3795806	31.2900828	0.40349200
RMR	GroupExercise:Week	-4.926027	-26.7608591	16.9088043	0.66188370
RMR	GroupNon-Exercise:Week	-7.241553	-29.0763842	14.5932792	0.52116900
Ketones	GroupKetogenic:Week	0.0312785	0.0227464	0.0398107	0.00000000
Ketones	GroupExercise:Week	0.0057534	-0.0027787	0.0142856	0.19248880
Ketones	GroupNon-Exercise:Week	0.0038813	-0.0046509	0.0124134	0.37701830

protocol, significantly increased EE, increased SEE and decreased RQ pointing to a substrate shift to beta oxidation. Hall et al.'s conclusions support strong clinical correlates between restored insulin signaling and a ketogenic protocol evidenced by homeostatic partitioning of fuel toward energy production (ATP) rather than adipose storage (triglycerides).

Furthermore, dietary CHO restriction with co-occurring lipolysis also demonstrates significant metabolic advantages for individuals with nonalcoholic fatty liver disease (NAFLD). Excess intrahepatic triglycerides are formed in response to hyperglycemia, with increased potentiation from dietary fructose. Increased hepatic synthesis of fat from carbohydrates occurs during lipogenesis induced by chronically elevated insulin. Browning et al. [8] studied NAFLD subjects who consumed a CHO restricted (<20 g/day) or calorie restricted (1200–1500 kcal/day) diet for two weeks. Hepatic triglycerides were measured before and after the intervention. The results of the CHO restricted group were significant; post-treatment plasma ketones ($r = -.755$, $p = .006$) and RQ ($r = -.797$, $p < .001$) were significantly related to a reduction in hepatic triglycerides showing a hepatic substrate shift. Two weeks after the intervention, the results revealed a sustained, 42% reduction in hepatic triglycerides in the subjects with NAFLD who were treated with a CHO restricted diet. Likewise, these results support the suggestion that reductions in dietary CHO have the metabolic potential to naturally reset, or restore, homeostatic insulin signaling within the liver, thus regulating hepatic triglyceride synthesis [8].

The results of a subsequent, 2015, study by Hall et al. [9], also supports the conclusions regarding the ability of beta-oxidation to restore homeostatic glucose regulation and cell signaling. Obese subjects were confined to a metabolic ward for 2–two-week periods, while receiving a selective isocaloric reduction in either dietary fat or dietary CHO. Subjects receiving the reduced CHO diet, as compared to those on reduced fat, showed a substantial decrease in RQ, a significant increase in fat oxidation and low net CHO oxidation. These

findings support the aforementioned suggestions that chronic and persistent hyperinsulinemia from a high CHO diet results in pervasive and systemic metabolic inflexibility with impaired cell signaling, which leads to metabolic pathologies of visceral fat storage, intra-muscle fat accumulation (IMTG) and impaired glucose tolerance. Again, a low CHO dietary intervention demonstrated the robust ability to flux tissue substrates from glucose to beta-oxidation as evidenced by the significant decrease in RQ, increase in fat oxidation and reduced dependency on CHO oxidation as seen in Fig. 3 [9]. Fig. 3 below reflects the results of two dietary interventions on identified biomarkers as indicated by reduced carbohydrates (RC) and reduced fat (RF).

Accurso et al. [10] did a similar comparison on the effects of a CHO restricted diet and dietary fat restriction. Likewise, the research demonstrated that CHO restriction improved glycemic control and normalized insulin fluctuations. Furthermore, carbohydrate restricted diets proved as effective for weight loss as low-fat diets; the beneficial effects of CHO restriction were shown to be independent of weight loss and inclusive of normalizing hormone pathways. Accurso et al. reiterate the suggestion that CHO restriction improves all features of MetS pathology [10].

With T2D and its precursor MetS rising at alarming levels in the US and abroad, there is an urgent need for alternative forms of care to reduce/eliminate the early biomarkers of risk, such as HgA1c, BMI and body fat mass. Physiological ketosis has clinical utility for prevention, reduction and reversal of metabolic disturbances and its progression into obesity, pre-diabetes and diabetes (T2D); therefore nutritional ketosis is a noteworthy modality of preventative and restorative care. The results provide ample evidence to support the hypothesis that benign dietary ketosis leads to measureable improvements in metabolic pathways, homeostatic glucose regulation and restored cell signaling with significant health benefits including sustainable reductions in HgA1c, body fat mass, intramuscular lipid accumulation with significant increases in measures of systemic, metabolic flexibility (RQ, SEE and EE).

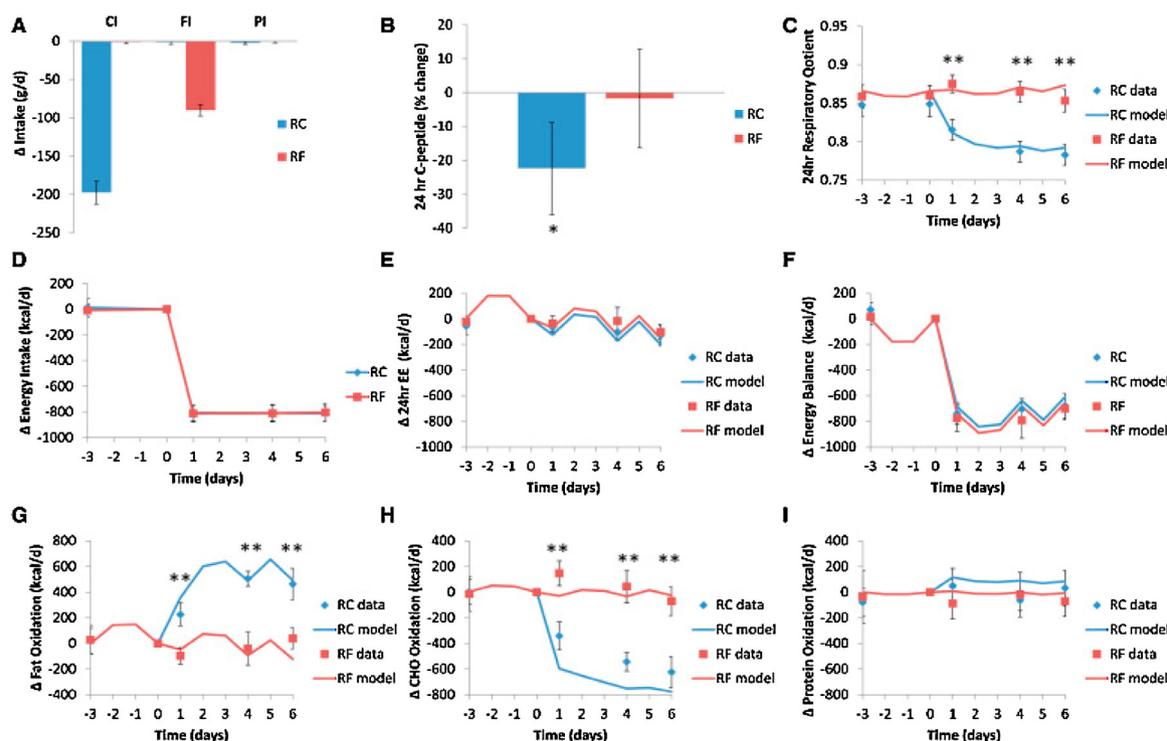


Fig. 3. Changes in daily diet, insulin secretion, and energy metabolism [9].

Endless opportunities exist for further research into MetS pathologies and possible ketogenic treatment modalities. Future research should aim to expound on the findings of this study in regard to the unique properties of beta-oxidation and ketogenic energy production to restore impaired cell signaling and homeostatic glucose pathways. Likewise, testing ketogenic dietary interventions with a larger sample size would prove advantageous. With increasing evidence to support the robust health benefits from a ketogenic dietary intervention, it is imperative that research is focused toward finding a standard of care for the safe and reliable implementation of benign dietary ketosis into clinical practice.

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