The Effects of the Dietary Glycemic Load on Type 2 Diabetes Risk Factors during Weight Loss

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Abstract

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Objective: To compare the effects of two calorie-restricted diets that differ in glycemic load (GL) on glucose tolerance and inflammation.

Research Methods and Procedures: Thirty-four healthy overweight adults, ages 24 to 42 years, were randomized to 30% provided calorie-restricted diets with high (HG) or low (LG) glycemic load for 6 months. Outcomes were changes in glucose-insulin dynamics and C-reactive protein (CRP) levels.

Results: Compared with baseline, levels of fasting insulin, homeostasis model assessment of insulin resistance, post-load insulin at 30 minutes, and incremental area-under-the-curve-insulin during the oral glucose tolerance test were significantly lower in both groups at 6 months (p range, 0.01 to 0.05), but after adjustment for baseline values and weight change, there were no differences between the two groups with regard to changes over time in any parameter. The mean percentage change in insulin sensitivity by a frequently sampled intravenous glucose tolerance test was +26% in the HG group and +24% in the LG group (p = 0.83); first-phase acute insulin release was −20% in the HG group and −21% in the LG group (p = 0.77). More participants on the LG diet (14 of 16 subjects) had a decline in serum CRP, compared with those on the HG diet (7 of 16 subjects) ($p < 0.05$).

Discussion: In healthy overweight adults provided with food for 6 months, the dietary GL did not seem to influence chronic adaptations in glucose-insulin dynamics above that associated with weight loss. This finding highlights the importance of absolute weight loss over the dietary macronutrient composition used to achieve weight loss. The finding of greater declines in CRP concentration after consumption of a low-GL diet warrants further investigation.

Key words: glycemic index, glucose tolerance, insulin sensitivity, insulin secretion, C-reactive protein

Introduction

The incidence and prevalence of type 2 diabetes (t2DM)[1] are increasing at an alarming rate both in the United States and worldwide (1). Insulin resistance, impaired pancreatic β cell function, and low-grade systemic inflammation are important contributors to the development of glucose intolerance and t2DM (2,3). Weight loss through energy restriction and increased energy expenditure is recognized to be successful in reducing t2DM risk through improvements in insulin sensitivity, insulin secretion, and systemic inflammation (4–6). Specific dietary factors or patterns may also be important, but this area remains controversial (7).

One dietary factor that may influence the development of t2DM is the amount and type of carbohydrate as defined by

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[1] Nonstandard abbreviations: t2DM, type 2 diabetes mellitus; GL, glycemic load; GI, glycemic index; CRP, C-reactive protein; HG, high-GL diet; LG, low-GL diet; $HOMA_{IR}$, homeostasis model assessment of insulin resistance; OGTT, oral glucose tolerance test; INS_{30}, insulin level at 30 minutes after glucose load; AUC, area under the curve; FSIVGTT, frequently sampled intravenous glucose tolerance test; S_I, insulin sensitivity index; AIR_g, acute insulin response to glucose; DI, disposition index; CV, coefficient of variation; SEM, standard error of the mean.

the dietary glycemic load (GL) [GL = glycemic index (GI) × carbohydrate amount. The GI is defined as the area under the glycemic response curve during a 2-hour period after consumption of 50 g of carbohydrate from a test food, and values are expressed relative to the effect of either white bread or glucose] (8). Several observational studies have suggested that diets high in GI (9,10) or GL (11,12) increase t2DM risk, but others have not found such an association (10,13,14). Weight gain, impaired insulin secretion, increased insulin resistance, and systemic inflammation have all been implicated as potential mechanisms mediating the association between the dietary GL and t2DM (15,16). Diets low in GL are cautiously recommended by the American Diabetes Association for prevention of t2DM (17). However, questions remain whether integrating the GL concept in energy-restricted nutritional interventions will decrease risk for glucose intolerance and t2DM above and beyond any benefits seen by weight loss (17). The controversy persists, at least in part, because of lack of data from long-term intervention studies with controlled diets that have focused on GL as a nutritional intervention modality for prevention of glucose intolerance.

As part of a larger investigation of the effect of calorie restriction in healthy overweight adults, we used data from the first 6 months of a longer trial, when all food was provided, to test the hypothesis that two calorie-restricted diets that differ in GL have differential effects on major risk factors for development of t2DM, in particular glucose-insulin dynamics and plasma C-reactive protein (CRP) concentration.

Research Methods and Procedures

This randomized controlled trial was conducted at the Human Nutrition Research Center on Aging at Tufts University with approval from the Tufts-New England Medical Center Human Investigation Review Committee, and written informed consent by all participants (Clinicaltrials.gov identification # NCT00099099). The study was one of three independent trials that make up the first phase of the Comprehensive Assessment of Long-term Effects of Reducing Intake of Energy study.

Study Participants

Healthy adults ages 24 to 42 years with a BMI of 25 to 29.9 kg/m^2 and a fasting plasma glucose level of <100 mg/dL (5.6 mM) were recruited from the greater Boston metropolitan area. Participants underwent a three-step screening process, during which they were excluded if they met the following criteria: greater than a 15-pound weight change during the previous year; known serious medical condition (such as diabetes, cancer, heart disease, endocrine disorder, acquired immunodeficiency syndrome, depression, eating disorder); anemia; hypertension; abnormal electrocardiogram; liver, kidney, or thyroid dysfunction; strong family history of heart disease, cancer, or diabetes; pregnancy, lactation, or plans to become pregnant in the following year; or heavy participation in sports activities (>12 h/wk). We also excluded participants with known nutritional and lifestyle issues that could prevent participation in and completion of the study and those unwilling or unable to complete an accurate food record. Data presented here were acquired during the first 6 months of the trial, when all food was provided to the participants.

Study Protocol

Nutritional Intervention. After a 7-week baseline period, when usual energy requirements for weight stability were assessed as total energy expenditure measured using the doubly labeled water method (18), participants were randomized for 24 weeks to either a high-GL diet (HG) (60% carbohydrate, 20% protein, 20% fat, 1 kcal/g energy density, fiber 15 g/1000 kcal, mean estimated daily GI of 86, and mean estimated daily GL of 116 g/1000 kcal) or a low-GL diet (LG) (40% carbohydrate, 30% protein, 30% fat, 1 kcal/g energy density, fiber 15 g/1000 kcal, mean estimated daily GI of 53, and mean estimated daily GL of 45 g/1000 kcal). Both diets were provided at 30% calorie restriction compared with individual baseline weight maintenance energy requirements. There were two additional small groups (n = 6 in each group) that received the two diets at 10% caloric restriction. These groups are not included in the present analysis because their main function was to provide us with experience in recruiting a control group and there were insufficient data for the present analyses. The GI and GL of the diets were determined using international tables of GI and GL (19).

Both diets approximated current dietary recommendations for healthy macronutrient ranges and contained Dietary Reference Intakes of micronutrients and essential fatty acids (20). The HG diet had higher GL, with adequate fiber to meet current dietary recommendations (20), emphasized low-energy-dense foods, including use of whole grains rather than refined carbohydrates, limited liquid calories, and had a higher variety of low-energy-dense foods such as fruits and vegetables and a low variety of high-energy-dense foods. The LG diet was similar in all respects to the HG diet except that the macronutrient balance was changed and the carbohydrate sources were of low GI, based on published GI of different carbohydrate sources (19). The diets were matched initially for dietary variety and palatability. Participants were also provided with a multivitamin supplement and calcium 500 mg/d to ensure that Dietary Reference Intakes for micronutrients were met.

During the 6-month intervention period, all food was provided by the research center and collected for home consumption twice weekly by the participants or their designated representative. Participants were requested to con-

sume only this food; however, they were to report additional foods and drinks if any were eaten. To maximize adherence to the study diet, participants attended regular behavioral group meetings and individual sessions with a dietitian. From participants' reports of leftover food and extra items, actual daily nutrient intake during the intervention period was calculated (21).

Randomization-Sequence Generation and Allocation Concealment

The study participants were randomized to the two diet groups and block-stratified by sex and BMI (27.5 or >27.5 kg/m^2). Participants were not informed of their randomization for the first 12 weeks of the intervention. The dietary intervention study personnel were non-blinded, whereas all outcome and data management study personnel were blinded to the treatment allocation.

Study Outcomes

Body weight (to ±100 grams) was measured weekly using an electronic calibrated scale (Model CN-20; Detecto-Cardinal Scale Manufacturing Co., Webb City, MO). Height (to ±0.1 cm) was measured at baseline using a wall-mounted stadiometer. At the end of the baseline period and in the intervention period at Weeks 12 and 24, participants resided at the Human Nutrition Research Center on Aging for 1 and 2 days, respectively, while continuing to eat their assigned diet. Metabolic measurements were performed after an overnight 12-hour fast, as described below.

Homeostasis Model Assessment of Insulin Resistance ($HOMA_{IR}$). Insulin sensitivity in the fasting state was estimated by $HOMA_{IR}$, an index based on fasting glucose and insulin values, which is calculated as: $HOMA_{IR}$ = [glucose (mM) × insulin (mU/L)]/22.5 (22). This model assumes that normal participants have an insulin resistance of 1. High $HOMA_{IR}$ scores denote low insulin sensitivity (increased insulin resistance), and they correlate well with insulin sensitivity obtained from the euglycemic clamp procedure (23).

Oral Glucose Tolerance Test (OGTT). After a 12-hour overnight fast, 75 grams of glucose was given orally and a blood draw for glucose and insulin was done before (0 minutes) and at 30, 60, 90, and 120 minutes after the glucose load. The insulin level at 30 minutes after the glucose load (INS_{30}) was used as a measure of pancreatic β cell early-phase insulin release (24). Incremental areas under the curve (AUC) for the glucose (AUC-glucose) and insulin (AUC-insulin) responses were determined as measures of glucose tolerance and insulin sensitivity, respectively (25).

Frequently Sampled Intravenous Glucose Tolerance Test (FSIVGTT). In a subgroup of participants (those who consented to the procedure and in whom it was technically feasible, $n = 15$ in the HG group and $n = 11$ in the LG group), glucose and insulin dynamics were assessed with an FSIVGTT at 0 and 6 months (26). After a 12-hour overnight fast, an intravenous cannula was inserted into each arm. One was used for infusion of glucose and insulin, and the other was used for withdrawal of blood. Dextrose (300 mg/kg total body weight) was injected intravenously over 2 minutes at time 0, and insulin (0.03 U/kg total body weight; Novolin R; NovoNordisk, Princeton, NJ) was injected rapidly at time 20 minutes. Blood for insulin and glucose was sampled at −15, −10, −5, 1, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16, 19, 22, 23, 24, 25, 27, 30, 40, 50, 60, 70, 80, 90, 100, 120, 140, 160, and 180 minutes. The data were analyzed through minimal model analysis using MinMod software (MinMod Millenium, version 5.18; MinMod, Inc., Pasadena, CA) to estimate insulin sensitivity index (S_i). The incremental first-phase acute insulin response to glucose (AIR_g) was determined by calculating the AUC-insulin above the baseline in the first 10 minutes after glucose infusion. The disposition index (DI, the product of S_i and AIR_g), was calculated as a measure of pancreatic β cell function that captures both insulin sensitivity and the ability of the β cell to secrete insulin in response to the prevailing insulin sensitivity (27). A low DI value indicates decreased β cell function.

Assays

Glucose was measured by the hexokinase method in a Cobas Mira Analyzer (Roche Diagnostics, Indianapolis, IN) with intra- and inter-assay coefficients of variation (CV) of 1.4 and 2.1%, respectively. Insulin was measured by a radioimmunoassay commercial kit (Linco Research, Inc., St. Charles, MO) with intra- and inter-assay CVs of 3.1 and 3.8%, respectively. High-sensitivity CRP, as a marker of systemic inflammation (28), was measured using a commercially available solid-phase chemiluminescent immunometric assay (Diagnostic Products Corp., Los Angeles, CA) with intra- and inter-assay CVs of 4.0 and 6.5%, respectively.

Statistical Analysis

Data on 32 (of 34) participants who completed the 6-month intervention period were analyzed. To examine differences in baseline characteristics between groups, we used Student's *t* test for differences in means for continuous data and the χ^2 test for differences in proportions for categorical variables. To compare within-group mean changes in outcomes (baseline, 3 months, and 6 months after the intervention), we used Student's paired *t* test. To compare between-group differences over time for all outcomes, we used general linear models adjusting for baseline values and changes in weight (PROC GLM procedure in SAS software; SAS Institute, Inc., Cary, NC). Statistical significance was set at $p < 0.05$. Data are presented as means ± standard error of the mean (SEM), unless otherwise noted. Statistical

Table 1. Baseline characteristics of study participants who completed the 6-month dietary intervention

Characteristic	HG ($n = 16$)	LG ($n = 16$)	p
Sex [no. (%) women]	13 (76)	12 (75)	0.92
Age (years)	34.3 ± 1.2	35.0 ± 1.5	0.72
Race [no. (%) white]	14 (82)	14 (88)	0.62
Weight (kg)	79.3 ± 3.1	78.8 ± 2.3	0.92
BMI (kg/m^2)	27.6 ± 0.4	27.6 ± 0.3	0.99
Energy requirement by doubly labeled water method (kcal/d)	2822 ± 122	2758 ± 99	0.69
Prescribed energy intake (kcal/d)	1956 ± 88	1931 ± 70	0.83
Fasting measurements and indices			
Plasma glucose (mg/dL)	83.8 ± 1.7	83.8 ± 1.6	0.75
Fasting insulin (mU/L)	11.1 ± 1.0	12.2 ± 1.2	0.22
$HOMA_{IR}$	2.3 ± 0.2	2.5 ± 0.3	0.18
CRP (mg/L)	2.2 ± 0.6	3.1 ± 0.7	0.65
OGTT measurements and indices			
2-hour glucose (mg/dL)	107.1 ± 8.0	118.2 ± 6.4	0.24
2-hour insulin (mU/L)	49.2 ± 8.6	54.6 ± 9.5	0.56
AUC-glucose	585 ± 28	609 ± 25	0.40
AUC-insulin	338 ± 35	335 ± 27	0.57
FSIVGTT measurements*			
S_i (10^{-4}/min/mU/mL)	4.2 ± 0.5	4.4 ± 0.5	0.79
AIR_g (mU/L/min)	448 ± 80	401 ± 33	0.64
DI	1571 ± 232	1730 ± 226	0.65

HG, high glycemic; LG, low glycemic; $HOMA_{IR}$, homeostasis model assessment of insulin resistance; CRP, C-reactive protein; OGTT, oral glucose tolerance test; AUC, area under the curve; FSIVGTT, frequently sampled intravenous glucose tolerance test; S_i, insulin sensitivity index; AIR_g, acute insulin response to glucose; DI, disposition index. Data are presented as means ± standard error of the mean, unless otherwise indicated. p Values are for Student's t test for differences in means or the χ^2 test for differences in proportions for categorical variables in comparisons between the two groups.

* For FSIVGTT measurements, data included 16 participants in the HG group and 12 participants in the LG group.

analysis was performed using SAS, version 8.2. The study was independently monitored for overall compliance and data accuracy by an external clinical trial monitor from the Duke Clinical Research Institute, Durham, NC. Clinical trial safety and efficacy were monitored by a data safety monitoring board.

Results

Baseline Characteristics and Dietary Intervention

At baseline, the mean age of the 32 participants who entered the analysis was 34.6 years, and their mean BMI was 27.5 kg/m^2 (Table 1). The mean target energy intake for the entire cohort was 1966 kcal/d, and the mean reported daily energy intake at 6 months did not differ between the two groups (2017 kcal on the HG diet vs. 1972 kcal on the LG diet, $p = 0.70$).

Metabolic Outcomes Related to Risk of t2DM

Body Weight. Participants maintained a stable body weight during the baseline period while on their usual diet. At 3 months and 6 months, both groups achieved statistically significant ($p < 0.001$) weight loss compared with their baseline weight. Adjusted for baseline weight, weight loss was equivalent in the two groups (7.2 kg in the HG group vs. 7.7 kg in the LG group at 6 months, $p = 0.69$).

Plasma Glucose, Serum Insulin, and Insulin Resistance by $HOMA_{IR}$. The mean ± SEM fasting plasma glucose of the participants was 84.0 ± 0.2 mg/dL (4.7 ± 0.01 mM). At baseline, $HOMA_{IR}$ correlated with BMI, as anticipated ($r = 0.48$, $p = 0.01$). Changes in fasting glucose, insulin, and $HOMA_{IR}$ during the course of the trial are shown in Figure 1. Compared with baseline, within-group small declines in fasting glucose at 3 and 6 months were not statistically significant (Figure 1A); however, within groups, fasting

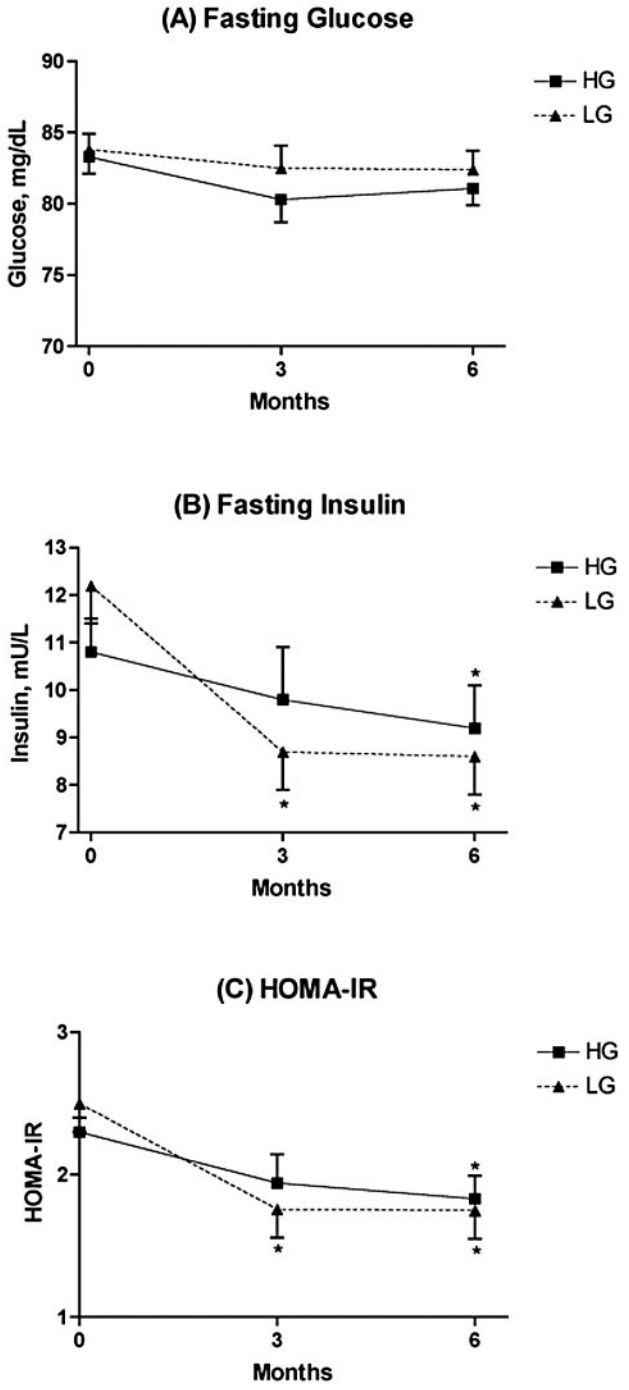

Figure 1: Mean ± SEM plasma glucose (A), serum insulin (B), and $HOMA_{IR}$ (C) during a 6-month feeding study of an HG diet ($n = 16$) vs. an LG diet ($n = 16$) in overweight adults with normal fasting glucose at baseline. * $p < 0.05$ for within-group change from baseline. p = not significant for changes between groups (adjusted for baseline values and change in weight). To convert to SI units, glucose (mM = 0.0555 × mg/dL), and insulin (pM = 7.175 × mU/L).

insulin and $HOMA_{IR}$ were lower at 6 months compared with baseline levels (Figure 1, B and C). After adjusting for baseline values and changes in weight, there were no statistically significant differences between the two groups at 3 or 6 months in fasting glucose, insulin, or $HOMA_{IR}$.

OGTT Measures. The glucose and insulin response to a 75-gram OGTT before and after the 6-month dietary intervention is shown in Figure 2. Within groups, there were no statistically significant differences in post-load timed glucose concentrations compared with baseline (Figure 2, A, C, and E); however, INS_{30} after the glucose load (Figure 2, B and D) and AUC-insulin (Figure 2F) were significantly lower at 6 months in both groups compared with baseline ($p < 0.01$). After adjustment for baseline values and change in weight, no statistically significant differences were observed between the two groups in post-load glucose or insulin values at any individual time-points, or in the AUC for either glucose or insulin.

FSIVGTT Measures. In those who underwent an FSIVGTT, S_i correlated with BMI at baseline, as anticipated ($r = 0.33$, $p < 0.05$). The mean percentage change at 6 months in S_i was +26% in the HG group and +24% in the LG group. The mean percentage change in AIR_g was −20% in the HG group and −21% in the LG group. After adjusting for baseline values and change in weight, there were no statistical differences in S_i, AIR_g, or DI between the two groups (data not shown). Figure 3 shows the relationship between S_i and AIR_g at baseline and at 6 months. The changes in these two parameters were of very similar degree and direction in both groups, and the direction of change was along the prediction curve after weight loss for individuals with normal glucose tolerance.

CRP. At 6 months, mean plasma CRP concentration decreased from baseline by 35% ($p < 0.01$) in the LG group, whereas it remained essentially unchanged in the HG group (Figure 4). The difference in the mean CRP change at 6 months between the two groups did not achieve statistical significance after adjusting for baseline values and change in weight (−1.44 ± 0.44 mg/L in the LG group vs. 0.41 ± 0.91 mg/L in the HG group, $p = 0.13$). Owing to the expected large individual variability in CRP levels, we also analyzed the data by examining whether participants experienced an increase or a decline in CRP values from baseline to follow-up. In this analysis, more subjects (14 of 16 participants) on the LG diet experienced a decline in CRP compared with those on the HG diet (7 of 16 participants) ($p < 0.05$ for χ^2).

Discussion

In overweight individuals with normal fasting plasma glucose, we found that energy-restricted provided diets with low or high GL for 6 months had equivalent weight-loss adjusted effects on chronic adaptations in glucose-insulin dynamics. Our very well-controlled study highlights the

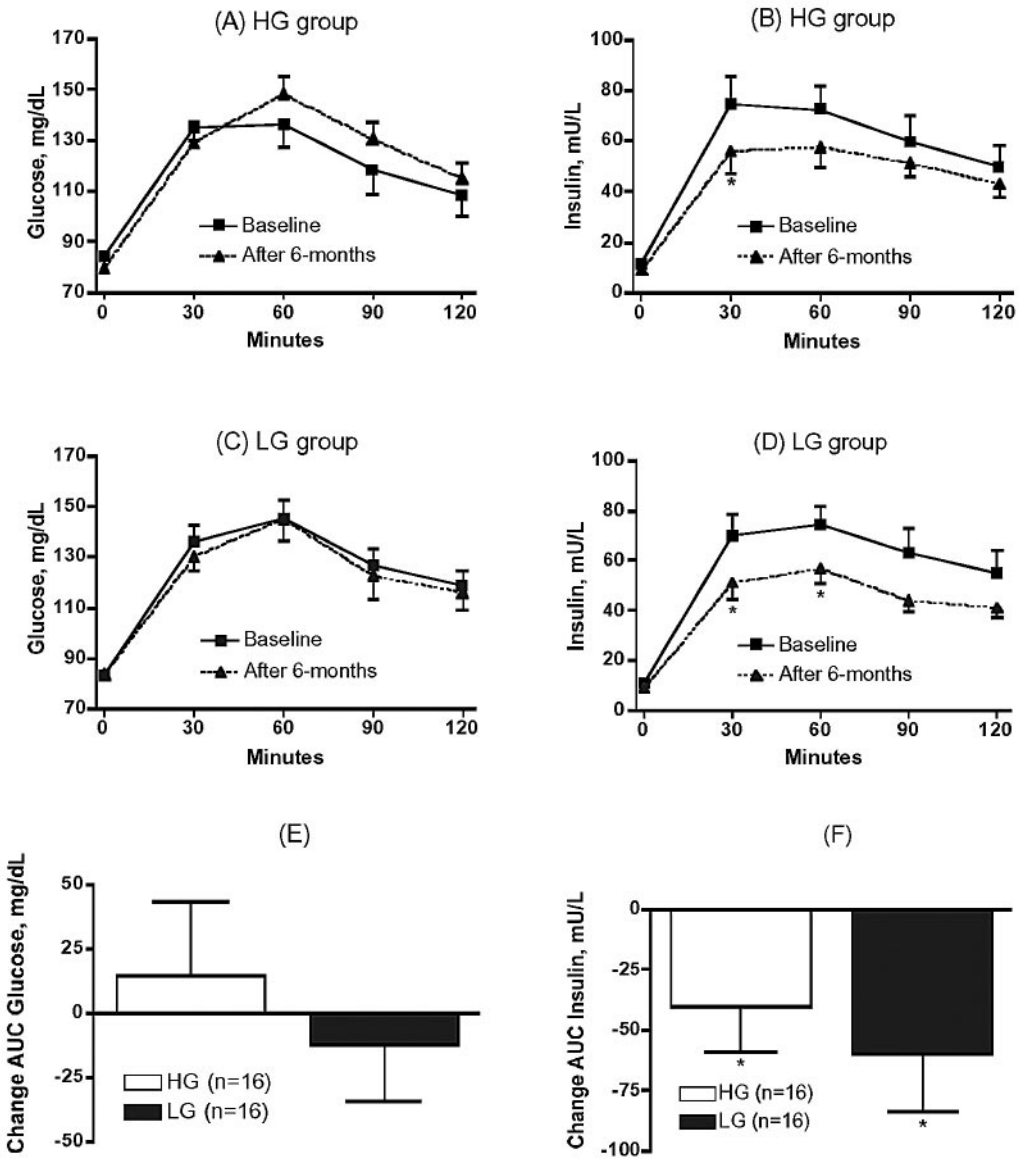

Figure 2: Mean ± SEM plasma glucose (A and C), serum insulin (B and D), and AUC (E and F) after a 75-gram OGTT before and after a 6-month feeding study of an HG diet (A and B, $n = 16$) vs. an LG diet (C and D, $n = 16$) in overweight adults with normal fasting glucose at baseline. * $p < 0.01$ for within-group change from baseline. $p =$ not significant for changes between groups (adjusted for baseline values and change in weight).

importance of absolute weight loss, rather than dietary macronutrient composition, as the primary determinant of improvements in glucose-insulin dynamics during weight loss treatment programs.

High postprandial glucose excursions are predictors of development of glucose intolerance and t2DM (4), and carbohydrates are the component of the diet that influences the glycemic response the most. Therefore, decreasing daily postprandial glucose excursions and hyperinsulinemia with a low GL diet may decrease t2DM risk, presumably by means of changes in insulin sensitivity and/or pancreatic β cell function (8). In our study, we examined glucose-insulin dynamics by several methods: while participants were fasting, after a standard oral glucose challenge, and after an intravenous glucose challenge, in an effort to discern chronic influences of the dietary GL on various physiological measures that define glucose tolerance. Our finding that glycemia remained essentially unchanged in both groups during the weight loss intervention can be explained on the basis that participants had normal glucose tolerance at baseline, and, therefore, one would not expect glycemia to improve any further even after significant weight loss. Our finding of no change in glucose is in accord with previous studies of diets that differ in GL in subjects with normal

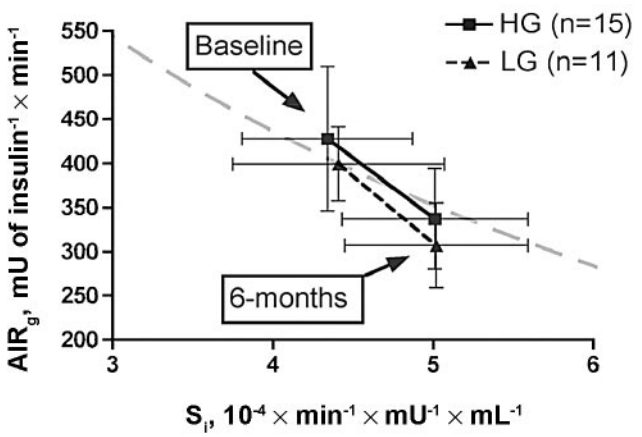

Figure 3: Relationship between S_i and AIR_g at baseline and after 6 months. The DI curve for euglycemic persons (constructed from the baseline data of the entire cohort) is shown as a dashed line.

baseline glucose tolerance (29–34), including studies with very low-carbohydrate diets (35,36). The declines in fasting and post-challenge timed and AUC-insulin levels after weight loss in both groups in the setting of maintaining euglycemia suggest an improvement in insulin sensitivity, which was confirmed by other measures of insulin sensitivity such as $HOMA_{IR}$ and S_i. However, there were no weight loss-adjusted differences in insulin sensitivity measures between the two groups, which is in accord with most other trials (duration over 1 month) with glucose-tolerant subjects (31,36–40), including studies with very-low-carbohydrate diets (35). In the two studies that showed improvements in

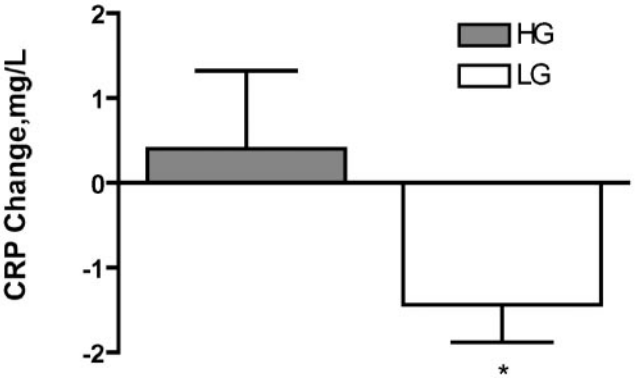

Figure 4: Mean ± SEM change in CRP after a 6-month feeding study of an HG diet ($n = 16$) vs. an LG diet ($n = 16$) in overweight adults with normal fasting glucose at baseline. * $p < 0.01$ for within-group change from baseline. p = not significant for changes between groups (adjusted for baseline values and change in weight). More participants (14 of 16) on the LG diet experienced a decline in CRP than those on the HG diet (7 of 16) ($p < 0.05$ for χ^2).

$HOMA_{IR}$ with low-GL diets, glucose and insulin values were not provided and changes in $HOMA_{IR}$ were not adjusted for weight changes, to assess the weight-independent effect of the dietary GL (41,42).

A limitation of using the OGTT to assess the effect of diets that vary in GL is that although the prevailing glycemia and insulinemia may be decreased with low-GI diets, this effect may not be evident during a standard OGTT. Furthermore, priming with a high-carbohydrate diet, such as a high-GL diet, improves the pancreatic β cell response, whereas chronic exposure to a low-GL diet may attenuate the response to a standard glucose load. Nevertheless, the OGTT does remain an accepted method for assessing glucose tolerance, and it also provides useful information regarding the ability of the pancreatic β cell to respond to a standard glucose load. In the subgroup of participants who underwent an FSIVGTT, S_i increased and AIR_g declined equivalently in both groups, resulting in a DI value that remained unchanged from baseline. Although there is a range of values for S_i and AIR_g, DI tends to remain constant in the euglycemic population. Individuals with low values of S_i, AIR_g, and DI are at increased risk for progressing to glucose intolerance and t2DM (43). In our study, the reciprocal changes in S_i and AIR_g resulting in an unchanged DI were expected, given that both groups remained euglycemic during the study and lost equivalent weight (27). A previous study in individuals with impaired glucose tolerance found no improvements in S_i or AIR_g among three diets that varied in GI or GL but found improvements in DI only in the group that lowered the dietary GI (40). In that study, the high-GI group achieved greater weight loss, which was not adjusted for in the analysis.

There are several possible explanations as to why risk factors for glucose tolerance did not differ between groups in our study. First, the effects of high- and low-GL/GI diets may be stronger in patients at very high risk for t2DM (obese, sedentary, genetically susceptible) (15). Although our participants were overweight, they had normal fasting glucose at baseline and only mild insulin resistance. Therefore, the potential beneficial effects of a low-GL diet may not be evident in this population, because they are less susceptible to changes in glucose-insulin dynamics. Second, because weight is the most important risk factor for t2DM, the significant and equivalent weight loss achieved in both groups in response to the two prescribed caloric-restricted diets may have masked any differences between the two dietary patterns that would be attributed to the individual macronutrient composition. Next, the short-term effects of low-GI or low-GL diets, seen in various studies, may not be seen in longer-term studies such as ours, because there is evidence that some adaptation to diets that vary in GI or GL takes place over time (44). Finally, the acute effects of a low-GI or low-GL diet on lowering postprandial glycemia

may be beneficial per se and need to be distinguished from its chronic effects, measured here (32).

High circulating CRP levels have been shown to be a risk factor of t2DM independent of conventional risk factors (6). Therefore, a decline in CRP is desirable when considering specific dietary interventions. Our finding of greater declines in CRP concentration in participants randomized to a low-GL diet is consistent with observational studies (16) and some, but not all, previous clinical trials (37,42,45,46). In a 3-month feeding study, a decline in CRP with a low-GL diet was seen despite equivalent weight loss (42). In a 6-month caloric-restricted ad libitum study of extremely low-carbohydrate vs. low-fat diets, CRP declined modestly in both groups, but the decline was greater in the low-carbohydrate diet only among participants with a high baseline CRP (46). In contrast, a study of high-protein vs. high-carbohydrate diet and a study of sucrose vs. artificial sweeteners found equivalent changes in CRP (37,45). Although our finding of greater CRP declines with lower-GL diets may have important health implications, it warrants further investigation because CRP measurements have substantial variability and the population size in this investigation was relatively small.

Our study has several strengths, including long duration, high retention rate, provided foods, use of the doubly labeled water method to estimate total energy requirement for calculations of individual energy-restricted prescriptions during the study, and measurements of glucose tolerance and glucose-insulin dynamics in several ways, both at basal state (fasting) and during dynamic testing with oral and intravenous glucose challenge. Despite these strengths, potential limitations also warrant consideration in relation to interpreting our results. Our study provided hypocaloric diets, and, therefore, the effect of the dietary GL independent of caloric restriction cannot be assessed. Although the two diets differ in carbohydrate quality and quantity, they also differ in protein and fat content. The latter two macronutrients also contribute to glucose and insulin response, so the findings should be attributed to macronutrient balance rather than carbohydrate content per se. Finally, our results may not be widely generalizable in individuals with glucose intolerance at baseline or others who are at higher risk of diabetes because of advanced insulin resistance or defective β cell function at baseline (47).

In conclusion, healthy overweight individuals with normal fasting glucose responded to calorie-restricted diets of varying GL with equivalent changes in glucose-insulin dynamics, which highlights the importance of absolute weight loss over the macronutrient composition of the diet used to achieve weight loss. The finding of greater declines in CRP concentration after the low-GL diet warrants further investigation. Long-term studies aimed toward individuals at high risk for t2DM are needed before embracing the GL as a viable option for effective prevention of t2DM.

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