Compliance with an intense dietary intervention and glycemic control in type 2 diabetes

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Abstract

Type 2 diabetes mellitus is considered to be one of the primary causes of premature illness and death in most countries, making the projected increase in prevalence a significant public health concern. A strong association between adiposity, diet, and both insulin resistance and beta-cell dysfunction has long been recognized. A randomized, controlled dietary intervention trial was conducted to test the effects of gastric bypass surgery versus an intense dietary lifestyle intervention on T2DM status. The primary aim of the study was to evaluate the relationship between compliance to the dietary intervention and glycemic control, assessed by hemoglobin A1c, at six months after the start of the intervention. We hypothesized that a higher compliance summary score will be associated with improved glycemic control among individuals in the lifestyle arm, compared to those with lower compliance summary scores. Our secondary aim was to evaluate the relationship between each of the 5 measures of diet quality in the summary score (energy density, percentage of calories from protein, percentage of calories from added sugars, sugar-sweetened beverage intake, and fiber intake) and measures of glycemic control and of adiposity. We hypothesized that better measures of diet quality will each be associated with improved markers of glycemic control. Our study's key findings did not support this hypothesis, as we did not find any significant associations between summary compliance score and HbA1c or other markers of glycemic control, suggesting that stricter compliance to this particular dietary intervention did not lead to lower HbA1c levels at 6 months. Our study's secondary findings were also surprising and largely unsupportive of our hypothesis, raising interesting questions regarding our dietary intervention and future studies.

Background and Significance

Diabetes and Obesity

Obesity is one of the most transparently discernable, yet unresolved, global epidemics, with prevalence doubling since 1980 (King, 2013). More than 1 billion adults are overweight worldwide, and over 300 million of them are obese (Smyth & Heron, 2006). Unfortunately, this trend is predicted to only increase in the foreseeable future (Smyth & Heron, 2006). The World Health Organization attributes the obesity epidemic primarily to sedentary lifestyles, energy-dense diets, and increased urbanization (Smyth & Heron, 2006). It is a complex condition that is associated with numerous complications, including significantly increased risks of cancer, cardiovascular disease, arthritis, gastrointestinal diseases, and, importantly, diabetes (Smyth & Heron, 2006). Excess adiposity and obesity are the primary modifiable risk factors for type 2 diabetes mellitus (T2DM), as 80% of people are overweight when they are diagnosed with T2DM (Smyth & Heron, 2006).

The alarmingly increasing rate of obesity is matched by that of T2DM, with the prevalence of diabetes increasing from 30 million people worldwide in 1985 to an anticipated 366 million by 2030 (Smyth & Heron, 2006). This growth is driven by the rapid increasing rates of T2DM, while type 1 diabetes mellitus rates remain relatively stable (Smyth & Heron, 2006). The World Health Organization attributes this growth primarily to increasing obesity rates, unhealthy diets, and increasingly sedentary lifestyles (Smyth & Heron, 2006). Diabetes is considered to be one of the primary causes of premature illness and death in most countries, making the projected increase in prevalence a significant public health concern (Smyth & Heron, 2006).

The costs of rapidly increasing obesity and diabetes rates are not isolated to health, but have economic consequences as well, as both currently place considerable demands on already stressed healthcare systems (Smyth & Heron, 2006). This is only projected to worsen (Smyth & Heron, 2006). Total costs of diabetes are expected to reach $192 billion in 2020 (Smyth & Heron, 2006). T2DM and its complications are not just costly to systems, but are expensive for individuals to manage as well (Smyth & Heron, 2006). Diabetic individuals are three times more likely to require hospitalization for complications due to T2DM, including kidney failure, heart disease, limb amputation, and blindness (Smyth & Heron, 2006).

The Pathophysiology of T2DM

T2DM is a heterogeneous syndrome illustrated by abnormalities in carbohydrate and fat metabolism (Scheen, 2004). Both reduced insulin sensitivity and beta cell dysfunction play important roles in the pathophysiology of T2DM (Scheen, 2004). Individuals with T2DM have the ability to produce insulin, but their tissues are insulin resistant (Nelms, 2011). Consequently, two effects are seen in individuals with T2DM: insulin resistance and relative insulin deficiency, also referred to as beta-cell dysfunction (Nelms, 2011). In insulin resistance, the body's cells have a diminished ability to respond to the action of the insulin hormone being released from the pancreas (Shulman, 1999). This increases the need for insulin, so the beta-cells of the pancreas, if functioning, secrete more insulin to compensate (Shulman, 1999).

A strong association between insulin resistance and adiposity has long been recognized (Paradis & Ruvkun, 1998). Insulin is an essential regulator of many biological

functions of adipocytes (Paradis & Ruvkun, 1998). Adipocytes are also one of the most highly insulin-responsive cell types. Insulin stimulates lipogenesis and inhibits lipolysis, fostering the storage of triglycerides in adipocytes (Paradis & Ruvkun, 1998). Insulin also increases the uptake of fatty acids derived from lipoproteins by stimulating lipoprotein lipase activity in adipose tissue (Paradis & Ruvkun, 1998). Insulin resistance in obesity and T2DM decreases insulin-stimulated glucose uptake into adipocytes by suppressing glucose output by the liver (Rondinone et al., 1997).

An important link between adiposity and insulin resistance is the chronic inflammatory state associated with obesity (Jianping Ye, 2013). This chronic low-grade inflammation is responsible for the development of several chronic diseases, including T2DM (Jianping Ye, 2013). Inflammation is a protective physiological process in which white blood cell count and proinflammatory cytokines increase in circulation and tissues (Jianping Ye, 2013). It is meant to control harmful insults to the body or initiate healing (Jianping Ye, 2013). Current hypotheses suggest that obesity causes several changes that contribute to initiation of chronic systemic inflammation, including endoplasmic reticulum stress, adiponectin reduction, leptin elevation, adipocyte death, lipolysis, and macrophage infiltration (Jianping Ye, 2013). Inflammation related to obesity is thought to begin in adipose and liver tissue, increasing macrophage permeation and expression of proinflammatory cytokines (Jianping Ye & Gimble, 2011). These cytokines enter the bloodstream and cause systemic inflammation (Jianping Ye & Gimble, 2011). The mechanisms of these particular processes are not fully understood (Jianping Ye & Gimble, 2011). Inflammation also increases plasma free fatty acid through stimulating lipolysis (J Ye, 2007). These effects occur only in adipose and liver tissue, not in muscle

(J Ye, 2007). This low-grade inflammation acts as the mediator between diet, obesity, and the development of T2DM (J Ye, 2007).

Beta-cells reside in the pancreas, where they produce and secrete insulin for the body when signaled by an increase in blood glucose levels and incretins (Alberts, 1998). Insulin secretion depends largely on beta-cell function and mass (Maedler & Donath, 2004). It is speculated that chronically elevated glucose levels seen in T2DM are detrimental to beta-cells, causing impaired insulin secretion and deregulating turnover (Maedler & Donath, 2004). The ability of beta-cells to adjust to changing glucose levels depends on their functioning and mass, both lost in T2DM (Maedler & Donath, 2004). Thus, elevated glucose concentrations may induce beta-cell apoptosis (Maedler & Donath, 2004). The mechanisms of this action, however, are not well understood (Maedler & Donath, 2004).

The Role of Diet in the Regulation of Body Weight and Adiposity

Diet plays a crucial role in the regulation of glucose homeostasis by affecting adiposity, insulin sensitivity, low-grade chronic inflammation, and possibly beta-cell function.

Though the more specific mechanisms remain unknown, it is clear that diet plays a vital role in regulating adiposity and the development of obesity. The relationship between diet and adiposity is not as simple as the concept of 'calories in versus calories out,' however. Diet has a mutually influential relationship with many hormones, hedonic influences, stress, and sleep. One example of how diet composition affects adiposity independent of calories is glycemic index. Consuming foods with a high glycemic index

(GI) causes blood glucose levels to spike much more rapidly than low GI foods (Ludwig et al., 1999). This rapid absorption of glucose alters hormonal and metabolic functions, promoting excessive food intake after ingestion of a high GI meal (Ludwig et al., 1999). Studies have found that a high glycemic load diet produces a greater decline in metabolic rate and greater voluntary food intake, promoting adiposity even when both diets are calorically restricted (Agus, Swain, Larson, Eckert, & Ludwig, 2000; Ludwig et al., 1999; Swinburn, Caterson, Seidell, & James, 2004). Thus, foods with a high GI increase adiposity via hormones, independent of calorie consumption (Swinburn et al., 2004).

Adiposity is controlled by negative feedback regulation via the hormones leptin and insulin (Schwartz & Niswender, 2004). Leptin and insulin circulate in proportion to body fat stores and affect brain pathways to promote reduced food intake and weight loss (Schwartz & Niswender, 2004). Therefore, adaptive responses such as increased food intake are hypothesized to be triggered by a lack of leptin and insulin signaling in the brain (Flier, 1998; Leibel, 2002). It is also speculated that the brain cannot respond to high leptin levels, referred to as the concept of leptin resistance (Flier, 1998; Leibel, 2002; Schwartz & Niswender, 2004). When leptin levels drop below a threshold, the brain responds by releasing potent neuroendocrine responses to compensate for perceived insufficiency of fat stores and increase food consumption (Flier, 1998; Leibel, 2002; Schwartz & Niswender, 2004). However, these hypotheses suggest that when leptin levels exceed their threshold in energy excess, the brain is less capable to respond in a similar manner to decrease food consumption, so food intake remains slightly higher than necessary to maintain energy homeostasis, and weight gain ensues (Flier, 1998; Leibel, 2002; Schwartz & Niswender, 2004). In other words, while the body is able to defend

against both weight gain and weight loss, the energy homeostatic defense against weight loss seems to be slightly more robust than the defense against weight gain.

Energy density refers to the amount of energy per unit weight of a food or beverage (for instance, kilocalories per gram) (Pérez-Escamilla et al., 2012). Water in the diet can account for variability in energy density because it provides a notable amount of weight without adding energy (Pérez-Escamilla et al., 2012). Dietary fiber follows similar suit, contributing significant weight but few kilocalories (Pérez-Escamilla et al., 2012). Therefore, foods high in water and/or fiber are commonly lower in energy density. Conversely, foods high in fat are generally high in energy density, as fat provides the greatest amount of energy per gram (Pérez-Escamilla et al., 2012). The 2010 Dietary Guidelines Advisory Committee reviewed strong and consistent evidence from both intervention trials and prospective cohort studies indicating that dietary patterns relatively low in energy density improve weight loss and weight maintenance in both adults and children (Pérez-Escamilla et al., 2012). Many of these studies have thus concluded that dietary patterns relatively high in energy density lead to weight gain and adiposity (Pérez-Escamilla et al., 2012). Among adults, short-term feeding studies have shown that serving lower-energy density foods leads to decreased energy intake and increased satiety (Bell, Castellanos, Pelkman, Thorwart, & Rolls, 1998; Rolls, Roe, & Meengs, 2006). Although the mechanisms for the relationship between energy density and weight have not been widely studied, it has been hypothesized that lowering energy density can enhance satiety and contribute to reductions in energy intake (Himaya & Louis-Sylvestre, 1998). Research has shown that people tend to consume a fairly consistent weight of food at a meal and over the course of a few days; consequently, it has been suggested that

eating foods lower in energy density instead of foods higher in energy density may decrease overall energy intake (Rolls, Roe, & Meengs, 2004).

The consumption of sugar-sweetened beverages (SSBs), including soda and fruit juices, has drastically increased in the past few decades, and has paralleled the increasing prevalence of both overweight and obesity in the United States (Nielsen & Popkin, 2004). Consumption of these beverages, particularly carbonated soft drinks, has been consistently supported by evidence to be a key contributor to adiposity, due to their high added sugar content, little nutritional benefit, low satiety, and incomplete compensation for total energy (Malik, Schulze, & Hu, 2006). Findings from several large cross-sectional investigations, well-powered prospective cohort studies with long follow-up and repeated measures of diet and weight, short-term feeding trials, school-based interventions targeting soda consumption, and randomized controlled trials assessing the effect of reducing sweetened beverage consumption have all provided very strong evidence for the independent role of the intake of SSBs in the promotion of weight gain and obesity in children, adolescents, and adults (Malik et al., 2006).

The Role of Other Lifestyle Factors in the Regulation of Body Weight and Adiposity

It is apparent in daily life that hedonic factors also play a discernible role in energy intake (John E. Blundell & Finlayson, 2004). The sensory features of foods have the potential to stimulate an exaggerated hedonic response, or perceived pleasantness to foods, promoting excessive food intake to satisfy that pleasure-seeking need (Pearcey & De Castro, 2002). Adiposity has been consistently associated with specific food habits, such as excessive consumption of high fat foods, eating out at restaurants, and eating fast

foods or junk foods, all of which are hyperpallatable (J E Blundell, Lawton, Cotton, & Macdiarmid, 1996). The enhanced palatability of these energy-dense foods can overwhelm physiological satiety signals and establish strong preferences for excessive consumption of these foods, thus promoting adiposity (John E. Blundell & Finlayson, 2004). Other lifestyle factors influencing energy homeostasis include stress and sleep.

Several studies and systemic meta-analyses have confirmed that psychosocial stress is positively associated with the development of adiposity and excessive energy intake (Wardle, Chida, Gibson, Whitaker, & Steptoe, 2011). This relationship between stress and eating behavior is suggested to be complex, with a multitude of considerations, including body weight, perception of stress, and psychological eating traits (Adam & Epel, 2007; Stone & Brownell, 1994; Wardle et al., 2011). The stress response that elicits these changes in behavior also involves metabolic changes that directly increase adiposity, marked by an increase in cortisol levels (Dallman et al., 2004). Cortisol stimulates the storage of fat in adipose tissue and increases hunger signals, therefore, its release promotes adiposity (Wood, 2006). Studies have confirmed this relationship between stress, cortisol, and adiposity by observing higher secretion rates of cortisol in obese individuals (Stewart, Boulton, Kumar, Clark, & Shackleton, 1999). In fact, metabolism of cortisol has been shown to be strikingly altered in subjects with increased adiposity (Stewart et al., 1999).

Sleep is an additional factor influencing the regulation of body weight and metabolism (Chaput, Després, Bouchard, & Tremblay, 2007). Studies have reported that sleep deficits stimulate physiological changes in hormonal signals that promote hunger (such as cortisol) and, thus, promote excessive energy intake and adiposity (Chaput et al.,

2007; Hasler et al., 2004; Heslop, Smith, Metcalfe, Macleod, & Hart, 2002; Kripke, Garfinkel, Wingard, Klauber, & Marler, 2002). Some studies have also shown a dose-response relationship between a lack of sleep and high body mass index (BMI) and/or weight gain (Chaput et al., 2007; Hasler et al., 2004). This relationship is explained by studies showing that sleep deprivation is associated with decreased leptin levels and increased ghrelin levels, increasing hunger, appetite, and a sense of seeking reward from food (Spiegel, Tasali, Penev, & Van Cauter, 2004).

The Role of Diet in the Regulation of Insulin Resistance

Independent of adiposity, diet has a direct influence on insulin resistance. Though little is fully understood surrounding this relationship, studies have suggested that this association might be mediated in part by consumption of advanced glycation end products, protein, and fiber. However, more research on the correlation is needed.

Reducing sugars, such as glucose, react non-enzymatically with amino groups in proteins, lipids, and nucleic acids through a series of reactions forming Schiff bases and Amadori products to produce advanced glycation end products (AGE), known as the Maillard reaction (Unoki & Yamagishi, 2008). Currently there is no universally accepted method to detect AGE, no internal standards, nor an internationally recognized standard unit of measurement (Singh, Barden, Mori, & Beilin, 2001). Consequently, this makes associations between AGE and T2DM difficult to detect (Singh et al., 2001). However, though the formation of AGE is usually endogenous, dietary exogenous sources have been determined (Singh et al., 2001). Dietary AGE are known to contribute to increased oxidant stress and inflammation, and are thought to be linked to the T2DM epidemic

(Uribarri et al., 2010). The proposed pathway by which this occurs is seen in Figure 1. Food sources of AGE include: French fries, pizza, hamburgers, grilled cheese sandwiches, and chips (Uribarri et al., 2010). Essentially, foods rich in fat and carbohydrates that have been subjected to high heat processing are a source of exogenous AGE (Uribarri et al., 2010).

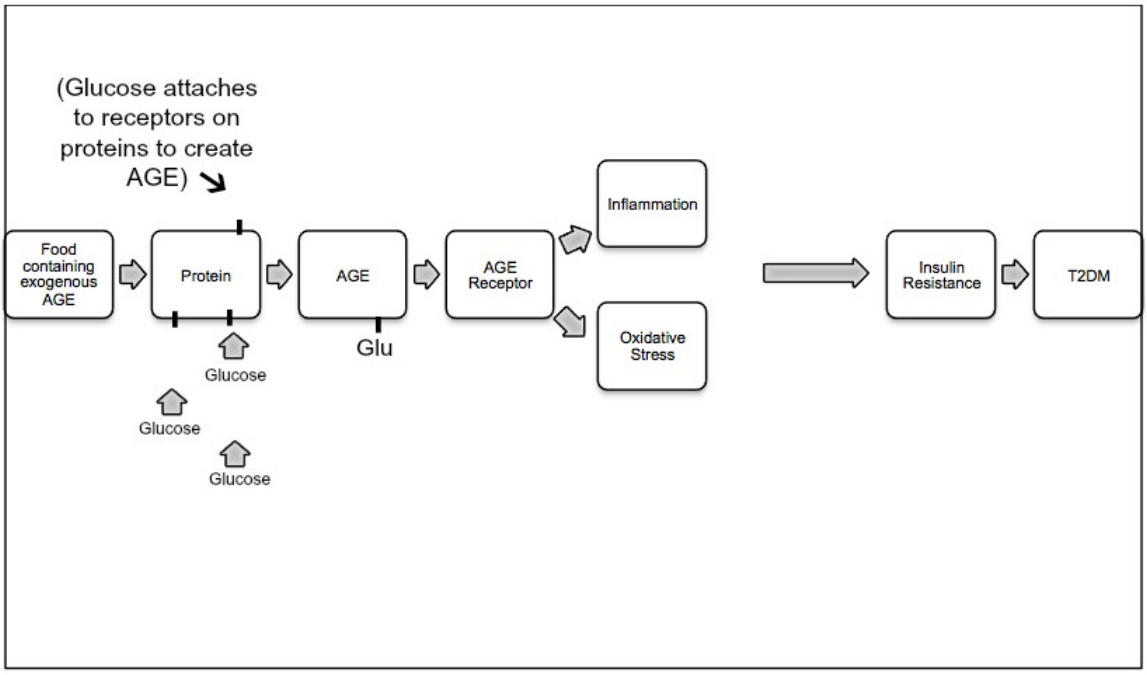

Figure 1: Potential pathway by which consumption of exogenous AGE leads to the development of T2DM. [no reference, created for this paper]

The resulting AGE production from consumption of exogenous AGE engages the AGE receptor, RAGE (Unoki & Yamagishi, 2008). This engagement between RAGE and AGE activates AGE's down-stream signaling and induces oxidative stress and inflammation, which is only accelerated in T2DM (Unoki & Yamagishi, 2008). Another study demonstrated that AGE induces the release of TNF-alpha, an important factor in insulin resistance (Naitoh, Kitahara, & Tsuruzoe, 2001). Since promotion of oxidative stress and inflammation are both additionally closely related to insulin resistance, it is likely that the AGE-RAGE system could play a role in the pathogenesis of insulin

resistance and, subsequently, development of T2DM (Unoki et al., 2007). Other pathways by which exogenous AGE has been linked to insulin resistance have also been found. Miele et al. showed that AGE stimulated insulin resistance by impairing insulin-induced insulin receptor substrate signaling in skeletal muscle cells (Miele et al., 2003). These several pathways have all established the general hypothesis that consumption of exogenous AGE plays a role in the development of insulin resistance, making the formation of AGE a characteristic feature of tissues in those with T2DM (Fukami et al., 2004; Unoki et al., 2007).

Protein has also been shown to have a distinct effect on insulin resistance. Several studies in healthy individuals, as well as in those with controlled T2DM, have shown that concurrent protein intake with carbohydrates reduces the glycemic response and thus, protein alone does not increase plasma glucose concentrations (Franz, Boucher, & Evert, 2014). Additionally, in a study comparing the effects of a high protein, high fat, or high carbohydrate diet on obese insulin-resistant women, a high protein diet resulted in a decrease in fasting insulin levels in the first 8 weeks, strongly suggesting an improvement in insulin sensitivity and having the most significant overall benefit in regard to insulin resistance (McAuley et al., 2005). Overall, when carbohydrates in the diet are partially replaced with a higher percentage of protein in the diet, post-meal glucose concentrations and glycohemoglobin (hemoglobin A1c, HbA1c) will both be reduced, indicative of improved blood glucose control (Gannon & Nuttall, 2004).

Research has demonstrated that a reduced-carbohydrate and higher protein diet may be the most appropriate dietary approach to improving glycemic control in T2DM;

however, on a high-carbohydrate diet, increasing fiber sources, such as legumes, fruits, and vegetables, has demonstrated similar benefits (McAuley et al., 2005).

A high intake of fiber is emphasized in most official diabetes nutritional recommendations, as it has consistently been shown to contribute to a number of metabolic effects independent of adiposity (Weickert & Pfeiffer, 2008). Importantly, it has been shown that fiber has significant positive effects on both insulin sensitivity and pancreatic functionality, also persisting after adjustment for caloric intake and adiposity (Liese et al., 2005). However, these findings are difficult to interpret because of the interrelation of glycemic index and fiber (Schulz et al., 2005). Soluble dietary fiber reduces postprandial glucose responses after carbohydrate-rich meals and lowers total and LDL cholesterol levels, likely by slowing gastric emptying and macronutrient absorption from the gut (Jenkins, Kendall, Axelsen, Augustin, & Vuksan, 2000). Insoluble fiber has also shown beneficial effects on insulin resistance, decreasing levels of fasting insulin and reducing inflammatory markers in several large cohort studies (De Munter, Hu, Spiegelman, Franz, & Van Dam, 2007; Liese et al., 2005; Schulze et al., 2007).

The Effect of Diet on Low-grade Chronic Inflammation

Diet not only has notable effects on insulin resistance, but it also plays a role in the low-grade chronic inflammatory processes that contribute to T2DM development (Ilich, Kelly, Kim, & Spicer, 2014). Low-grade chronic inflammation is a major etiologic factor in the development of insulin resistance. Thus, diet may affect insulin resistance through its effect on low-grade inflammatory processes. In other words, inflammation

may be the mediating mechanism through which diet affects insulin resistance and sensitivity (Heilbronn & Campbell, 2008). The modern diet includes more than 70% of energy consumed from refined sugars, refined vegetables oils, and highly processed products, in addition to a high ratio of omega-6 to omega-3 polyunsaturated fatty acids (Ilich et al., 2014). Research suggests that these characteristics of the modern diet may potentially contribute to the development of low-grade chronic inflammation and resulting obesity and T2DM, in addition to several other chronic diseases (Ilich et al., 2014). Excess omega-6 fatty acid consumption via foods like meat, eggs, and certain oils, leads to overproduction of arachidonic acid originating from high intake of linoleic acid, which metabolizes into pro-inflammatory eicosanoids, including prostaglandin-2, tromboxane-2, and leucotriene-4 (Ilich et al., 2014). However, foods high in omega-6 fatty acids are not the only culprits in an exaggerated immune response to food; consumption of foods containing AGE, foods that have undergone refinement and processing, foods high in glucose, and foods high in saturated and trans fats are all pro-inflammatory (Calder et al., 2011). Overall, consuming greater amounts of these foods causes higher circulating levels of pro-inflammatory cytokines (TNF-alpha, interleukin-6, and CRP), creating an environment of persistent low-grade chronic inflammation, sustaining itself in a perpetual feedback cycle (Ilich et al., 2014).

The Effect of Diet on Beta-cell Function

Diet's effects on insulin resistance and low-grade chronic inflammation are not well understood. Effects of diet on a third factor of T2DM development, beta cell function, have been seen; however, the mechanisms of the effects of diet are also poorly

understood, despite beta cell function and dysfunction in T2DM having been relatively well described (Weyer, Bogardus, Mott, & Pratley, 1999). One study in particular found that dietary energy restriction alone was able to normalize beta cell function in T2DM, indicating that the abnormalities underlying T2DM may be reversible by reducing dietary intake (Lim et al., 2011). This change in beta cell function was accompanied by decreases in pancreatic and liver triacylglycerol concentrations (Lim et al., 2011). Thus, a relationship between dietary intake and beta cell dysfunction is clear. Still, the mechanisms and specific dietary factors that contribute to pancreatic β-cell function are poorly understood (Lim et al., 2011).

Conclusion

Overall, T2DM is comprised of several physiological changes and dysfunctions, which are all worsened and complicated by aspects of diet, increased stress, and decreased sleep. Additionally, certain changes to dietary intake have shown significant positive effects on these mechanisms, with potential implications for T2DM prevention, management, and maybe even reversal. However, there is still so much unknown about diet and T2DM, and the research surrounding the topic has several holes. Additionally, although research is acknowledging a relationship between certain dietary factors and T2DM management, clinical practice does not always consider diet when treating T2DM. Mainly, we have yet to fully determine how to improve or even normalize glucose tolerance and glycemic control through dietary changes. This study aims to help address that gap in research.

Specific Aims and Hypotheses

A randomized, controlled dietary intervention trial was conducted to test the effects of gastric bypass surgery versus an intense dietary lifestyle intervention on T2DM status. The goal of that study was to determine if gastric bypass surgery improves glycemic control more than even the strictest lifestyle intervention, combined with optimal medical therapy, in randomized subjects. The subjects receiving the lifestyle intervention reported their dietary intake and physical activity for one year, in addition to having their blood glucose and HbA1c monitored. Compliance to the dietary intervention was assessed by developing a summary score based on adherence to 5 specific dietary recommendations: reduce energy density, increase percentage of calories from protein, reduce percentage of calories from added sugars, reduce sugar-sweetened beverage intake, and increase fiber intake.

The primary aim of this study was to evaluate the relationship between compliance to the dietary intervention and glycemic control, as assessed by HbA1c, at six months after the start of the intervention. We hypothesized that a higher compliance summary score would be associated with improved glycemic control among individuals in the lifestyle arm, compared to those with lower compliance summary scores.

Our secondary aim was to evaluate the relationship between each of the 5 measures of diet quality in the summary score (energy density, percentage of calories from protein, percentage of calories from added sugars, sugar-sweetened beverage intake, and fiber intake) and measures of glycemic control, including HbA_{1c}, fasting glucose levels, fasting insulin levels, HOMA-IR (homeostasis model assessment insulin resistance index), waist circumference, hip circumference, BMI, and body weight. We

hypothesized that better measures of diet quality will each be associated with improved markers of glycemic control.

Implications of Research

Investigating relationships among measures of diet quality, glucose metabolism, and body weight in an at-risk sample will contribute to our understanding of how dietary changes can improve glycemic control and body weight, with implications for more effective T2DM treatment and management in the future. This research is imperative because of the imminent health threat posed by the increasing prevalence of diabetes and its implications for individual health, healthcare systems, and economic systems.

Approach and Methods

Participant Selection

The parent study was a randomized controlled trial using a population-based recruitment strategy to enroll patients with T2DM and a BMI of 30-45 kg/m^2 to test the effects of gastric bypass surgery versus an intensive dietary lifestyle intervention on T2DM status. In this project, we focused on those randomized to the lifestyle arm only. A total of 16 overweight and obese adults with T2DM were randomly assigned to the lifestyle intervention arm. Recruitment methods used a shared decision making (SDM) approach to identify, screen, and randomize all adults who demonstrated equipoise between surgical and lifestyle treatment of obesity and diabetes in a large, integrated healthcare delivery system in Washington state. Candidates were considered eligible if they were 25-64 years old, had a BMI of 30-45 kg/m^2, were taking medications for T2DM, were covered by insurance that had a bariatric-surgery rider (if BMI 35-45 kg/m^2), and were willing to accept randomization into either intervention group and follow the full protocol for at least one year. Candidates were considered ineligible if any of the following were present: pregnancy, cancer (except non-melanoma skin cancer), ascites, peritoneal effusion, dementia, bipolar disorder, schizophrenia, cirrhosis, end-stage renal disease, human immunodeficiency virus, inflammatory bowel disease, diagnosed type 1 diabetes, diabetes secondary to a specific disease or glucocorticoid therapy, prior bariatric or major gastrointestinal surgery, or organ transplantation. These exclusions were designed to eliminate patients who were at greater-than-average risk for complications, disease-related weight change, or non-adherence to treatment and follow-up visits.

Intervention and data collection

The lifestyle intervention was free-of-charge and participants were paid $25/visit for attending in-person study data-collection visits outside of routine care. During the one-year intervention, subjects recorded all physical activity and food consumed either in a written food log or online using MyFitnessPal. The intervention was modeled after the Diabetes Prevention Program (DPP) (Knowler et al., 2002). Although reduced calorie intake and weight loss were still strongly encouraged, participants were not given specific weight-loss goals. Instead, the dietary intervention emphasized food quality by encouraging consumption of protein, fresh fruits and vegetables, and avoidance of processed foods. The program advocated a slightly higher percentage of energy from protein and fat, combined with avoidance of high glycemic-index foods.

To evaluate dietary compliance, the first 6 months of the intervention were divided into three sets of two-month blocks. Twelve non-consecutive days were chosen randomly from each of the three sets using a random date generator (http://www.random.org). If a chosen day had less than two meals of 100 calories recorded, it was excluded and another day was randomly generated until complete data for 7 days was obtained for each 2-month period. Food consumed on those 7 days was entered into ProNutra dietary analysis software (VioCare, Princeton, New Jersey). This was repeated three times for each subject to achieve a total of 21 days of complete diet data per subject.

Subjects attended clinic visits at baseline, 6, and 12 months following the start of the intervention. The following measurements were collected at each clinic visit: height, weight, waist circumference, hip circumference, percent lean and fat mass (determined by

Dual Energy X-Ray Absorptiometry (DEXA) and bioelectrical impedance plethysmography), blood pressure, resting heart rate, fasting plasma levels of glucose, insulin, HbA1c, cholesterol, quality of life (assessed by the EQ-5D questionnaire), and any adverse events that occurred during the intervention [as captured at each study visit using a standardized questionnaire (available from authors by request) and by automated surveillance of our electronic databases]. The homeostasis model of insulin resistance (HOMA-IR) index was calculated as a measure of insulin resistance (Matthews et al., 1985).

Data obtained from the written or electronic food records were used to calculate an overall dietary adherence summary score. Components of the score included: energy density (kcal/g), percentage of total energy provided by protein, percentage of total energy provided by sugar-sweetened beverages, percent of total energy provided by added sugars (i.e. any sugars in baked products, processed foods, and any other sugar not naturally occurring), and grams of dietary fiber (g/1000 kcal). Each variable was assigned a categorical score between 1 and 5 according to **Table 1**. Ranges for each dietary variable score were determined such that full compliance with the dietary guidelines given to participants would yield 5 points within each category, and no compliance (i.e., continued consumption of an average American diet) would yield 1 point.

Statistical Analysis Plan

All data was analyzed using SPSS for Macintosh, version 21 (IBM Corp., Armonk, NY). We first assessed the distribution of all variables by checking histograms and normality plots of the data, and tested for normal distribution by conducting Shapiro-

Wilk tests. Non-normally distributed data were log(10)-transformed prior to analyses, or the use of appropriate non-parametric tests was considered. The data were analyzed using a linear regression model. Our exposures of interest included subjects' adherence summary score (primary exposure), and each individual factor of the summary score [energy density (kcal/g), percent of total energy obtained from protein (%), percent of total energy from sugar-sweetened beverages (%), percent of total energy from added sugar (%), and fiber intake (g/1000 kcals)] (secondary exposures). Our endpoints of interest at 6 months were: HbA1c (%) (primary outcome), fasting glucose (mg/dL), fasting insulin level (μU/mL), HOMA-IR, waist circumference (cm), hip circumference (cm), BMI (kg/m^2), and body weight (kg) (secondary outcomes).

The primary hypothesis was tested using three models. Model 1A tested the association between the adherence summary score and each outcome of interest. Model 2A tested the association between the summary score and each outcome of interest adjusted for baseline data of each outcome of interest. Model 3A tested the association between the summary score and each outcome of interest adjusted for the change in body weight between the baseline and the 6-month clinic visits. The secondary exposures were tested using four models. Model 1B also tested the association between each of the secondary exposures of interest and each outcome of interest. Model 2B tested the association between each of the secondary exposures of interest and each outcome of interest adjusted for the baseline data of each outcome of interest. Model 3B adjusted for the other secondary dietary variables by incorporating a summary score of covariates that excluded the variable of interest, in addition to the baseline data of each outcome of interest. Finally, model 4B adjusted for changes in body weight, the potential mediating

variable, in addition to the baseline data of each outcome of interest. We compared each individual exposure with each endpoint of interest using a linear regression model. This totaled 48 individual tests, 1 primary analysis and 47 secondary analyses. We used an α-error level of 5% for all analyses. All secondary analyses were analyzed and interpreted together, i.e. a single significant association was not considered meaningful in the absence of other consistent associations for each dietary variable of interest. Thus, we did not adjust for multiple testing in these secondary analyses.

Results

Sixteen subjects were randomized to the one-year lifestyle intervention arm, of which 13 underwent the 6-month clinic visit and completed daily diet records for the duration of the study. Baseline characteristics of these 13 participants who were included in the present analysis are presented in **Table 2**. Body weight, BMI, waist and hip circumference were all significantly lower at 6 months compared to the baseline clinic visit ($p < 0.001$). Markers of glucose homeostasis also improved to a significant degree over the 6-month period as indicated by reduced fasting insulin from a median (min, max) of 20.9 (9.3, 87.1) to 11.2 μU/mL (5.6, 41.6) ($p=0.008$) and HbA1c from a mean (SD) of 7.25% (0.83) to 6.56% (0.76) ($p=0.004$). HOMA-IR improved to a significant degree from a median (min, max) value of 8.2 (3.1, 30.1) to 4.9 (1.65, 10.3) ($p=0.004$). However, fasting glucose at the 6-month visit was not significantly changed from baseline ($p = 0.314$).

Participants' dietary patterns during the first 6 months of the study are presented in **Table 3**. Incorporating each of these variables into an overall dietary adherence summary score yielded a mean (SD) score of 17.7 (3.5) out of 25. The lowest summary score among participants was 13 and the highest was 23.

Relation between dietary composition and measures of weight loss

In a first step, we assessed the relationship between dietary factors and measures of adiposity at the 6-month clinic visit (**Table 4**). Overall summary compliance score, which represents compliance to all five factors of compliance to the intervention, had an inverse association with hip circumference after adjustment for baseline hip

circumference (p=0.024), and trend toward an inverse association with BMI after adjustment for baseline BMI (p=0.056). Among the components of dietary composition analyzed (**Table 4**), protein intake was positively associated with waist circumference after adjustment for baseline waist circumference and for all other dietary factors not including protein (p=0.014). Adjustment for baseline data and for other dietary factors attenuated the association between protein intake and BMI in the crude model.

Relation between dietary composition and measures of glucose homeostasis

Concerning our main study outcome, there were no significant associations or even trends toward associations between the dietary compliance score and HbA1c. Additionally, no significant associations or trends toward associations between dietary compliance score and the other markers of glucose homeostasis, including fasting plasma glucose, fasting plasma insulin, or HOMA-IR, were found.

In regard to the relationship between constituents of dietary composition and measures of glucose homeostasis (**Table 5**), energy density was inversely associated with fasting plasma insulin after adjustment for baseline fasting plasma insulin (p=0.016) and after adjustment for both baseline fasting plasma insulin and the summary score not including energy density (p=0.023). Energy density was also inversely associated with HOMA-IR after adjustment for baseline HOMA-IR (p=0.028) and after adjustment for both baseline HOMA-IR and the summary score not including energy density (p=0.038). The association between energy density and both fasting insulin and HOMA-IR was attenuated and no longer statistically significant after adjustment for weight change. A positive association was found between added sugar intake and fasting plasma glucose in

both the crude model (p=0.021) and after adjusting for both baseline fasting plasma glucose and for the portion of the summary score not including added sugar intake (p=0.024). Fiber intake had a positive association with HbA1c levels after adjustment for baseline HbA1c (p=0.022), adjustment for baseline HbA1c and the portion of the summary score excluding fiber intake (p=0.017), and persisted with adjustment for change in body weight (p=0.025) in addition to baseline HbA1c.

Discussion

The primary aim of this study was to evaluate the relationship between compliance to the dietary intervention and glycemic control, as assessed by HbA1c, at six months after initiation of an intensive lifestyle intervention. We calculated a compliance score based on the degree to which subjects adhered to five specific dietary recommendations and hypothesized that a higher compliance summary score would be associated with improved glycemic control. Our secondary aim was to evaluate the relationship between each individual dietary variable in the summary score (energy density, percentage of calories from protein, percentage of calories from added sugars, sugar-sweetened beverage intake, and fiber intake) and HbA1c, fasting glucose and insulin, HOMA-IR, waist circumference, hip circumference, BMI, and body weight. We hypothesized that a larger diet compliance score would be associated with improved markers of glycemic control and adiposity.

Our study's key findings did not support this hypothesis, as we did not find any significant associations between summary compliance score and HbA1c or other markers of glycemic control, suggesting that stricter compliance to this particular dietary intervention did not lead to lower HbA1c levels at 6 months. It is notable that we did not even observe a trend in this regard for the association between the compliance score and HbA1c as well as any of the other measures related to glucose homeostasis. This could be explained by the fact that red blood cell life is roughly 115 days, making HbA1c a measure of average blood glucose over the previous three months, rather than immediate past (Nathan et al., 2009). We may be able to conclude from this lack of association that

improvement in blood glucose control may be more strongly associated with a specific aspect of the diet rather than compliance with all five facets of the dietary intervention.

What we did find significantly associated with increased compliance to the dietary intervention were markers of adiposity. A decrease in hip circumference, which is a marker of loss of fat mass, was significantly associated with increased compliance to the dietary intervention, indicating that compliance improved weight loss. In addition to hip circumference, decreased BMI trended toward a significant association with increased compliance, also suggesting that greater compliance improved weight loss.

In regard to each of the five dietary factors we tested for our secondary hypothesis, we noticed some unforeseen associations. Though we had expected improvement in each factor to be individually associated with an improvement in each measure of adiposity and each measure of blood glucose control, we found that all but two significant associations were the inverse of what was expected.

The only significant association that supported our hypothesis was the association between percentage of calories from added sugars and fasting plasma glucose. This association between increased sugar intake and increased fasting glucose levels are supported by prospective cohort studies (Meyer et al., 2000). A recent cross-sectional study has even determined that added sugar intake may be associated with markers of glucose control, such as fasting glucose levels, independent of differences in calorie consumption (Basu, Yoffe, Hills, & Lustig, 2013).

The overwhelming body of published research supports a positive association between protein consumption and weight loss or healthy weight maintenance, likely due to increased thermogenesis, satiety, and energy expenditure accompanying protein

utilization (Paddon-Jones et al., 2008; Westerterp-Plantenga, Nieuwenhuizen, Tomé, Soenen, & Westerterp, 2009). A potential explanation for our discrepant findings includes the types of protein-rich foods consumed by our subjects, which included a large amount of hamburgers, hot dogs, and red meat products. These are not only associated with higher fat and greater energy density, but are also typically consumed with high-carbohydrate and other high-fat products, which may help explain the positive association between protein intake and measures of adiposity in our study.

Some research has determined that increased protein consumption independent of weight loss has little effect on glucose control unless it is accompanied by a corresponding decrease in carbohydrate consumption (Gannon & Nuttall, 2004). Thus, our null association between protein intake and improved glucose control may be due to isolating protein consumption without taking potentially associated changes in carbohydrate consumption into account.

Energy density was not significantly associated with any markers of adiposity. The relationship between increased energy density and weight gain has been well-established, making the lack of association in our results unanticipated (Mendoza, Drewnowski, & Christakis, 2007). Additionally, we found an inverse association between energy density and both fasting insulin and HOMA-IR. These results are surprising as well, as previous research has consistently supported that increased energy density contributes to increased fasting insulin levels (Mendoza et al., 2007). This contradictory association found between energy density and both fasting insulin and HOMA-IR was attenuated and no longer statistically significant after adjustment for weight change.

Surprisingly, fiber intake was positively associated with HbA1c in the model adjusted for baseline data, baseline data and other summary score variables, and baseline data and change in weight, suggesting that fiber intake may have an association with HbA1C levels, independent of weight change and other dietary factors.

The effects of fiber on weight loss and regulation remains relatively controversial, so our lack of an association between fiber and measures of adiposity is not necessarily atypical (Howarth, Saltzman, & Roberts, 2001). On the other hand, due to fiber's supported effects on satiety, energy intake, and body composition, intake of fiber is widely supported to manage glucose control, making our positive association between fiber intake and HbA1c anomalous (Howarth et al., 2001). In many studies supporting fiber's effect on glucose control, the primary source of fiber was low-glycemic index fruits and vegetables, which also provided valuable phytochemicals and micronutrients to aid in weight loss, management, and improved glycemic control. (Anderson, Smith, & Gustafson, 1994; Liu et al., 2006). Conversely, in our study, our fiber variable comprised all forms of fiber, including the fiber found in many foods that are also rich sources of digestible and highly glycemic carbohydrates, such as breads and pastas. This may be the reason behind our unexpected correlations.

Finally, because there is a multitude of studies supporting the idea that sugar-sweetened beverages play a significant role in both adiposity and in the development of diabetes, it may seem surprising that no associations were found between consumption of sugar-sweetened beverages and any of the endpoints regarding adiposity or regarding glucose homeostasis (Malik et al., 2010). This was very likely related to the fact that our

subjects consumed few sugar-sweetened beverages, and many subjects did not consume any sugar-sweetened beverages on the days analyzed at all.

Our study has several limitations that likely contributed to our unanticipated results. The first relates to the validity and reliability of food journals kept by subjects. Individuals have been known to underreport food intake (and over report physical activity level) on self-report questionnaires and logs (Macdiarmid & Blundell, 1998). Additionally, inaccurate or missing information from food journals might account for additional effects on endpoints. For example, a participant may list that they consumed a "medium baked potato," when in reality they had a large potato, or maybe a potato with butter and salt. Thus, some error in measurement of portion sizes, in addition to inaccurate food consumption information, likely exists. This is in part controlled by participants' motivation to comply with the study for weight loss and attendance of dietary education sessions in which they were encouraged to be as detailed and honest as possible in their journals.

A second limitation of this study is the small sample size. Due to this limited sample, it remains inconclusive whether the primary null finding of no association, and not even an apparent trend, between compliance score and HbA1c is due to a lack of power (the small sample size) or if there is truly no association and the recommended diet composition was not in fact ideal.

A third limitation of this study is the inability to adjust for each individual exposure in our analysis, due to a lack of power and a lack of degrees of freedom. Had we been able to analyze the diets of a larger sample size, power of the study would have increased and appropriate adjustments could have been made. Because we did not adjust

for each individual exposure in our analysis, we ran the risk of confounding among variables. Thus, we had limited ability to distinguish between the contributions of the individual dietary factors. However, this limitation could exist in a much larger study as well. We account for this potential confounding by adjusting for all of the covariates.

Because all secondary analyses were analyzed and interpreted together and without adjustment for multiple testing, it is important to consider the meaning of the data, as a single 'significant' association should not be over interpreted due to the likelihood of false positive findings without adjustment for multiple testing.

The limitations of this study stem from the quality and amount of dietary data collected in food logs; thus, this study gives insight into the challenges of collecting dietary data, standing as a reminder that a study is only as strong as its data. The primary strength of this study is the awareness it brings into how diet data is collected and the dire need for improvements in dietary data collection and methodology. Other strengths of this study include that it was a randomized trial of surgery vs. non-surgical treatment for T2DM, the population was recruited from a typical healthcare setting, and the lifestyle intervention was intense.

It is important to question if the primary null finding between summary compliance score and HbA1c, in addition to the other markers of glucose homeostasis tested, was due to a suboptimal composition of the intervention diet, and, by translation, the summary compliance score. For example, the data suggest that consumption of high protein foods may have impaired weight loss, possibly because protein consumed by subjects was largely calorically dense and fatty rather than lean. A second example of this would be that the recommendation to consume more fiber might have led to increased

consumption of highly glycemic grains. This is important to learn from an analysis like this in order to improve upon dietary interventions for T2DM. From these findings, future studies would potentially focus on the role of specific foods in metabolic health. For instance, lean protein-rich foods may differ substantially from fatty, energy dense protein-rich foods; or, the effect on glycemic control and insulin sensitivity of fiber from fruits, vegetables, and legumes may be very different than the effect of fiber from grains. A valuable conclusion from this study may be that the diet we recommended might not have been ideal. However, while suggestive, it is critical to take into consideration that the data are too weak to be conclusive, and further studies are necessary.

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Table 1. Categorical scores and associated ranges for each of the five dietary components of the adherence summary score**.**

	1	2	3	4	5
Energy density (kcal/g)	>3.25 kcal/g	2.5-3.25 kcal/g	1.75-2.5 kcal/g	1-1.75 kcal/g	<1 kcal/g
Protein (% of total energy)	<17.5%	17.5-20%	20–22.5%	22.5-25%	>25%
Fiber (g/1,000 kcals)	<8 g/1,000 kcal	8-12 g/1,000 kcal	12-16 g/1,000 kcal	16-20 g/1,000 kcal	>20 g/1,000 kcal
SSBs (% of total energy)	>3%	2-3%	1-2%	0-1%	0%
Added Sugar (% of total energy)	>8%	6-8%	4-6%	2-4%	<2%

Table 2. Baseline characteristics and main intervention effects in participants randomized to the lifestyle intervention *.

	Baseline clinic visit	6-month clinic visit	p-value
Age (years)	55.5 ± 6.6	-	-
Sex (male / female)	6 / 7	-	-
Height (cm)	174 ± 11	-	-
Weight (kg)	115 ± 18	108 ± 17	*p < 0.001*
Body mass index (kg/m^2)	37.6 ± 2.8	35.5 ± 3.3	*p < 0.001*
Waist circumference (cm)	123 ± 10	115 ± 9	*p < 0.001*
Hip circumference (cm)	126 ± 10	121 ± 8	*p = 0.001*
Fasting plasma glucose (mg/dL)	135 (108, 217)	124 (98, 198)	*p = 0.314*
Fasting plasma insulin (uU/mL)	20.9 (9.3, 87.1)	11.2 (5.6, 41.6)	*p = 0.008*
HOMA-IR	8.21 (3.1, 30.1)	4.94 (1.65, 10.3)	*p = 0.004*
HbA_{1c} (%)	7.25 ± 0.83	6.56 ± 0.76	*p = 0.004*

* n=13, data are means ± standard deviations or medians (min – max). Abbreviations: HOMA-IR: Homeostatic model assessment of beta-cell function and insulin resistance ; HbA_{1c}: Hemoglobin A_{1c}.

Table 3. Dietary patterns during lifestyle intervention*.

Energy intake (kcals)	1,669 (1,118-3,164)
Energy density (kcals/g)	1.03 (0.87-1.71)
Fat intake (% of total energy)	43.4 ± 4.3
Carbohydrate intake (% of total energy)	32.3 ± 5.2
Protein intake (% of total energy)	23.8 (20.0-35.2)
Sugar-sweetened beverage intake (% of total energy)	0.0 (0.0-2.71)
Added sugar intake (% of total energy)	4.11 (2.05-11.0)
Fiber intake (g/1,000 kcals)	9.97 ± 3.26
Summary compliance score (5-25)	17.69 ± 3.5

* n=13, data are means ± standard deviations or medians (min – max).

Table 4. Relationship between diet composition and compliance with the dietary regimen and measures of adiposity at the 6-month clinic visit *.

	Weight (kg)	Body mass index (kg/m^2)	Waist circumference (cm)	Hip circumference (cm)
Energy density (kcals/g)				
Model 1	β=80 (-17, 176), p=0.096	β=2.5 (-18, 23), p=0.787	β=12 (-45, 69), p=0.656	β=-9.0 (-61, 43), p=0.712
Model 2	β=0.5 (-33, 34), p=0.973	β=0.31 (-10, 10), p=0.945	β=-6.3 (-40, 28), p=0.690	β=2.3 (-21, 25), p=0.827
Model 3	β=-0.8 (-34, 32), p=0.957	β=0.26 (-8.4, 8.9), p=0.948	β=-6.4 (-42, 30), p=0.698	β=4.9 (-15, 24), p=0.581
Protein intake (% of total energy)				
Model 1	β=84 (-63, 231), p=0.233	β=25 (1.5, 49), **p=0.039**	β=53 (-21, 127), p=0.144	β=57.4 (-7.2, 122), p=0.076
Model 2	β=-6.2 (-51, 38), p=0.762	β=-15 (-35, 5.5), p=0.134	β=14 (-37, 65), p=0.545	β=-26 (-67, 16), p=0.194
Model 3	β=65 (-12, 143), p=0.087	β=11 (-34, 57), p=0.591	β=99 (25, 174), **p=0.014**	β=27 (-30, 84), p=0.315
SSB intake (% of total energy)				
Model 1	β=-1.9 (-14, 10), p=0.736	β=-0.44 (-2.7, 1.8), p=0.676	β=0.46 (-5.9, 6.8), p=0.877	β=-1.6 (-7.3, 4.2), p=0.560
Model 2	β=1.4 (-1.6, 4.5), p=0.311	β=0.76 (-0.29, 1.8), p=0.136	β=0.62 (-3.1, 4.3), p=0.715	β=1.8 (-0.6, 4.3), p=0.124
Model 3	β=1.3 (-3.3, 5.8), p=0.542	β=0.44 (-0.96, 1.8), p=0.494	β=1.4 (-4.2, 6.9), p=0.590	β=0.64 (-2.4, 3.6), p=0.643
Added sugar intake (% of total energy)				
Model 1	β=-14 (-67, 38), p=0.557	β=-3.6 (-13, 6.0), p=0.426	β=-8.4 (-36, 19), p=0.508	β=-0.59 (-26, 25), p=0.960
Model 2	β=5.4 (-8.4, 19), p=0.405	β=2.9 (-2.0, 7.8), p=0.217	β=0.66 (-16, 17), p=0.931	β=9.4 (-0.05, 19), p=0.051
Model 3	β=2.9 (-18, 24), p=0.752	β=0.58 (-5.5, 6.7), p=0.834	β=1.3 (-23, 26), p=0.911	β=5.1 (-8.9, 19), p=0.432
Fiber intake (g/1,000 kcals)				
Model 1	β=-0.46 (-4.0, 3.1), p=0.781	β=0.35 (-0.28, 0.97), p=0.248	β=0.63 (-1.2, 2.5), p=0.462	β=1.26 (-0.22, 2.74), p=0.087
Model 2	β=-0.12 (-1.0, 0.8), p=0.780	β=-0.16 (-0.52, 0.20), p=0.347	β=0.13 (-0.97, 1.2), p=0.793	β=-0.15 (-1.06, 0.76), p=0.723
Model 3	β=0.07 (-0.9, 1.1), p=0.873	β=-0.12 (-0.44, 0.20), p=0.423	β=0.20 (-1.0, 1.4), p=0.717	β=-0.04 (-0.79, 0.71), p=0.909

Summary compliance score (5-25)				
Model 1	β=0.43 (-2.9, 3.8), p=0.783	β=0.22 (-0.39, 0.83), p=0.444	β=0.36 (-1.4, 2.1), p=0.658	β=0.57 (-1.0, 2.1), p=0.440
Model 2	β=-0.44 (-1.3, 0.41), p=0.275	β=-0.28 (-0.57, 0.01), p=0.056	β=-0.13 (-1.2, 0.91), p=0.783	β=-0.74 (-1.4, -0.12), **p=0.024**

* n=13. Model 1: unadjusted. Model 2: adjusted for the baseline data of the respective measure. Model 3: adjusted for baseline data of the respective measure and portion of the summary score not including the respective measure.

Table 5. Relationship between diet composition and compliance with the dietary regimen and measures of glucose homeostasis *.

	Fasting plasma glucose (mg/dL)	Fasting plasma insulin (μU/mL)	HOMA-IR	HbA_{1c} (%)
Energy density (kcals/g)				
Model 1	β=-0.21 (-0.83, 0.42), p=0.487	β=0.60 (-1.1, 2.3), p=0.440	β=0.39 (-1.1, 1.9), p=0.565	β=0.60 (-4.1, 5.3), p=0.784
Model 2	β=-0.14 (-0.66, 0.39), p=0.570	β=-2.0 (-3.6, -0.47), **p=0.016**	β=-1.7 (-3.2, -0.23), **p=0.028**	β=-1.2 (-5.5, 3.1), p=0.543
Model 3	β=-0.14 (-0.68, 0.41), p=0.580	β=-2.0 (-3.7, -0.36), **p=0.023**	β=-1.7 (-3.3, -0.12), **p=0.038**	β=-1.3 (-5.9, 3.3), p=0.541
Model 4	β=-0.13 (-0.69, 0.43), p=0.600	β=-1.7 (-3.5, 0.15), p=0.068	β=-0.94 (-2.7, 0.86), p=0.267	β=-0.81 (-5.3, 3.7), p=0.691
Protein intake (% of total energy)				
Model 1	β=-0.42 (-1.3, 0.46), p=0.315	β=0.98 (-1.4, 3.3), p=0.379	β=0.56 (-1.5, 2.7), p=0.569	β=-0.40 (-7.2, 6.4), p=0.899
Model 2	β=-0.12 (-0.93, 0.69), p=0.744	β=0.77 (-1.0, 2.6), p=0.363	β=0.61 (-1.1, 2.3), p=0.441	β=1.4 (-4.5, 7.3), p=0.614
Model 3	β=0.24 (-1.2, 1.7), p=0.717	β=2.2 (-1.4, 5.7), p=0.197	β=2.7 (-0.34, 5.7), p=0.075	β=4.1 (-7.0, 15), p=0.425
Model 4	β=-0.11 (-0.98, 0.75), p=0.771	β=1.1 (-0.50, 2.66), p=0.157	β=0.92 (-0.29, 2.1), p=0.119	β=.17 (-4.3, 7.6), p=0.547
Sugar-sweetened beverage intake (% of total energy)				
Model 1	β=0.05 (-0.02, 0.11), p=0.130	β=-0.05 (-0.23, 0.14), p=0.606	β=0.003 (-0.16, 0.16), p=0.974	β=0.14 (-0.38, 0.66), p=0.564
Model 2	β=0.02 (-0.05, 0.09), p=0.553	β=-0.003 (-0.15, 0.15), p=0.970	β=0.01 (-0.12, 0.15), p=0.832	β=0.024 (-0.44, 0.48), p=0.909
Model 3	β=0.01 (-0.10, 0.11), p=0.864	β=0.07 (-0.16, 0.29), p=0.535	β=0.06 (-0.15, 0.26), p=0.559	β=0.15 (-0.51, 0.80), p=0.628
Model 4	β=0.02 (-0.06, 0.09), p=0.610	β=-0.06 (-0.20, 0.09), p=0.387	β=-0.05 (-0.16, 0.07), p=0.376	β=-0.04 (-0.53, 0.45), p=0.858
Added sugar intake (% of total energy)				
Model 1	β=0.29 (0.05, 0.54), **p=0.021**	β=-0.37 (-1.2, 0.41), p=0.317	β=-0.08 (-0.80, 0.64), p=0.812	β=1.1 (-1.1, 3.3), p=0.283
Model 2	β=0.21 (-0.02, 0.45), p=0.071	β=-0.23 (-0.85, 0.40), p=0.435	β=-0.04 (-0.63, 0.56), p=0.895	β=0.56 (-1.4, 2.6), p=0.548

Model 3	β=0.36 (0.06, 0.66), **p=0.024**	β=-0.31 (-1.3, 0.67), p=0.496	β=0.02 (-0.90, 0.94), p=0.963	β=1.9 (-0.61, 4.5), p=0.119
Model 4	β=0.21 (-0.04, 0.47), p=0.092	β=-0.46 (-1.0, 0.08), p=0.087	β=-0.27 (-0.72, 0.19), p=0.217	β=0.36 (-1.8, 2.5), p=0.709
Fiber intake (g/1,000 kcals)				
Model 1	β=0.004 (-0.02, 0.03), p=0.658	β=-0.01 (-0.07, 0.04), p=0.592	β=-0.01 (-0.06, 0.04), p=0.675	β=0.05 (-0.11, 0.20), p=0.524
Model 2	β=0.006 (-0.01, 0.02), p=0.424	β=0.004 (-0.04, 0.05), p=0.838	β=0.01 (-0.04, 0.05), p=0.704	β=0.14 (0.02, 0.25), **p=0.022**
Model 3	β=0.01 (-0.01, 0.03), p=0.219	β=0.002 (-0.05, 0.05), p=0.940	β=0.01 (-0.04, 0.06), p=0.675	β=0.15 (0.03, 0.26), **p=0.017**
Model 4	β=0.01 (-0.01, 0.02), p=0.438	β=0.004 (-0.04, 0.05), p=0.828	β=0.01 (-0.03, 0.04), p=0.733	β=0.131 (0.02, 0.24), **p=0.025**
Summary compliance score (5-25)				
Model 1	β=-0.01 (-0.03, 0.01), p=0.242	β=0.01 (-0.05, 0.06), p=0.811	β=-0.01 (-0.05, 0.04), p=0.830	β=-0.03 (-0.17, 0.12), p=0.673
Model 2	β=-0.01 (-0.02, 0.01), p=0.496	β=0.01 (-0.03, 0.05), p=0.738	β=0.00 (-0.04, 0.04), p=0.992	β=0.01 (-0.12, 0.14), p=0.840
Model 4	β=-0.01 (-0.02, 0.01), p=0.558	β=0.02 (-0.02, 0.06), p=0.259	β=0.02 (-0.02, 0.05), p=0.298	β=0.03 (-0.10, 0.17), p=0.599

* n=13. Model 1: unadjusted. Model 2: adjusted for the baseline data of the respective measure. Model 3: adjusted for baseline data of the respective measure and portion of the summary score not including the respective measure. Model 4: adjust for baseline data of respective measure and change in weight.