# Effects of a Low–Glycemic Load Diet on Resting Energy Expenditure and Heart Disease Risk Factors During Weight Loss

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T HE POOR LONG-TERM EFFICACY of conventional obesity treatment has promoted the notion of a body weight *set point*,[1,2] more recently termed *settling point*. According to this concept, deviations in body weight from baseline elicit physiological adaptations that antagonize further weight change. During energy restriction, humans and experimental animals have increased hunger, decreased thyroid hormone levels, and down-regulation of reproductive and growth functions,[3-5] changes that increase energy intake and lower energy expenditure. To examine this phenomenon, Leibel et al[6] underfed or overfed participants who were lean or obese to obtain an approximate 10% decrease or increase in body weight from baseline. Resting energy expenditure (REE) and total energy expenditure relative to fat-free body mass declined following weight reduction, whereas total energy expenditure increased following weight gain.

A decline in REE and associated neuroendocrine changes have been consistently reported during active weight loss, although controversy exists as to whether these adaptations are permanent[6-8] or transient.[9,10] In any event, defended body weight level is evidently not deter-

**Context** Weight loss elicits physiological adaptations relating to energy intake and expenditure that antagonize ongoing weight loss.

**Objective** To test whether dietary composition affects the physiological adaptations to weight loss, as assessed by resting energy expenditure.

**Design, Study, and Participants** A randomized parallel-design study of 39 overweight or obese young adults aged 18 to 40 years who received an energy-restricted diet, either low–glycemic load or low-fat. Participants were studied in the General Clinical Research Centers of the Brigham and Women's Hospital and the Children's Hospital, Boston, Mass, before and after 10% weight loss. The study was conducted from January 4, 2001, to May 6, 2003.

**Main Outcome Measures** Resting energy expenditure measured in the fasting state by indirect calorimetry, body composition by dual-energy x-ray absorptiometry, cardiovascular disease risk factors, and self-reported hunger.

**Results** Resting energy expenditure decreased less with the low–glycemic load diet than with the low-fat diet, expressed in absolute terms (mean [SE], 96 [24] vs 176 [27] kcal/d; $P=.04$) or as a proportion (5.9% [1.5%] vs 10.6% [1.7%]; $P=.05$). Participants receiving the low–glycemic load diet reported less hunger than those receiving the low-fat diet ($P=.04$). Insulin resistance ($P=.01$), serum triglycerides ($P=.01$), C-reactive protein ($P=.03$), and blood pressure ($P=.07$ for both systolic and diastolic) improved more with the low–glycemic load diet. Changes in body composition (fat and lean mass) in both groups were very similar ($P=.85$ and $P=.45$, respectively).

**Conclusions** Changes in dietary composition within prevailing norms can affect physiological adaptations that defend body weight. Reduction in glycemic load may aid in the prevention or treatment of obesity, cardiovascular disease, and diabetes mellitus.

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mined by endogenous mechanisms exclusively, as demonstrated by the increasing mean body mass index (BMI, calculated as weight in kilograms divided by the square of height in meters) among genetically stable populations observed in recent years.[11] Thus, body weight settling point may best be conceptualized as representing the integrated influences of numerous genetic, behavioral, and environmental factors.[1]

Previously, the novel dietary factor glycemic load has been proposed to play a role in body weight regulation based on experimental and theoretical grounds.[12,13] Glycemic load (glycemic in-

dex × carbohydrate amount) is a validated measure of the increase of blood glucose following a meal.[14] A high–glycemic load diet appears to elicit hormonal changes that limit availability of metabolic fuels in the postprandial period, stimulating hunger and voluntary food intake.[12,13,15] Several short-term or small-scale studies have reported increased body weight and/or fat loss on low–glycemic index/glycemic load diets compared with control diets, although the clinical relevance of these findings remains the subject of debate.[16,17] Recently, we examined the effects that glycemic load has on REE in 10 overweight young men.[18] After 1 week consuming energy-restricted diets providing 50% of predicted total energy requirements, REE decreased by 10.5% on the high–glycemic load diet compared with 4.6% on the low–glycemic load diet ($P$=.04).

The goal of this study was to determine whether dietary composition can influence the physiological adaptations of a weight-reducing diet, as assessed by REE. To test this hypothesis, we studied 2 energy-restricted diets with large differences in glycemic load. Because glycemic load has been linked to risk for heart disease in epidemiological studies, we also examined several conventional and novel cardiovascular disease risk factors as secondary end points.

## METHODS

### Overview

We randomly assigned 46 participants to low–glycemic load or low-fat diet groups using a parallel-design study, which was performed at the General Clinical Research Centers of the Brigham and Women's Hospital and the Children's Hospital in Boston, Mass, and conducted from January 4, 2001, to May 6, 2003. The participants were given a standard weight–maintaining diet during a 9-day run-in period and then were admitted to a metabolic unit for 3 days to obtain baseline measurements. The food preparation, inpatient stays, and most data collection were performed at the Brigham and Women's Hospital, while

the body composition analysis and laboratory assay of C-reactive protein were performed at the Children's Hospital. At discharge, participants began the experimental or control diets, providing 60% of predicted energy requirements. After achieving a 10% reduction in body weight, participants were readmitted for 5 days to obtain final measurements of study end points (during active weight loss on the low-glycemic load and low-fat diets). All foods, for both inpatient and outpatient phases, were prepared in a metabolic kitchen. Ethics approval for human subjects research was provided by institutional review boards at both hospitals. All participants gave written informed consent before enrollment.

### Participants

Participants were recruited primarily through posted fliers and newspaper advertisements in the Boston metropolitan area. Inclusion criteria were assessed by telephone, an inperson interview, and a physician-conducted physical examination. Participants meeting the following criteria were included in the study: aged between 18 and 40 years; BMI of at least 27 and weight of less than 135 kg (<300 lb); change in body weight of less than 10% during the past year; good general health; no medical conditions or medications that might affect body weight, appetite, or energy expenditure; nonsmoker; not regularly engaged in heavy/vigorous physical activities; normal laboratory screening test results, including complete blood cell count, serum electrolytes, thyroid-stimulating hormone, blood glucose, glycosylated hemoglobin, urinalysis, and liver functions (alanine aminotransferase up to twice normal limit, suggestive of fatty liver, acceptable); not currently following a special diet; no history of an eating disorder; no allergies or aversions to foods on the study menu; not taking dietary supplements; willing to abstain from alcohol consumption for duration of study; and able to come to research unit on a daily basis to obtain study foods. In addition, the following inclusion criteria applied to women: not pregnant

**Figure 1.** Participant Flow Diagram
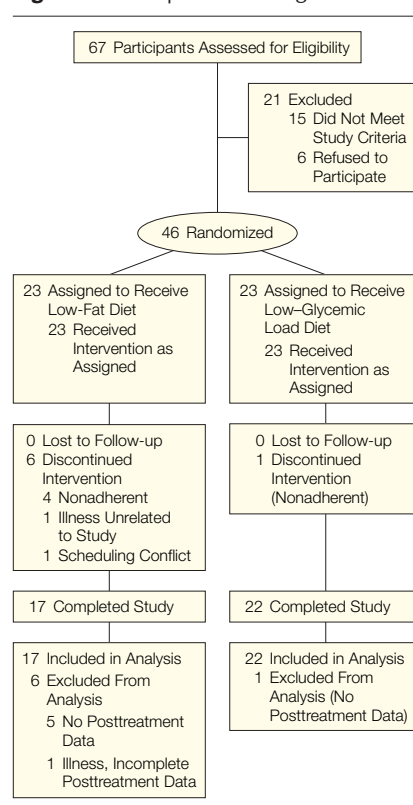


during the last year, no plans to become pregnant in the next year, not lactating, and not taking birth control pills. To characterize the diversity of the participant population, race/ethnicity was classified by the participants according to investigator-defined options. All participants were paid US $1500 on completion of the study.

We assessed 67 individuals for eligibility; 46 were enrolled in the study and randomly assigned to 1 of 2 diet groups (n=23 in both the low–glycemic load and low-fat diet groups) (**FIGURE 1**). One participant from the low–glycemic load group and 6 from the low-fat group did not complete the study, for an overall retention rate of 85%. Five of these noncompleters (1 in low–glycemic load group and 4 in low-fat group) did not comply with the intervention as evidenced by inability to achieve the target weight loss goal of 2.5% weight loss per month despite intensive behavioral counseling by the dietitians. One participant (low-fat group) dropped out

of the study due to work-related scheduling difficulties. One additional participant (low-fat group) developed an acute febrile illness with vomitting during the post-weight loss admission. The characteristics of the remaining participants are shown in TABLE 1. The 7 noncompleters did not differ from the completers in age (mean [SD], 30.5 [5.76] years for completers vs 33.1 [5.90] years for noncompleters; P=.26) or in REE (1509 [240] vs 1567 [347] kcal/d; P=.58) but the noncompleters did have higher baseline BMI (33.2 [4.59] vs 42.3 [6.03]; P<.001).

## Diets

TABLE 2 lists the macronutrient and micronutrient composition of the run-in, low–glycemic load, and low-fat diet groups, and TABLE 3 lists a representative day's menu from the low–glycemic load and low-fat groups. All participants received the same run-in diet before and during the first inpatient admission. This diet, resembling a "typical" US diet,[19] was intended to stabilize body weight and provide the same nutrient profile to participants in both groups before collection of baseline clinical end points. The low-fat diet was low in fat, high in carbohydrate and glycemic load, and generally consistent with National Cholesterol Education Program guidelines for a heart healthy diet.[20] This diet satisfied recommendations for servings of whole grain products, fruits and vegetables, and saturated fat and cholesterol. The low–glycemic load diet was designed to be as low in glycemic load as possible, while providing more than ample carbohydrate to prevent ketosis. Glycemic load was reduced by modifications of both the amount and type of carbohydrate. Thus, some high–glycemic index carbohydrate in the low-fat diet (eg, conventional bread, instant oatmeal, corn) was replaced with food that had other macronutrients (eg, cheese, soy, vegetable oil) or a low glycemic index (eg, whole kernel bread, steel-cut oats, pasta). Mean daily predicted glycemic load was calculated as grams of available carbohydrate × glycemic index (using white bread as 100%) and summed over all foods.

Total energy intake for the low–glycemic load and low-fat groups was 60% of energy requirements, with a minimum of 1100 kcal/d. We calculated energy requirement from REE and an activity factor.[21] Resting energy expenditure was determined before beginning the di-

**Table 1.** Baseline Characteristics of the Patients by Dietary Treatment Group*

| Characteristics | Low-Fat Diet Group (n = 17) | Low–Glycemic Load Diet Group (n = 22) |
|---|---|---|
| Age, y | 32.6 (4.3) | 28.8 (6.3) |
| Women, No. (%) | 13 (76.5) | 17 (77.3) |
| Race, No. (%) | | |
| White | 8 (47.0) | 13 (59.1) |
| Black | 5 (29.4) | 4 (18.2) |
| Latino | 3 (17.6) | 4 (18.2) |
| Other | 1 (6.0) | 1 (4.5) |
| Body weight, kg | 92.2 (15.4) | 91.0 (13.6) |
| Body fat, % | 38.4 (6.2) | 39.4 (7.1) |
| REE, kcal/d | 1513 (287) | 1507 (203) |
| Fasting glucose, mg/dL | 88.7 (3.7) | 88.9 (6.2) |
| Fasting insulin, μIU/mL | 6.6 (3.9) | 6.8 (3.5) |
| Serum levels, mg/dL† | | |
| Fasting triglycerides | 92.4 (29.9) | 78.3 (32.5) |
| HDL-C | 49.4 (14.8) | 46.9 (9.1) |
| LDL-C | 124.3 (32.7) | 138.7 (39.2) |
| Blood pressure, mm Hg | | |
| Systolic | 107 (8.0) | 110 (14.2) |
| Diastolic | 68 (6.2) | 69 (9.7) |
| C-reactive protein, mg/dL | 0.19 (0.22) | 0.28 (0.30) |

Abbreviations: HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; REE, resting energy expenditure.
SI conversions: To convert fasting glucose to mmol/L, multiply by 0.0555; insulin to pmol/L, multiply by 6.945; fasting triglycerides to mmol/L, multiply by 0.0113; and HDL-C and LDL-C to mmol/L, multiply by 0.0259.
*Data are presented as mean (SD) unless otherwise specified.
†For low-fat diet group, n=11; and for low–glycemic load diet group, n=14.

**Table 2.** Composition of the Average Run-in, Low-Fat, and Low–Glycemic Load Diet Groups

| Nutrients | Run-in Diet (N=39) | Low-Fat Diet Group (n = 17) | Low–Glycemic Load Diet Group (n = 22) |
|---|---|---|---|
| Relative energy, % of energy needs | 100 | 60 | 60 |
| Standard energy level, kcal/d* | 2600 | 1500 | 1500 |
| Glycemic index† | 89 | 82 | 50 |
| Glycemic load‡ | 287 | 205 | 82 |
| Carbohydrate, % total kcal | 49 | 65 | 43 |
| Protein, % total kcal | 14 | 17 | 27 |
| Fat, % total kcal | | | |
| Total | 37 | 18 | 30 |
| Polyunsaturated | 7 | 4.3 | 7.6 |
| Monounsaturated | 13 | 6.1 | 9.7 |
| Saturated | 16 | 5.6 | 8.7 |
| Cholesterol, mg/d | 233 | 166 | 257 |
| Dietary fiber, g/d | 13 | 20 | 32 |
| Calcium, mg | 527 | 633 | 930 |
| Magnesium, mg | 205 | 272 | 298 |
| Potassium, mg | 2051 | 2476 | 2666 |
| Sodium, mg | 3503 | 2072 | 2627 |

*Energy level varied by study participant depending on individual energy needs, as described in the "Methods" section.
†Calculated as the weighted average glycemic index of all the carbohydrate-containing foods in the diet.
‡Calculated as each food's carbohydrate amount (grams) × the respective glycemic index value and divided by 100, then summed over all foods from each menu.

ets using the Harris Benedict equation[21] and during the first inpatient stay by indirect calorimetry. For most participants, these methods yielded results within 10% and the value obtained from the Harris Benedict equation was used throughout the study; for 3 participants, energy requirements were adjusted within the first week of the weight loss diet according to data obtained by indirect calorimetry.

For the run-in diet, we created a 3-day menu cycle, and for the low–glycemic load and low-fat diet groups, a 7-day menu cycle (calculated with Food Processor version 7.9, ESHA Research, Salem, Ore). Percentage of calories at meals was distributed as 25% breakfast, 30% lunch, 30% dinner, and 15% snack. The macronutrient ratio for each meal was similar within each diet. Investigators and staff participated in extensive quality control and taste testing procedures until all meals for low–glycemic load and low-fat groups were of acceptable appeal with respect to appearance and palatability. All recipes were standardized for production consistency and individual foods were weighed to within 0.5 g. Care was taken in preparing foods to minimize changes that might affect glycemic index, such as cooking times, reheating, freezing, or overripening.

Participants were required to eat only the food provided and to consume 1 meal (lunch) onsite Monday through Friday. The remainder of the day's food was provided as take-home meals. Weekend food was provided in its entirety. Spatulas to clean out all dishes were provided for participants at home and at the feeding site. A dietitian or nutrition assistant was present throughout mealtime to monitor and facilitate adherence. Special attention was given to participants who had difficulty following the diet. Participants were encouraged to consume their meals at regularly scheduled times throughout the day and to not skip mealtimes. Participants

**Table 3.** Sample Menus for the Low-Fat and Low–Glycemic Load Diet Groups*

| Low-Fat Diet Group | | | | Low–Glycemic Load Diet Group | | | |
|---|---|---|---|---|---|---|---|
| Food | Weight, g | Glycemic Index | Glycemic Load | Food | Weight, g | Glycemic Index | Glycemic Load |
| **Breakfast** | | | | | | | |
| Instant oatmeal | 48.6 | 117 | 30.9 | Steel-cut oats | 22.4 | 50 | 7.7 |
| Dextrose powder | 4.5 | 141 | 6.2 | Fructose | 5.1 | 27 | 1.4 |
| Skim milk (low lactose) | 106.9 | 60 | 3.1 | 2% Milk | 118.2 | 42 | 2.6 |
| Raisins | 14.9 | 91 | 10.7 | Blueberries | 41.6 | 57 | 2.9 |
| Turkey sausage links | 37.4 | 0 | 0 | Soy sausage links | 65.7 | 20 | 0.8 |
| Butter | 4.5 | 0 | 0 | Half & half cream | 2.5 | 38 | 1.0 |
| Orange juice | 119.6 | 81 | 10.3 | | | | |
| **Lunch** | | | | | | | |
| Grapefruit juice | 93.4 | 69 | 5.8 | Grapefruit sections | 109.4 | 36 | 3.2 |
| Chicken breast meat | 26.2 | 0 | 0 | Chicken breast meat | 51.1 | 0 | 0 |
| Refried beans | 59.8 | 64 | 5.4 | Three-bean salad | 109.4 | 68 | 10.7 |
| Tomato salsa | 37.4 | 54 | 2.0 | Cracked wheat bread | 19.0 | 79 | 6.1 |
| Yellow corn kernels | 62.0 | 67 | 8.6 | 2% Milk | 109.4 | 42 | 2.4 |
| Tortilla chips | 28.4 | 97 | 23.3 | Low–glycemic index custard | 57.6 | 28 | 2.7 |
| High–glycemic index custard | 86.0 | 85 | 13.6 | Butter | 2.9 | 0 | 0 |
| Butter | 5.2 | 0 | 0 | | | | |
| **Dinner** | | | | | | | |
| White tuna | 38.9 | 0 | 0 | White tuna | 37.9 | 0 | 0 |
| Whole wheat bread | 41.9 | 101 | 19.5 | Three-grain bread | 82.4 | 58 | 15.9 |
| Light mayonnaise | 11.2 | 0 | 0 | Lentil walnut salad | 100.6 | 41 | 4.7 |
| Iceberg lettuce | 26.2 | 0 | 0 | Light mayonnaise | 10.2 | 0 | 0 |
| Tomato slices | 26.2 | 0 | 0 | 2% Milk | 81.7 | 42 | 1.8 |
| Couscous with broccoli | 183.1 | 83 | 26.4 | 1% Cottage cheese | 78.0 | 34 | 0.7 |
| Peaches, syrup | 112.1 | 83 | 18.6 | Peaches in juice | 54.7 | 54 | 3.4 |
| **Snack** | | | | | | | |
| Yogurt, nonfat | 164.4 | 34 | 5.9 | Yogurt, nonfat | 122.5 | 34 | 3.9 |
| Graham crackers | 14.9 | 84 | 9.6 | Peanuts | 8.8 | 21 | 0.4 |
| Peanut butter, reduced fat | 9.0 | 55 | 1.6 | Soybean nuts | 20.4 | 20 | 1.3 |
| Grapes | 6.8 | 66 | 4.0 | Strawberries | 43.8 | 57 | 2.3 |

*The mean glycemic index (for the day shown) for the low-fat diet group was 83 and for the low–glycemic load diet group, 47; the total glycemic load (for the day shown) for the low-fat diet group was 206 and for the low–glycemic load diet group, 76. Data for entire diets are shown in Table 2.

were allowed to consume selected non-caloric beverages ad libitum and caffeinated beverages up to 3 servings per day, but were not allowed any alcoholic drinks. To minimize the likelihood of micronutrient deficiencies or marked micronutrient differences between the low–glycemic load and low-fat diet group, each participant was provided a daily multivitamin.

Emergency meals were provided for use in the event of unexpected situations (eg, severe weather) that might prevent participants from coming to the on-site meal. Emergency bars consistent with diet assignment (low–glycemic load diet: apple cinnamon crunch [Zone Perfect, The ZonePerfect Nutrition Co, Columbus, Ohio]; low-fat diet: apple cinnamon [PowerBar Performance, PowerBar, Berkeley, Calif]) were also provided to participants in the event of extreme hunger, to minimize deviations from dietary prescription.

The low–glycemic load and low-fat diets were designed to produce 10% weight loss during a 6- to 10-week period if no other foods were consumed. We provided the participants with daily logs for recording instances of nonadherence to the diet, as well as any adverse effects, hunger levels, or exercise bouts. This information was used in conjunction with changes in body weight to evaluate adherence on an ongoing basis throughout the trial. The dietitians provided behavioral support and encouragement on a daily basis, and special attention was given to the few participants whose weight loss did not meet expectations.

## Data Collection

Before enrollment, height and weight measurements were performed by a calibrated balance beam scale and physical activity level was assessed using a modified version of the Seven-Day Physical Activity Questionnaire.[22] Body composition (fat and lean mass) was measured before beginning the weight-reducing diet and again after weight loss by dual-energy x-ray absorptiometry using Hologic instrumentation (Model QDR 4500, Hologic, Waltham, Mass).

During the outpatient run-in period before the baseline admission, and during the outpatient weight loss phase between clinic admissions, participants arrived in clinic at noon for measurement of body weight to complete a daily questionnaire and eat the lunch meal. Daily body weight was measured before the lunch meal, with participants wearing light clothing, shoes removed, and pockets emptied. Daily weight measurements were used to track the progress of the participants toward their goal of 10% weight loss, and served as the criterion measure for dietary adherence. In response to the question, "How hungry have you been over the past 24 hours?" which was asked before lunch, participants circled a number from 1 to 10, with 1 corresponding to "not hungry at all" and 10 corresponding to "extremely hungry." In response to the question, "How hungry are you right now?" which was asked before lunch, participants made a single vertical mark on a 10-cm line anchored to the left by the text "not hungry at all" and on the right by the text "extremely hungry." A more in-depth questionnaire was completed weekly to assess adverse effects and medical problems.

Participants were admitted to the General Clinical Research Center as inpatients at baseline and after achieving 10% weight loss. When possible, admissions for women were scheduled during the same menstrual cycle phase (follicular) to minimize potential confounding of metabolic end points. On 3 mornings of the admission, participants were awakened by a nurse between 6:00 and 6:30 AM. The participants were instructed to empty their bladder and then were weighed (always with the same scale) wearing a light hospital gown and no footwear. Subsequently, REE was measured by indirect calorimetry (Deltatrac I, SensorMedics Corp, Yorba Linda, Calif) with participants awake and lying quietly in bed. Room temperature was maintained at a constant level for participant comfort, and lighting and noise were kept to a minimum during calorimetry. The calorimeter barometer and

gas analyzers were calibrated immediately before each test according to recommendations by the manufacturer. For each of the 3 days, REE was computed as the mean energy expenditure value of minutes 11 though 30. The mean of the 3 daily values was then taken as the best REE estimate for each participant (day-to-day coefficient of variation [CV], 5.6% [84 kcal] at baseline and 4.1% [54 kcal] posttreatment).

Blood pressure (BP) was measured and blood samples were obtained following calorimetry but before the breakfast meal, with participants in the fasting state. Blood pressure was obtained in the right arm after participants were seated quietly for 5 minutes with feet flat on the floor. Three BP readings were taken by a nurse with an automated unit (Dinamap, Criticon Inc, Tampa, Fla). The first reading was disregarded and the second 2 readings were averaged. Blood was drawn from the antecubital vein into plain vacutainers and centrifuged within 30 minutes, then the serum was stored in cryovials at −80°C until the assays were performed in batches. Pre–weight loss and post–weight loss samples for each participant were included in the same assay run to avoid interassay variability within participants. Blood was drawn in the fasting state on 3 successive mornings for glucose and insulin and on 2 mornings (first and third) for lipids and C-reactive protein. Assay results and BP for these multiple days were averaged within person to minimize intraindividual variability.

To describe the effect of the 2 treatment meals (breakfast) on postprandial blood glucose and insulin, we sampled blood via an indwelling catheter in the antecubital vein every 30 minutes for 3 hours following the meal on the last day of the inpatient stay. The incremental areas under the curve for glucose and insulin were calculated by the trapezoidal rule.[23]

All secondary end points were obtained from all completers, with the exception of serum lipids, which were measured in the first 25 participants. An ACE hexokinase assay (Alfa Wasserman, West Caldwell, NJ) with a within-

assay CV of less than 1% was used for serum glucose. The Beckman ultrasensitive immunoassay (Fullerton, Calif) was used for insulin (CV, approximately 2%). Serum C-reactive protein concentration was measured on a high-sensitivity immunoturbidimetric assay on a Hitachi 911 analyzer (Roche Diagnostics, Indianapolis, Ind) with reagents and calibrators from Denka Seiken (Niigata, Japan) (CV, approximately 2%). An automated Olympus analyzer (Melville, NY) was used to measure total cholesterol, high-density lipoprotein cholesterol, and triglyceride levels (CV, approximately 1%). Low-density lipoprotein cholesterol was calculated by the Friedewald formula.[24] The homeostasis model for insulin resistance was calculated as glucose (mmol/L) $\times$ insulin (µIU/mL) divided by 22.5.[25]

### Randomization, Masking, and Statistical Analysis

Before participant enrollment, dietary treatment group (low–glycemic load vs low-fat) sequence was randomly generated by computer. Randomization was blocked by sex. Envelopes were prepared separately for male and female participants, numbered sequentially beginning with 1, enclosed with dietary group assignment, and sealed until randomization. During the baseline admission before weight loss, the envelope corresponding to the participant's sex and enrollment number was opened by the bionutrition manager of the General Clinical Research Center. Only the dietary staff was privy to the participant-treatment assignments. Study personnel who measured the main process measure (body weight) and the main end point (REE) were masked to the diet group assignment of the participants, and these data were collected in an objective fashion (eg, digital reading from an electronic instrument). Other personnel could not be masked in this fashion because of obvious differences in meal appearance. Participants also could not be masked, although they were not informed of the study's hypotheses.

**Figure 2.** Body Weight for Each Participant at Baseline and Post-Diet for the Low-Fat and Low–Glycemic Load Diet Groups
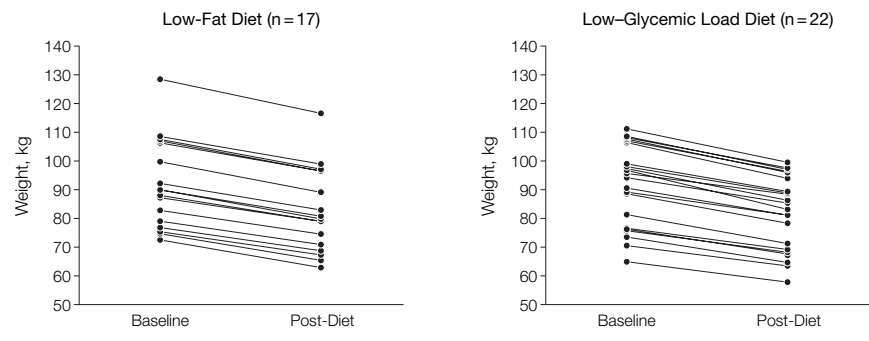


We used general linear models (SAS PROC GLM, SAS Institute Inc, Cary, NC) to test the effect of dietary treatment (independent variable) on change in REE and cardiovascular disease risk factors (dependent variables). We adjusted end points for baseline values using analysis of covariance, as recommended by Laird,[26] to avoid potential bias that might result if the magnitude of change depended on starting point. Additional analyses of posttreatment data, rather than change or percent change data, adjusted for baseline yielded similar results in most cases. Although we also included sex as a covariate in the models, we were unable to test treatment $\times$ sex interactions because only 9 men were enrolled in the study. Results are presented as adjusted means (SE), with statistical significance set at $P \le .05$.

Because our goal was to compare the effect of these diets on the metabolic adaptations with 10% weight loss, we did not attempt to assess follow-up outcomes in the 7 noncompleters. We have no reason to believe that the noncompleters would differ from the completers in any way that would bias our primary end point in the hypothesized direction. If any bias did exist, we speculate that individuals with the greatest decrease in REE would be less likely to complete the study, an effect that would favor the null hypothesis, as there were more noncompleters in the low-fat group than in the low–glycemic load group. However, to address this issue in intention-to-treat models, we used 2 different strategies to impute REE change scores for the noncompleters: 14% decrease in REE as reported by Leibel et al[6] following 10% weight loss in obese participants, and 8.3% decrease in REE that was equal to the overall mean response from the 39 completers.

Sample size for the study was based on the mean (SD) difference between treatments in a previous study (−51 [74] kcal/d for low–glycemic index and −175 [146] kcal/d for high–glycemic index).[18] Forty-six participants (23 per group) were estimated to provide 80% power to detect a difference between diets in REE of 125 kcal/d with $\alpha = .05$.

## RESULTS

The 2 weight loss diets differed as intended in their effect on postprandial glycemia and insulinemia. Incremental area under the curves for glucose (mean [SE], 2706 [394] vs 1070 [336] mg/dL per minute, $P = .003$) and insulin (5581 [859] vs 2044 [733] µIU/mL per minute, $P = .003$) were more than 2-fold greater for test meals from the low-fat vs low–glycemic load diet groups, respectively.

Per study design, all participants who completed the protocol lost approximately 10% of their initial body weight (**FIGURE 2**). The mean (SE) time between the baseline and post–weight loss clinic visits was 69.4 (3.8) days for low-fat and 65.2 (3.3) days for low–glycemic load groups ($P = .41$ for treatment effect). Individual rates of weight loss were nonsignificantly greater in the low–glycemic load compared with the low-fat groups (1.09 [0.05] vs 0.99

[0.05] kg/wk, $P$=.19). Changes in body weight and composition in both groups were very similar (TABLE 4). We observed no difference in physical activity, based on daily exercise logs describing type, frequency, and duration, during the course of the trial between the 2 groups (101 [9.1] vs 94 [10.4] min/wk for low–glycemic load and low-fat, respectively, $P$=.64).

Resting energy expenditure decreased less in the low–glycemic load group compared with low-fat group following weight loss, whether expressed in absolute terms (mean [SE], 96 [24] vs 176 [27] kcal/d, $P$=.04) (FIGURE 3) or as a proportion (5.9% [1.5%] vs 10.6% [1.7%], $P$=.05). These findings were not materially affected by adjustment for baseline BMI, body composition, or time to achieve target weight loss. Intention-to-treat analyses based on imputing values for the 7 noncompleters did not materially alter these findings ($P$≤.05 for both models).

Participants in the low–glycemic load group reported less hunger than those in the low-fat group in response to the question, asked each day before lunch, "How hungry have you been over the past 24 hours?" (mean [SD], 3.3 [0.28] vs 4.2 [0.3] units; $P$=.04). A nonsignificant difference in the same direction was observed in response to the question, "How hungry are you right now?" (mean [SD], 3.6 [0.33] vs 4.5 [0.38] units; $P$=.10).

Effects of dietary treatment on measures of cardiovascular disease risk with weight loss are shown in TABLE 5. Insulin resistance, as assessed by homeostasis model assessment (HOMA) score, decreased by more than twice as much with weight loss in the low–glycemic load vs the low-fat group ($P$=.01). Serum concentrations of triglyceride levels also decreased more in the low–glycemic load vs the low-fat group ($P$=.01). No group differences were observed for changes in low-density lipoprotein or high-density lipoprotein cholesterol with weight loss. C-reactive protein declined by nearly 50% with weight loss in the low–glycemic load group but remained essentially unchanged in the low-fat group ($P$=.03 for

dietary treatment effect). There was a trend toward larger decrease in both systolic ($P$=.07) and diastolic ($P$=.07) BPs in the low–glycemic load vs the low-fat group; mean arterial BP declined more in the low–glycemic load group ($P$=.04).

## COMMENT

The primary finding of our study was that physiological adaptations that serve to defend baseline body weight can be modified by dietary composition. The REE declined by 80 kcal/d less and hunger was less on the low–glycemic load diet vs the low-fat diet during weight loss, similar to results from a prior short-term study.[18] In addition, the low–glycemic load diet studied here produced favorable changes in insulin resistance, lipids, chronic inflammation, and BP compared with a conventionally recommended diet that was lower in saturated fat, cholesterol, and sodium. We found no evidence to support a previous hypothesis derived from analysis of nitrogen balance that high–glycemic index, energy-restricted diets would have adverse effects on body composition,[18] although our study may not be of sufficient length to adequately examine this question.

Two methodological issues warrant discussion. First, to maximize differences in glycemic load, we did not control for macronutrient composition; therefore, the question arises as to whether any conventionally recognized effect of macronutrient composition could explain the study's primary finding. The increase in energy expenditure during the postprandial state, termed the *thermic effect of food*, is greater for protein than for carbohydrate or fat. However, the REE was measured in our study after a fast of more than 10 hours, eliminating the possibility of confounding by the thermic effect of food. Diets with different protein content might also alter REE through effects on lean body mass. However, changes in body composition as assessed by dual-energy x-ray absorptiometry scan were not different among participants who were treated with the low–glycemic load vs the low-

**Table 4.** Weight Loss and Body Composition by Dietary Treatment Group

| | Mean (SE) Adjusted for Baseline Values | | |
| | Low-Fat Diet Group (n = 17) | Low–Glycemic Load Diet Group (n = 22) | *P* Value |
| --- | --- | --- | --- |
| Final weight, kg | 82.1 (0.3) | 81.9 (0.3) | .75 |
| Weight loss, kg | 9.5 (0.3) | 9.6 (0.3) | .75 |
| Weight loss, % | 10.5 (0.3) | 10.5 (0.3) | .93 |
| Final lean mass, kg | 50.1 (0.3) | 50.5 (0.3) | .45 |
| Final fat mass, kg | 28.8 (0.6) | 28.7 (0.5) | .85 |

**Figure 3.** Resting Energy Expenditure (REE) for Each Participant at Baseline and Post-Diet for the Low-Fat and Low–Glycemic Load Diet Groups
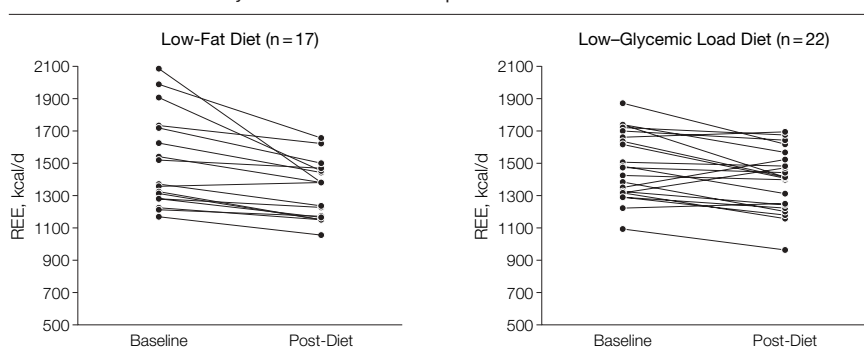
fat diet, and adjustment for change in body composition did not alter the REE effect. Of particular significance, differences in dietary protein of the same or greater magnitude as that used in our study did not result in any differences in REE, either following weight maintenance or weight loss, in 5 previous articles.[27-31]

A second methodological issue is that measurement of REE was made during ongoing weight loss. The magnitude of observed effect could change with weight stabilization and additional research is needed to assess this possibility. Nevertheless, the physiological adaptations that occur during active weight loss may be especially relevant to understanding why most obese individuals become noncompliant with conventional energy-restricted diets long before a normal body weight has been reached. Indeed, diet-induced differences in REE were observed after our participants had lost less than half of their excess adiposity, and after just 1 week of energy restriction in a previous study.[18]

The difference in REE is too small to account for any significant change in body composition over the short term. For example, 80 kcal/d over 10 weeks (5600 kcal) would amount to less than 1 kg of body weight. Thus, our study does not support claims that popular diets can cause rapid weight loss by inducing major shifts in energy metabolism.

Nevertheless, the REE difference here could amount to several pounds of weight change per year, given this effect would persist over the long term. For comparative purposes, an energy balance of –80 kcal/d could be obtained by walking approximately 1 mile/d or by decreasing sugar-sweetened soft drink consumption 6 oz/d. Indeed, this difference (560 kcal/wk) would explain most of the mean difference in rate of weight loss between groups (0.09 kg/wk × 7500 kcal/kg = 675 kcal/wk).

A potentially more important question is whether the magnitude of change in REE during weight loss would predict likelihood of achieving and maintaining clinically significant weight loss. Some studies[32,33] but not all[34] suggest an inverse relationship between REE and weight gain or regain. An individual experiencing a larger decline in REE during weight loss may feel more fatigued, cold, and hungry than an individual experiencing a small decline, and these symptoms may make compliance with dietary energy restriction increasingly difficult over time.

The physiological mechanisms relating dietary composition to REE during weight loss remain speculative but may involve altered availability of metabolic fuels. Blood glucose and free fatty acids are reduced in the postabsorptive phase following a high– vs low–glycemic index meal, and this reduction can be sufficient in magnitude to trigger release of

stress hormones.[12] Low circulating concentrations of metabolic substrate might directly impair energy metabolism at the cellular level, as occurs with frank hypoglycemia.[35] Alternatively, the decrease in REE may come from neuroendocrinological adaptations designed to conserve energy, involving thyroid hormone, growth hormone, sex hormones, or leptin (an adipocyte-derived factor that acts in the hypothalamus)[3,5]; lack of data on these hormones comprises a limitation of our study. Interestingly, rodents treated with nutrient-controlled high–glycemic index diets compared with low–glycemic index diets demonstrate an increase in metabolic efficiency analogous to that observed by our participants taking the low-fat (high–glycemic index) diet.[36]

Epidemiological analyses have found associations between glycemic load and high triglycerides, low high-density lipoprotein cholesterol, and elevated C-reactive protein levels.[37] In 1 study,[38] individuals in the highest vs lowest quintile of glycemic load had double the risk of developing heart disease, after controlling for potentially confounding factors. However, these effects have not previously been examined in interventional studies. We found that during weight loss, a diet focused on glycemic load reduction produced greater improvements in several important cardiovascular disease–related and diabetes mellitus–related end points than a

**Table 5.** Cardiovascular Disease Risk Factors Before and After 10% Weight Loss by Dietary Treatment Group

| | Mean (SE) | | | | | | |
|---|---|---|---|---|---|---|---|
| | Low-Fat Diet Group (n = 17) | | | Low–Glycemic Load Diet Group (n = 22) | | | |
| | Baseline | Posttreatment | % Change (Adjusted) | Baseline | Posttreatment | % Change (Adjusted) | P Value* |
| HOMA score | 1.45 (0.20) | 1.10 (0.13) | –15.8 (5.13) | 1.50 (0.18) | 0.97 (0.11) | –33.9 (4.51) | .01 |
| Triglycerides, mg/dL† | 92.4 (9.47) | 102.3 (8.11) | 16.2 (5.24) | 78.3 (8.40) | 72.4 (7.19) | –3.5 (4.63) | .01 |
| HDL-C, mg/dL† | 49.4 (3.61) | 44.1 (2.41) | –8.1 (3.49) | 46.9 (3.20) | 42.2 (2.14) | –8.9 (3.09) | .87 |
| LDL-C, mg/dL† | 124.3 (9.86) | 104.6 (9.73) | –15.0 (4.12) | 138.7 (9.75) | 115.9 (8.63) | –16.1 (3.65) | .84 |
| C-reactive protein, mg/dL | 0.19 (0.06) | 0.13 (0.04) | –5.1 (13.61) | 0.28 (0.06) | 0.10 (0.03) | –47.7 (11.94) | .03 |
| Systolic BP, mm Hg | 107.5 (2.90) | 104.6 (2.35) | –3.1 (1.32) | 110.4 (2.55) | 102.3 (2.06) | –6.4 (1.16) | .07 |
| Diastolic BP, mm Hg | 67.8 (2.03) | 66.2 (1.80) | –2.5 (1.61) | 69.2 (1.78) | 64.2 (1.58) | –6.5 (1.42) | .07 |
| Mean arterial pressure, mm Hg | 94.1 (2.48) | 91.7 (2.03) | –3.0 (1.27) | 96.6 (2.18) | 89.5 (1.78) | –6.5 (1.12) | .04 |

Abbreviations: BP, blood pressure; HDL-C, high-density lipoprotein cholesterol; HOMA, homeostasis model assessment; LDL-C, low-density lipoprotein.
SI conversions: To convert HDL-C and LDL-C to mmol/L, multiply by 0.0259; triglycerides to mmol/L, multiply by 0.0113.
*Effect of dietary treatment on % change.
†For low-fat diet group, n=11; for low–glycemic load diet group, n=14.

diet focused on reduction of total and saturated fat in accordance with conventional practice. We speculate that these improvements were caused by reduction in insulin concentration; hyperinsulinemia plays a critical role in development of the insulin resistance syndrome (metabolic syndrome) consisting of hypertension, dyslipidemia, chronic inflammation, and other heart disease risk factors in the setting of central obesity.[39] Our participants did not have the metabolic syndrome at baseline (Table 1), sample size was relatively small, the study was of relatively short duration, and all meals were prepared in a metabolic kitchen; therefore, the generalizability of these findings requires further study.

In conclusion, we found that the physiological adaptations to a weight-reducing diet thought to antagonize ongoing weight loss, involving energy expenditure and hunger, can be modified by dietary composition. In addition, the low–glycemic load diet had beneficial effects on several obesity-related risk factors compared with a low-fat diet that was consistent with current nutritional guidelines. Incorporation of glycemic load principles into current dietary guidelines may aid in the treatment of obesity and prevention of cardiovascular disease and diabetes mellitus, a possibility that warrants evaluation in long-term randomized controlled trials.

**Author Contributions:** Dr Ludwig had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
*Study concept and design:* Pereira, Swain, Ludwig.
*Acquisition of data:* Pereira, Swain, Goldfine, Rifai, Ludwig.
*Analysis and interpretation of data:* Pereira, Swain, Goldfine, Rifai, Ludwig.
*Drafting of the manuscript:* Pereira, Swain, Ludwig.
*Critical revision of the manuscript for important intellectual content:* Pereira, Swain, Goldfine, Rifai, Ludwig.
*Statistical analysis:* Pereira.
*Obtained funding:* Pereira, Ludwig.
*Administrative, technical, or material support:* Pereira, Swain, Rifai.
*Study supervision:* Pereira, Swain, Ludwig.

## REFERENCES

1. Harris RB. Role of set-point theory in regulation of body weight. *FASEB J*. 1990;4:3310-3318.
2. Hirsch J, Hudgins LC, Leibel RL, Rosenbaum M. Diet composition and energy balance in humans. *Am J Clin Nutr*. 1998;67(suppl 3):S551-S555.
3. Ahima RS, Prabakaran D, Mantzoros C, et al. Role of leptin in the neuroendocrine response to fasting. *Nature*. 1996;382:250-252.
4. Schwartz MW, Seeley RJ. Seminars in medicine of the Beth Israel Deaconess Medical Center: neuroendocrine responses to starvation and weight loss. *N Engl J Med*. 1997;336:1802-1811.
5. Chan JL, Heist K, DePaoli AM, et al. The role of falling leptin levels in the neuroendocrine and metabolic adaptation to short-term starvation in healthy men. *J Clin Invest*. 2003;111:1409-1421.
6. Leibel RL, Rosenbaum M, Hirsch J. Changes in energy expenditure resulting from altered body weight. *N Engl J Med*. 1995;332:621-628.
7. Elliot DL, Goldberg L, Kuehl KS, Bennett WM. Sustained depression of the resting metabolic rate after massive weight loss. *Am J Clin Nutr*. 1989;49:93-96.
8. Astrup A, Gotzsche PC, van de Werken K, et al. Meta-analysis of resting metabolic rate in formerly obese subjects. *Am J Clin Nutr*. 1999;69:1117-1122.
9. Weinsier RL, Nagy TR, Hunter GR, et al. Do adaptive changes in metabolic rate favor weight regain in weight-reduced individuals? *Am J Clin Nutr*. 2000;72:1088-1094.
10. Rattan S, Coxon A, Kreitzman S, Lemons A. Maintenance of weight loss with recovery of resting metabolic rate following 8 weeks of very low calorie dieting. *Int J Obes*. 1989;13(suppl 2):189-192.
11. Flegal KM, Carroll MD, Ogden CL, Johnson CL. Prevalence and trends in obesity among US adults, 1999-2000. *JAMA*. 2002;288:1723-1727.
12. Ludwig DS. The glycemic index: physiological mechanisms relating to obesity, diabetes, and cardiovascular disease. *JAMA*. 2002;287:2414-2423.
13. Ebbeling CB, Ludwig DS. Treating obesity in youth: should dietary glycemic load be a consideration? *Adv Pediatr*. 2001;48:179-212.
14. Brand-Miller JC, Thomas M, Swan V, et al. Physiological validation of the concept of glycemic load in lean young adults. *J Nutr*. 2003;133:2728-2732.
15. Ludwig DS, Majzoub JA, Al-Zahrani A, Dallal GE, Blanco I, Roberts SB. High glycemic index foods, overeating, and obesity. *Pediatrics*. 1999;103:E26.
16. Pawlak DB, Ebbeling CB, Ludwig DS. Should obese patients be counselled to follow a low-glycaemic index diet? yes. *Obes Rev*. 2002;3:235-243.
17. Raben A. Should obese patients be counselled to follow a low-glycaemic index diet? no. *Obes Rev*. 2002;3:245-256.
18. Agus MS, Swain JF, Larson CL, et al. Dietary composition and physiologic adaptations to energy restriction. *Am J Clin Nutr*. 2000;71:901-907.
19. Appel LJ, Moore TJ, Obarzanek E, et al. A clinical trial of the effects of dietary patterns on blood pressure. *N Engl J Med*. 1997;336:1117-1124.
20. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation*. 2002;106:3143-3421.
21. Harris JA, Benedict FG. *Biometric Studies of Basal Metabolism in Man*. Washington, DC: Carnegie Institute of Washington. 1919:279.
22. Pereira MA, FitzGerald SJ, Gregg EW, et al. A collection of physical activity questionnaires for health-related research. In: Kriska AM, Caspersen CJ, eds. *Medicine and Science in Sports and Exercise*. Vol 29. 1997:S1-S205.
23. Matthews JN, Altman DG, Campbell MJ, Royston P. Analysis of serial measurements in medical research. *BMJ*. 1990;300:230-235.
24. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem*. 1972;18:499-502.
25. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia*. 1985;28:412-419.
26. Laird N. Further comparative analyses of pretest-posttest research designs. *Am Stat*. 1983;37:329-330.
27. Luscombe ND, Clifton PM, Noakes M, Farnsworth E, Wittert G. Effect of a high-protein, energy-restricted diet on weight loss and energy expenditure after weight stabilization in hyperinsulinemic subjects. *Int J Obes Relat Metab Disord*. 2003;27:582-590.
28. Luscombe ND, Clifton PM, Noakes M, Parker B, Wittert G. Effects of energy-restricted diets containing increased protein on weight loss, resting energy expenditure, and the thermic effect of feeding in type 2 diabetes. *Diabetes Care*. 2002;25:652-657.
29. Westerterp KR, Wilson SA, Rolland V. Diet induced thermogenesis measured over 24h in a respiration chamber: effect of diet composition. *Int J Obes Relat Metab Disord*. 1999;23:287-292.
30. Soares MJ, Sequeira J, Shetty PS. The effect of the preceding day's protein intake on basal metabolic rates in young adults. *Br J Nutr*. 1988;60:425-431.
31. Durrant ML, Garrow JS, Royston P, Stalley SF, Sunkin S, Warwick PM. Factors influencing the composition of the weight lost by obese patients on a reducing diet. *Br J Nutr*. 1980;44:275-285.
32. Ravussin E, Gautier JF. Metabolic predictors of weight gain. *Int J Obes Relat Metab Disord*. 1999;23(suppl 1):37-41.
33. Yoshida T, Sakane N, Umekawa T, Kondo M. Relationship between basal metabolic rate, thermogenic response to caffeine, and body weight loss following combined low calorie and exercise treatment in obese women. *Int J Obes Relat Metab Disord*. 1994;18:345-350.
34. Weinsier RL, Hunter GR, Zuckerman PA, Darnell BE. Low resting and sleeping energy expenditure and fat use do not contribute to obesity in women. *Obes Res*. 2003;11:937-944.
35. Fruehwald-Schultes B, Kern W, Dantz D, Born J, Fehm HL, Peters A. Preserved hypothermic response to hypoglycemia after antecedent hypoglycemia. *Metabolism*. 2000;49:794-798.
36. Pawlak DB, Kushner JA, Ludwig DS. Effects of dietary glycemic index on adiposity, glucose homeostasis, and plasma lipids in animals. *Lancet*. 2004;364:778-785.
37. Ludwig DS. Glycemic load comes of age. *J Nutr*. 2003;133:2695-2696.
38. Liu S, Willett WC, Stampfer MJ, et al. A prospective study of dietary glycemic load, carbohydrate intake, and risk of coronary heart disease in US women. *Am J Clin Nutr*. 2000;71:1455-1461.
39. Reaven GM. Pathophysiology of insulin resistance in human disease. *Physiol Rev*. 1995;75:473-486.