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A Low-Glycemic Load Diet Reduces Serum C-Reactive Protein and Modestly Increases Adiponectin in Overweight and Obese Adults[1–4]

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Abstract

Low-glycemic load (GL) diets improve insulin resistance and glucose homeostasis in individuals with diabetes. Less is known about whether low-GL diets, independent of weight loss, improve the health profile for persons without diabetes or other preexisting conditions. We conducted a randomized, cross-over feeding study testing low- compared to High-GL diets on biomarkers of inflammation and adiposity in healthy adults. Eighty participants (n = 40 with BMI 18.5–24.9 kg/m^2; n = 40 with BMI 28.0–40.0 kg/m^2) completed two 28-d feeding periods in random order where one period was a high-GL diet (mean GL/d = 250) and the other a low-GL diet (mean GL/d = 125). Diets were isocaloric with identical macronutrient content (as percent energy). All food was provided and participants maintained weight and usual physical activity. Height, weight, and DXA were measured at study entry and weight assessed again thrice per week. Blood was drawn from fasting participants at the beginning and end of each feeding period and serum concentrations of high-sensitivity CRP, serum amyloid A, IL-6, leptin, and adiponectin were measured. Linear mixed models tested the intervention effect on the biomarkers; models were adjusted for baseline biomarker concentrations, diet sequence, feeding period, age, sex, and body fat mass. Among participants with high-body fat mass (>32.0% for males and >25.0% for females), the low-GL diet reduced CRP (P = 0.02) and marginally increased adiponectin (P = 0.06). In conclusion, carbohydrate quality, independent of energy, is important. Dietary patterns emphasizing low-GL foods may improve the inflammatory and adipokine profiles of overweight and obese individuals. J. Nutr. 142: 369–374, 2012.

Introduction

Multiple metabolic and endocrine pathways are dysregulated in obesity. Impaired glucose tolerance; increased insulin resistance; chronic, low-grade inflammation; and disturbances in the normal balance of adipocyte-derived hormones and growth factors are some of the many metabolic disturbances in obese individuals (1–3). Both inflammation and disordered metabolism increase the risk for numerous chronic diseases, including cardiovascular disease, cancer, and diabetes mellitus (1,3–6). Weight loss and weight management are critical components of improving the health profile of overweight and obese persons. However, it is less clear whether specific dietary patterns, macronutrient distributions, or diet quality (e.g., low GL[9], Mediterranean diet, Healthy Eating Index) independent of weight loss or energy restriction will improve the metabolic and inflammatory milieu and lower chronic disease risk (7–11).

Over the past two decades, the dietary GL has emerged as a useful way to evaluate carbohydrate quality in relation to a food's effect on postprandial glycemia (12–14). High-GL diets rapidly increase blood glucose and insulin concentrations, whereas low-GL diets attenuate the glucose and insulin postprandial responses (12,15). Frequent and sustained elevations in glucose and insulin lead to numerous adverse health events. More recently, evidence suggests that low-GL diets may be inversely associated with inflammation and antioxidant status (16,17). Low-GL diets are very useful in the therapeutic setting for individuals with diabetes or glucose intolerance, because they have been shown to improve diabetic glycemic control in

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[3] This trial was registered at clinicaltrials.gov as NCT00622661.
[4] Supplemental Figures 1 and 2 and Supplemental Table 1 are available from the "Online Supporting Material" link in the online posting of the article and from the same link in the online table of contents at jn.nutrition.org.
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[9] Abbreviations used: CRP, C-reactive protein; FHCRC, Fred Hutchinson Cancer Research Center; GI, glycemic index; GL, glycemic load; *hs*-CRP, high-sensitivity CRP; SAA, serum amyloid A.

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many (18,19) but not all studies (20). However, data are lacking on whether GL influences health in persons without diabetes or whether it is a useful dietary approach for chronic disease prevention among otherwise healthy individuals.

Observational data from cohort and case-control studies examining the association among GI, GL, and either surrogate endpoint biomarkers or specific disease endpoints are limited. Existing reports generally provide conflicting results and only a limited number of controlled, intervention studies have been conducted in healthy participants (21–23). One small study in young healthy persons reported modest associations of a low-GI diet with glucose, insulin, or lipid measures (24). Sloth et al. (25) conducted a 10-wk parallel arm study testing low-GI compared to High-GI test foods in 45 healthy, overweight women. Women consuming the low-GI foods had a 10% decrease in LDL cholesterol, but there were no other differences between the two groups for other outcomes, including body weight, HOMA, fasting insulin, glucose, and TG (25). The Legume Inflammation Study was a randomized, cross-over, controlled feeding study testing a high-legume, low-GI diet compared to a high-GI diet in 64 weight-stable men. The primary objective was to test the effects of the diets on biomarkers of inflammation and insulin resistance. Changes in serum concentrations of CRP, sTNFRI, sTNFRII, and C-peptide did not vary between the study arms, whereas the high-legume, low-GI diet unexpectedly increased fasting glucose compared to the high-GI diet (26). These limited data suggest that further research is necessary to understand the relationship of GL to measures of disease susceptibility biomarkers, including beneficial biomarkers such as adiponectin, which is an adipose-derived hormone that modulates glucose homeostasis and fatty acid oxidation (27). We conducted a randomized, cross-over feeding study testing low- vs. high-GL experimental diets on biomarkers of inflammation and obesity in normal and overweight/obese healthy adult men and women. We hypothesized that compared to a high-GL diet, a low-GL diet would reduce serum concentrations of *hs*-CRP, SAA, leptin, and IL-6 and increase that of adiponectin. We also hypothesized that the response would vary between normal weight and overweight or obese people.

Methods

Experimental design. The Carbohydrates and Related Biomarkers Study was a randomized, cross-over, feeding study testing the effect of low- and high-GL diets on chronic disease susceptibility biomarkers, including biomarkers of inflammation and adipokines, which have been associated with increased risk of cancer, cardiovascular disease, and other chronic diseases (1,28–30). The Carbohydrates and Related Biomarkers Study was conducted between June 2006 and July 2009. Participants were block-randomized on BMI (BMI >18.5 to <25.0 kg/m^2 and ≥ 28.0–40.0 kg/m^2) and sex and race/ethnicity (African American, Hispanic, and all others) using a cross-over design where each participant received 2 isocalorically controlled experimental diets (low GL and high GL) in random order. Participants consumed each diet for 28 d then resumed their habitual diet during a 28-d washout period (**Supplemental Fig. 1**). All foods and most beverages for the feeding periods were prepared in a standardized manner using strict hazard analysis critical control point procedures in the Human Nutrition Laboratory at the FHCRC.

Participants. Healthy, nonsmoking men (n = 41) and women (n = 41), aged 18–45 y, were recruited from the Seattle area via advertisements in local newspapers, the FHCRC Web site, local college and university newspapers, and flyers distributed around the campus of local colleges and universities. A special recruitment for minority enrollment was conducted using publications targeted to the local African American and Hispanic communities and by working with organizations and on-campus student groups that serve these communities. Interested individuals completed an eligibility questionnaire and were excluded for any of the following: *1*) physician-diagnosed diseases requiring dietary restriction, including but not limited to diabetes, kidney disease, other metabolic diseases (e.g., thyroid disease or other disorders requiring chronic steroid or antiinflammatory use), and cardiovascular disease requiring dietary modifications; *2*) BMI <18.5 kg/m^2, 25.0–28.0 kg/m^2, or ≥ 40.0 kg/m^2. We excluded those with BMI 25.0–27.9 kg/m^2 in order to have sufficient contrast between the normal weight and overweight/obese groups; *3*) current pregnancy or lactation or plans to become pregnant; *4*) regular use of hormones, antiinflammatory medications, or other medications that might interfere with outcome measures; *5*) tobacco use or >2 alcoholic drinks/d; *6*) restrained eating habits or food allergies; *7*) impaired fasting glucose (fasting blood glucose ≥5.6 mmol/L). Fasting blood glucose was tested as part of eligibility screening. Participants were asked to discontinue use of all dietary supplements prior to beginning the feeding study. Study procedures were approved by both the Institutional Review Board and the Clinical Trials Office of the FHCRC and all participants provided written, informed consent.

Study diets. As part of baseline data collection, participants completed 3-d diet records to estimate their habitual energy intake. We used these data, together with individually calculated results from the Mifflin equation (31), to estimate each person's energy needs during the feeding study. Within each intervention diet, we created a 7-d menu rotation using ProNutra (version 3.2, Viocare). The two diets were designed to be identical in macronutrient composition (15.0% energy from protein, 30.0% energy from fat, and 55.0% energy from carbohydrate); the diets differed only by GL (125 vs. 250 for the low- and high-GL diets, respectively) and fiber (55 and 28 g/d for the low- and high-GL diets, respectively). GL calculations were based on our previous work (32). Participant weight was monitored thrice weekly and energy adjustments were made (in 200-kcal increments) as needed to maintain baseline weight. Examples of study menus are in **Supplemental Table 1**.

Participants were instructed to consume only the foods and beverages provided to them during both study periods. They were permitted to consume their own coffee or tea but used sugar and/or cream/whitener as provided by study staff. Participants ate 1 meal/d (typically the evening meal) Monday through Friday at the Human Nutrition Laboratory under the supervision of study staff. After the meal, participants were given food for the next day's breakfast, lunch, and snack. Following the Friday evening meal, participants were provided with all food for the weekend plus Monday breakfast and lunch. Any unconsumed food was returned to the Human Nutrition Lab where staff weighed and recorded the amount of remaining food. Participants completed a daily checklist confirming consumption of the day's meals and consumption of any nonstudy foods.

Specimen collection and analysis. On d 1 and 28 of each feeding period [first (baseline) and last days], a 12-h fasting morning blood sample was collected, processed, and stored at −80°C using a standard protocol. Stored serum samples were used for the analyses in this report. Concentrations of *hs*-CRP and SAA were measured by latex-enhanced nephelometry using high sensitivity assays on the Behring Nephelometer II analyzer (Dade Behring Diagnostics) at the University of Washington Medical Center. The lowest limits of quantification for *hs*-CRP and SAA assays were 0.2 and 0.8 mg/L, respectively. Blinded duplicates from pooled samples were included in each batch and the CV for these samples were <1.0%. Inter-assay CV were 5–9% for *hs*-CRP and 4–8% for SAA. Participants (n = 4) with *hs*-CRP concentrations > 10.0 mg/L were excluded, because this concentration assumes a concurrent acute infection even among obese participants (33,34). Control materials from Bio-Rad Laboratories were run with each assay for quality control purposes. ELISA was used to assay IL-6 (Human HS IL-6 Quantikine, R&D Systems), leptin (Human leptin, Millipore.), and total adiponectin (total adiponectin, Alpco Diagnostics). Each participant's four samples (beginning and end of each feeding period) were included in the same batch run for all assays. Blinded quality control samples were included on each plate and inter-assay CV were all <10.0%.

Anthropometry and body composition. Baseline height was measured to the nearest 0.5 cm in participants wearing light clothing without shoes by using a wall-mounted stadiometer. Weight was measured to the nearest 0.5 kg at baseline and thrice weekly using a calibrated digital platform scale. Baseline waist circumference was measured to the nearest 0.5 cm using a cloth tape at the narrowest point between the iliac crest and the lowest rib. Hip circumference was measured to the nearest 0.5 cm using a cloth tape at the broadest point below the iliac crest. Body composition was assessed with the use of whole-body DXA scanning by using a GE Lunar DPX-Pro.

Demographic characteristics. Participants completed baseline questionnaires that included information on age, sex, race/ethnicity, personal and family health history, usual diet, and usual physical activity.

Statistical analyses. Our overall analytic goal was to test the intervention effect of the low- compared to high-GL diets on the blood-based biomarkers. We first performed a natural logarithmic transformation on the serum concentrations of *hs*-CRP, SAA, IL-6, leptin, and adiponectin to improve the normality of the distributions. We employed a linear mixed model where diet treatment, diet sequence, and diet period were fixed effects and participant was a random effect (35,36). All models were adjusted for age, sex, d-1 biomarker concentrations (i.e., baseline), diet sequence, and feeding period. A priori subgroup analyses were planned to examine whether the intervention effect varied by participant adiposity status. The percentage of body fat mass was used instead of BMI in these stratified analyses, because initial exploration of the data revealed that some participants were misclassified as lean when based on BMI alone, particularly at the high end of the normal BMI distribution and the lower end of the overweight distribution. Body fat mass was classified as high if >32.0% for females and >25.0% for males (37,38). Two participants had missing DXA data (one refused and one was too large for the DXA machine). We used the following empirical approach to impute the two missing values for percentage of body fat. Using the overlap of the distributions of BMI and percentage of body fat mass, these two individuals were placed in the high-body fat mass group, because the probability of having low-body fat mass for these two participants would have been close to zero (39,40).

All values presented are back-transformed, adjusted least squared means, and 95% CI; the P values indicate the significance of the intervention effect. All statistical tests were 2-sided with $\alpha = 0.05$. Analyses were conducted with SAS (version 9.2, SAS Institute).

Results

Of the 82 participants initially recruited, 80 completed both feeding periods. The block randomization ensured that equal numbers of males and females, and normal weight and overweight/obese individuals, comprised the participant group (**Table 1**). The overweight/obese group was, on average, slightly older than the normal weight group ($P < 0.001$). Over one-half of study participants were racial/ethnic minorities, but race/ethnicity did not vary across the normal weight and overweight/obese groups. Self-reported data from the daily check-off forms and food returned to study staff indicated that participants complied with the study protocol; 97% of participants consumed >90.0% of the provided foods (data not shown). There were no significant differences in adherence by study diet treatment.

The multivariable-adjusted main effects of the low- and high-GL diets on the biomarkers of inflammation (*hs*-CRP, SAA, and IL-6) and the adipokines (leptin and adiponectin) revealed no significant differences in the biomarkers by diet treatment (**Table 2**). However, in analyses stratified by baseline body fat mass (**Table 3**), results tended to differ and there was a significant interaction effect by body fat mass (P-interaction = 0.02 in the *hs*-CRP model; data not shown). Among participants with low-body fat, *hs*-CRP tended to be higher ($P = 0.09$) and IL-6 concentrations were higher ($P = 0.02$) following the low-GL diet compared to the high-GL diet. Among those with high-body fat, *hs*-CRP was 27% lower following the low-GL diet than the high-GL diet ($P = 0.02$), but there were no intervention effects on either SAA or IL-6 concentrations. Of the two adipokines measured, there was an intervention effect only for adiponectin, where the low-GL diet tended to increase serum adiponectin concentrations ($P = 0.06$). Serum leptin tended to be lower ($P = 0.13$) following the low-GL diet in the high-body fat mass participants, but the diet differences were not significant (**Supplemental Fig. 2**).

Discussion

This randomized, cross-over, controlled feeding study tested the effect of low-GL compared to high-GL experimental diets on biomarkers of inflammation and adiposity in normal weight and overweight/obese adults. Our principal finding was that the low-GL diet decreased serum *hs*-CRP concentrations and tended to increase serum adiponectin concentrations in participants with high-body fat mass. The effect sizes were substantial; the differences between the high-GL and low-GL diets were 0.24 and 0.21 mg/L for *hs*-CRP and adiponectin, respectively. The study was highly controlled in terms of energy intake and uniform food preparation and all participants maintained their weight during the trial. Therefore, the results are directly attributed to the dietary intervention effects. We interpret the study findings to suggest that low-GL diets influence two critical mechanisms linked to adverse health outcomes: inflammation and synthesis of adipose-derived peptides. Among participants with a low-body fat mass, the low-GL diets had no effect on *hs*-CRP and inexplicably increased IL-6. We are unclear why seemingly healthy people with normal baseline serum concentrations of these inflammation markers displayed increases following the low-GL diet but not the high-GL diet. It is possible that other, unmeasured aspects of the controlled diet that were new to them triggered slight increases in inflammation. It is also possible that *hs*-CRP is more sensitive to changes in diet than IL-6.

Inflammation is one of the proposed biological mechanisms mediating associations between obesity and cancer, cardiovascular disease, and other chronic diseases (1,28,41,42). CRP is an acute phase protein, which reduces NO production, stimulates production of endothelin I, and disrupts the normal balance in the renin-angiotensin system (43,44). CRP has also been associated with platelet activation, lipid peroxidation, and transformation of colonic adenoma cells to adenocarcinoma cells (30). Overweight and obese individuals are particularly susceptible to these events, because obesity causes a perpetual state of low-grade inflammation with chronically elevated serum concentrations of proinflammatory biomarkers, such as CRP (1,45). The results of this study support the notion that lifestyle interventions, including dietary modification, may be an important approach to reducing chronic inflammation in overweight and obese individuals.

Adipose tissue is an active endocrine organ (46,47). Among the many hormones and peptides synthesized by adipocytes is adiponectin. This peptide is inversely associated with obesity and low serum concentrations are associated with increased risk of invasive breast and other cancers (27,48). Adiponectin improves insulin sensitivity, increases fatty acid oxidation, inhibits NF-κB signaling, and is inversely associated with several

TABLE 1 Characteristics of study participants[1]

Characteristics	All participants (n = 82)	Normal weight[2] participants (n = 40)	Overweight/obese[3] participants (n = 42)	P[4]
Age, *y*	29.5 (8.1)	26.5 (6.4)	32.5 (8.6)	<0.001
Male sex, *n (%)*	41 (50.0)	20 (50.0)	21 (50.0)	>0.99
Race/ethnicity, *n (%)*				0.19
Non-Hispanic white	36 (43.9)	14 (35.0)	22 (52.4)	
Hispanic	20 (24.4)	11 (27.5)	9 (21.4)	
African American	17 (20.7)	8 (20.0)	9 (21.4)	
Asian/Pacific	9 (11.1)	7 (17.5)	2 (4.8)	
Islander/Native American				
Weight, *kg*	81.4 ± 21.3	65.0 ± 8.2	97.0 ± 17.9	<0.001
BMI, *kg/m²*	27.5 ± 5.9	22.4 ± 1.8	32.5 ± 3.7	<0.001
Body fat, *%*	27.8 ± 15.3	17.2 ± 10.7	38.4 ± 11.5	<0.001
Waist circumference, *cm*	87.6 ± 19.5	74.9 ± 6.7	99.4 ± 20.0	<0.001
Hip circumference, *cm*	103.3 ± 15.5	92.1 ± 5.8	113.7 ± 14.4	<0.001

[1] Data are means ± SD or *n* (%). Block randomization was used to ensure equal numbers of males and females, and normal weight and overweight participants.
[2] BMI 18.0 to <25.0 kg/m².
[3] BMI 28.0–40.0 kg/m².
[4] *P* values are for tests of comparisons between the normal weight and overweight/obese participants. Continuous variables were compared using the *t* test and proportions were compared using the chi-squared test.

inflammatory markers, including CRP, IL-6, and TNFα (27,44). To our knowledge, this is the first intervention study to demonstrate that a low-GL diet significantly increases adiponectin in overweight and obese individuals.

The low-GL diets improved the biomarker risk profiles of the overweight and obese study participants by decreasing CRP and increasing adiponectin. The two study diets were identical in macronutrient content (as a percent of total energy) and energy was individually calculated for each participant based on standard formulas (31), as we designed the study such that participants would maintain weight during the entire study period. Two mechanisms may explain the effectiveness of the low-GL diets. First, accumulating evidence suggests that insulin resistance and inflammation are inter-related (1,28,49). Dietary patterns that rapidly increase blood glucose and insulin concentrations postprandially (i.e., high GL) not only stimulate insulin resistance but also induce an inflammatory response due to the acute excess of cellular glucose (50). Our observation that the low-GL diet reduced inflammation biomarkers only in overweight and obese, but not normal weight, participants suggests that those who may already be slightly insulin resistant or at risk for insulin resistance may benefit the most from a low-GL dietary pattern. Second, although the macronutrient distributions (as percent of total energy) were identical in the low- and high-GL diets, the fiber content differed (25 vs. 48g/d for high- and low-GL diets, respectively). Fiber is well known to be inversely associated with inflammatory factors, although the exact mechanism is unclear (51–53). It is possible that our low-GL diets were effective due to the high fiber content, which is not surprising given that fiber is inextricably linked to the glycemic response (54).

A direct comparison of our study with other intervention studies is a challenge because of varying study designs, study populations, and specific intervention content. Nonetheless, the results reported here are consistent with other published interventions demonstrating that low-GL diets reduce inflammation and modify adipocyte-derived peptides. Wolever et al. (20) reported a 29% decrease in serum CRP in individuals with diabetes who followed a low-GI diet for 1 y compared to those following a high-GI diet or a low-carbohydrate diet. Kelly et al. (17) conducted a parallel-arm, 12-wk, randomized, controlled feeding study in 28 obese, insulin-resistant adults testing low- compared to high–GI diets plus aerobic exercise. They reported a significant decrease in serum TNFα and MCP-1 in the low-GI arm and, unlike our study, they also reported a significant decrease in IL-6. In contrast, Hartman et al. (26) reported no significant differences by diet arm in CRP, sTNFRI, or sTNFRII following a legume-enriched, low-GI diet compared to a healthy American diet. We are unaware of any other intervention studies testing low compared to high GL in relation to serum adiponectin. However, Jensen et al. (16) reported that compared to a high-GI diet, a low-GI diet intervention significantly reduced serum plasminogen activator inhibitor-1 by 15%. Plasminogen activator inhibitor-1 may play a role in adipose tissue synthesis (16), providing some support along with our

TABLE 2 Intervention effect of high- and low-GL experimental diets on serum biomarkers of inflammation and adipokines in normal and overweight or obese participants combined[1]

Biomarkers	High-GL diet (n = 80)	Low-GL diet (n = 80)	P[2]
hs-CRP, *ng/L*	0.6 (0.6–0.7)	0.6 (0.5–0.7)	0.88
SAA, *mg/L*	2.2 (1.9–2.6)	2.4 (2.0–2.8)	0.46
IL-6, *ng/L*	1.2 (1.1–1.3)	1.3 (1.2–1.5)	0.09
Leptin, μ*g/L*	9.2 (8.3–10.2)	8.7 (7.9–9.7)	0.49
Adiponectin, *mg/L*	3.9 (3.8–4.1)	4.1 (3.9–4.3)	0.30

[1] Values are least square means (95% CI), n = 80 from a model adjusted for baseline biomarker concentrations, diet sequence, feeding period, age, sex, and BMI. All participants completed both diets in a randomized, cross-over design. GL, glycemic load; *hs*-CRP, high-sensitivity CRP; SAA, serum amyloid A.
[2] *P* values are from linear mixed models testing the intervention effect of the low- vs. high-GL diets.

TABLE 3 Intervention effect of low-GL vs. high-GL experimental diets on serum biomarkers of inflammation in normal weight and overweight or obese participants stratified by baseline body fat mass[1,2]

	High GL		Low GL			
Biomarkers	*n*		*n*		(High GL-low GL)	*P*[3]
hs-CRP, *mg/L*						
Low-body fat	28	0.3 (0.2–0.4)	29	0.4 (0.3–0.6)	−0.17	0.08
High-body fat	50	0.9 (0.7–1.1)	51	0.7 (0.5–0.8)	0.24	0.02
SAA, *mg/L*						
Low-body fat	29	1.8 (1.3–2.6)	29	2.4 (1.7–3.5)	−0.61	0.2
High-body fat	52	2.6 (2.3–3.0)	52	2.5 (2.1–2.8)	0.14	0.5
IL-6, *ng/L*						
Low-body fat	29	0.8 (0.7–1.0)	29	1.1 (0.9–1.3)	−0.25	0.02
High-body fat	52	1.5 (1.3–1.7)	52	1.5 (1.3–1.7)	−0.02	0.8
Leptin, *μg/L*						
Low-body fat	29	2.6 (2.0–3.3)	29	2.5 (1.9–3.3)	0.04	0.9
High-body fat	52	18.7 (17.2–20.4)	52	17.4 (16.0–19.0)	1.30	0.13
Adiponectin, *mg/L*						
Low-body fat	29	4.5 (4.2–4.8)	29	4.3 (4.1–4.6)	0.13	0.5
High-body fat	52	3.8 (3.6–3.9)	52	4.0 (3.8–4.2)	−0.21	0.06

[1] Values are least squared means (95% CI) adjusted for baseline biomarker concentrations, diet sequence, and feeding period. GL, glycemic load; *hs*-CRP, high-sensitivity CRP; SAA, serum amyloid A.
[2] Body fat was derived from baseline DXA; high-body fat was >32.0% for females and >25.0% for males.
[3] *P* values are from linear mixed models testing the intervention effect of low vs. high GL experimental diets.

finding of increased adiponectin after the low-GL diet that dietary patterns have the capability of influencing adipose tissue biology.

This study has several strengths. The randomized, controlled, cross-over feeding study design is a rigorous test of the effect of dietary components on biomarkers of health, including whether or not diet can influence disease risk susceptibility biomarkers. All study foods were provided and participants were adherent with the protocol. Unlike some previous studies, all participants maintained weight during the entire study, allowing us to draw direct inferences about the diet effects. In studies where weight is allowed to vary, it is very difficult to separate the effects of the diets from the effects of weight change on the biomarker outcomes. Moreover, because we excluded people with abnormal blood glucose and those with a history of diabetes or other diet-related chronic diseases, we could test the effect of the low- and high-GL diets in healthy individuals. Most such previous studies have been conducted in persons with diabetes or individuals with other preexisting health conditions. Study limitations must also be mentioned. Most of our study participants were young (mean age = 29.6 y) and results may differ among older individuals who may have experienced decades of excess weight. Participants reported minor deviations from the study protocol, such as not consuming all study food or eating a food not prepared by the Human Nutrition Laboratory. However, there is always the possibility that some protocol deviations were not reported, because participants were free-living and consumed most of the study meals in their own homes. Further, because this was not a population-based sample, our study participants may not be representative of the general population. Finally, we acknowledge that both inflammation and adipose-derived hormones and peptides are complex systems ultimately involving numerous molecules that interact in complex ways. We were limited in our ability to measure only a few of these molecules. A more thorough understanding of the relationship between GL and biomarkers of health and disease will require more scrutiny with a more comprehensive array of biomarkers and consideration of novel analytic approaches, such as pathway analysis.

In conclusion, a low-GL diet reduces inflammation and tends to increase a beneficial adipokine (adiponectin) in overweight and obese but otherwise healthy adult men and women. Although weight loss and maintenance of energy balance should remain one of the critical components of any lifestyle intervention for the overweight and obese, the results from this study suggest that diet composition, particularly carbohydrate quality, plays a key role. Adhering to a low-GL diet may help individuals at risk of obesity-related metabolic dysfunction improve their overall health.

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