Effects of a reduced-glycemic-load diet on body weight, body composition, and cardiovascular disease risk markers in overweight and obese adults1–3

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ABSTRACT

Background: Lowering the dietary glycemic load and increasing protein intake may be advantageous for weight management.

Objective: This randomized controlled trial was designed to evaluate the effects of an ad libitum reduced-glycemic-load (RGL) diet on body weight, body composition, and cardiovascular disease (CVD) risk markers in overweight and obese adults during an initial weight-loss phase (12 wk) and a weight-loss maintenance phase (weeks 24–36).

Design: Subjects were assigned to RGL (n = 43) or low-fat, portion-controlled (control; n = 43) diet groups. The RGL group was instructed to eat until satisfied, maintaining a low carbohydrate intake during weeks 0–2 and adding low-glycemic-index carbohydrate thereafter. Control subjects were instructed to reduce fat intake and decrease portion sizes, with a targeted energy deficit of 500 to 800 kcal/d.

Results: The RGL group had lost significantly more weight than did the control group at week 12 (−4.9 and −2.5 kg, respectively; P = 0.002), but the 2 groups did not differ significantly at week 36 (−4.5 and −2.6 kg, respectively; P = 0.085). Changes in fat mass differed between the groups at week 12 (−1.9 and −0.9 kg, respectively; P = 0.016) but not at week 36 (−2.0 and −1.3 kg, respectively; P = 0.333). At the end of the study, no differences were found in responses for CVD risk markers except a larger mean change in HDL cholesterol in the RGL group than in the control group (3.8 and 1.9 mg/dL, respectively; P = 0.037).

Conclusion: These findings provide evidence that an ad libitum RGL diet is a reasonable alternative to a low-fat, portion-controlled eating plan for weight management.

KEY WORDS Glycemic load, obesity, weight loss, body composition, cardiovascular disease risk markers, glucose tolerance, randomized controlled trial

INTRODUCTION

The prevalence of obesity in the United States has more than doubled during the past 25 y (1). Recent estimates from population-based samples suggest that nearly two-thirds of adults in the United States are overweight or obese (2). This fact is generating considerable public health concern because excess adiposity is associated with a greater risk of the development of diabetes mellitus, atherosclerotic cardiovascular disease (CVD), and several forms of cancer (1).
weight-loss period and at the end of a weight-maintenance period at week 36. Secondary outcomes included changes in body composition, selected CVD risk markers, and health-related quality of life at weeks 12 and 36.

SUBJECTS AND METHODS

Subjects

Potential participants were recruited from the Chicago metropolitan area and screened by telephone. Eligibility was further assessed at a screening visit. To qualify for entry into the study, men and women had to be aged 18–65 y, have a waist circumference measurement at week —1 of ≥87 cm for women and ≥90 cm for men, and be judged by the investigators to be in good health on the basis of medical history and routine laboratory tests. Subjects had to be willing to discontinue all use of dietary supplements or multivitamins, except those provided during the study, and to follow the assigned diet and maintain their usual level of physical activity throughout the trial.

Volunteers were excluded from participation if they had experienced a weight loss of >4.5 kg in the 2 mo before screening, had a body mass index (BMI; in kg/m²) ≥37.0, were current smokers (any cigarette use), or had a history of smoking in the 6 mo before screening. Subjects were also excluded from participation if they had diabetes mellitus, uncontrolled hypertension, or a history of cancer (other than successfully resected basal cell carcinoma) in the past 2 y.

Subjects with a history of or current significant cardiac, renal, pulmonary, hepatic, biliary, or endocrine disease were excluded, as were those with a history of recurrent nephrolithiasis or acute nephrolithiasis within the year before screening. Subjects were excluded from participation if they had used any weight-loss medication, supplements, programs, or meal-replacement products intended to alter body weight during the 4 wk before screening or if they had any diagnosed eating disorder, a history of surgery for weight-reducing purposes, or a clinically significant gastrointestinal disorder.

Additional exclusion criteria included the use of systemic corticosteroids, androgens, phenytoin, or pseudoephedrine; lipid-lowering therapies (unless dose-stable for 2 mo before enrollment); drugs for regulating hemostasis other than dose-stable aspirin; thyroid hormones (except stable-dose replacement therapy for ≥2 mo before enrollment); or psychiatric medications.

Postmenopausal women who were current users of sex hormone therapy or who had discontinued use in the 2 mo before screening were excluded. Female subjects who were pregnant, planning to be pregnant during the study period, or lactating or those of childbearing potential who were not using an approved method of contraception were also excluded.

This trial was performed according to Good Clinical Practice Guidelines, the Declaration of Helsinki (2000), and US 21 CFR Part 50 – Protection of Human Subjects, and Part 56 – Institutional Review Boards. An institutional review board, Quorum (Seattle, WA), approved the protocol and the informed consent document before the initiation of the study. Study procedures were reviewed with subjects, and each participant provided written informed consent and authorization for the release of protected health information before study procedures were carried out.

Clinic visits

This trial used a randomized, controlled design with 2 parallel treatment arms. Subjects were randomly assigned to either the RGL or portion-controlled (control) diet. Weeks 0–12 were weight-loss treatment. At some point between weeks 12 and 24, each subject transitioned to a weight-maintenance phase. From week 24 on, all subjects were in the weight-maintenance phase.

The study included 15 clinic visits: 1 screening visit (week —1), 1 visit at baseline (week 0), 7 visits during the weight-loss treatment phase (weeks 1, 2, 4, 6, 8, 10, and 12), 3 visits during the transition from weight-loss treatment to weight-loss maintenance (weeks 16, 20, and 24), and 3 visits during the weight-loss maintenance phase (weeks 28, 32, and 36).

Visits were conducted between 0700 am and 1200. Subjects were asked to refrain from consuming any foods or beverages except water for ≥10 h and to abstain from consuming alcohol for ≥24 h before visits.

At week —1, subjects provided written informed consent and completed a medical history questionnaire. Concomitant medications used 8 wk before and during the study were recorded at this and subsequent visits. Body weight, height, and waist circumference were measured, and vital signs were assessed. Samples were taken for serum chemistry, hematology, lipid panel, and urinalysis.

At the randomization (baseline) visit (week 0), subjects received diet instruction and information on their assigned diets for them to take home. All subjects were provided with daily multivitamins (Centrum; Wyeth Consumer Healthcare, Madison, NJ) and were instructed to bring back any unused multivitamins at each subsequent study visit.

At each visit, vital signs were assessed and anthropometric measurements were taken, daily food checklists were reviewed and used in dietary counseling or reinforcement, and any concomitant use of medication and adverse events were assessed. Fasting serum lipid values were obtained at weeks —1, 0, 10, 12, 32, and 36. Serum chemistry, hematology, urinalysis, and fasting insulin and glucose values were measured at weeks —1, 12, and 36. Dual-energy X-ray absorptiometry (DXA) was conducted at weeks 0, 12, 24, and 36 for assessment of body composition. Three-day diet records were analyzed by using the NUTRIENT DATA SYSTEM FOR RESEARCH (version 4.06; University of Minnesota, Minneapolis, MN) at weeks 0, 2, 6, 12, 24, and 36. The Willett Food-Frequency Questionnaire was completed at weeks 0, 12, and 36 for estimation of dietary GI and GL (20). The questionnaire uses published sources of GI values for carbohydrates from specific foods for calculation of the weighted average GI of the diet (20). GL is calculated as the weighted average GI multiplied by the total daily carbohydrate intake (20).

Laboratory measurements

The dipstick test (Ketostix; Bayer Diagnostics, Tarrytown, NY) was used to assess urinary ketone concentrations. Other laboratory measurements, including serum chemistry, hematology, insulin, urinalysis, and lipid concentrations, were conducted by Medical Research Laboratories (MRL, Highland Heights, KY). Serum chemistry analysis (including fasting glucose) was completed with a chemistry analyzer (Hitachi 747–200; Roche Diagnostics Corporation, Indianapolis, IN), and hematologic testing was conducted with the use of a complete count analyzer (Coulter STKS; Coulter Corporation, Miami, FL).
cholesterol and triacylglycerol were measured enzymatically by using the Hitachi 747–200. Heparin and manganese chloride were used to precipitate apolipoprotein-containing particles to allow measurement of HDL cholesterol. LDL cholesterol in mg/dL was calculated by using the Friedewald equation: LDL cholesterol = (total cholesterol – HDL cholesterol – triacylglycerol)/5 (21). The homeostasis model assessment (HOMA) of insulin resistance was calculated as glucose (mmol/L) × insulin (mU/L)/22.5 (22).

Blood pressure

Blood pressure was obtained after the subject had been sitting quietly for 5 min. Systolic and diastolic pressures were measured with a standard manual mercury sphygmomanometer. Two measurements, separated by 2 min, were taken and averaged. If the measurements differed by >5 mm Hg, an additional reading was obtained, and all 3 readings were averaged.

Body composition and anthropometric measurements

Whole-body DXA scans were performed (QDR 4500A; Hologic Inc, Waltham, MA). Body composition values (fat mass and fat-free mass) were measured with the use of Hologic SYSTEMS Software (version 9.03D; Hologic Inc) according to the procedures outlined in the Hologic QDR 4500 user’s guide of 1995.

Anthropometric measurements included subjects’ height (first visit only), weight, and waist circumference. At each visit, the measurement of waist circumference was performed at the level of the iliac crest by using a nonstretchy anthropometric tape measure. Two measurements were taken and averaged. If these differed by >0.5 cm, a third measurement was taken and the outlying value was discarded.

Diet implementation

Diet counselors were the same for both groups. Diet training manuals were created to standardize training of the counselors, all of whom were Registered Dietitians with extensive experience in counseling for weight management. For both diet groups, handouts were provided to each subject for at-home use, and dietary guidance was reinforced at each treatment visit.

For subjects assigned to the control diet, energy needs for weight maintenance were estimated from basal EE calculated with the Harris-Benedict equation (23) multiplied by an activity factor of 1.2, 1.3, or 1.4 after evaluation of activity level from the results from the intent-to-treat analyses, only the latter being considered primary, the last nonbaseline observation was carried forward for missing data points. A secondary analysis for body weight was also completed, in which the baseline weight was substituted after discontinuation for all subjects who dropped out during the treatment period. In addition, analyses were completed that excluded subjects who did not complete the 36-wk study or who violated the protocol in some material way. However, because results from these analyses did not differ materially from the results from the intent-to-treat analyses, only the latter are presented.

For all continuous variables, repeated-measures ANOVA models were employed for values at baseline and weeks 2 (dietary variables only), 12, and 36. These models each included primary, the last baseline observation was carried forward for missing data points. A secondary analysis for body weight was also completed, in which the baseline weight was substituted after discontinuation for all subjects who dropped out during the treatment period. In addition, analyses were completed that excluded subjects who did not complete the 36-wk study or who violated the protocol in some material way. However, because results from these analyses did not differ materially from the results from the intent-to-treat analyses, only the latter are presented.

For all continuous variables, repeated-measures ANOVA models were employed for values at baseline and weeks 2 (dietary variables only), 12, and 36. These models each included terms for treatment, time, and treatment × time interaction. Pairwise comparisons between groups were completed for individual timepoints when the treatment × time interaction term was significant (P ≤ 0.05) in the repeated-measures model. Body weight responses at weeks 12 and 36 were considered the primary outcome variables and were assessed by ANOVA, with baseline body weight and treatment group as factors in the model. For both the primary and secondary body weight response analyses, the P values obtained at weeks 12 and 36 were adjusted (multiplied by 1.724) to account for the 2 comparisons (26). This adjustment equated to the requirement of a nominal, 2-sided P value of 0.029 to obtain statistical significance.
In addition, previously specified analyses of changes from baseline to week 12 (end of the initial weight-loss period) and week 36 (end of the weight-maintenance period) were completed for body composition, anthropometric, and laboratory variables by using 1-factor ANOVA with treatment as a fixed effect. Exploratory analyses were completed to assess maximal weight loss and the changes from the point of maximal weight loss to week 36 in both treatment groups. Multiple linear regression analysis was used to explore determinants of the changes in body composition. For all secondary outcome and exploratory variables, unadjusted P values are presented.

Safety analyses included all subjects who were randomly assigned. Safety and tolerability were assessed by evaluation of adverse events that occurred during treatment, laboratory test results, and vital signs measurements. Adverse events were coded by using the World Health Organization dictionary. Fisher’s exact test was used to test for differences between groups in adverse events overall and for each body system and coded term.

RESULTS

Subjects

A summary of subject disposition is shown in Figure 1. A total of 122 men and women were screened for entry into the trial, 86 of whom qualified and were randomly assigned (n = 43/group). No significant differences were observed between groups in the percentage of subjects who participated in the study through weeks 12 (81.4% in each group; P = 1.00) and 36 (53.5% in the RGL group and 69.8% in the control group; P = 0.120), respectively.

Baseline characteristics of the study sample are shown in Table 1. Subjects were approximately two-thirds female. Fifty-two percent classified themselves as non-Hispanic white and 35% as African American. The mean age of the participants was 50 y; mean BMI was 32, and 67% of the subjects were obese (BMI ≥30). The fasting insulin concentration tended to be higher among subjects in the RGL group than among those in the control group (10.3 and 9.0 mU/L, respectively; P = 0.061). Otherwise, the groups were well matched with regard to baseline characteristics.
time and treatment

Body weight and composition

At the end of the initial 12-wk weight-loss period, the mean weight change was $-4.9 \pm 0.5$ kg in the RGL arm and $-2.5 \pm 0.5$ kg in the control arm (adjusted $P = 0.002$), as shown in Figure 2. At week 12, 24 subjects (55%) in the RGL group and 9 subjects (21%) in the control group had achieved a loss of $5\%$ of body weight ($P = 0.002$). An exploratory analysis showed that mean maximum weight loss was significantly ($P = 0.018$) greater weight loss apparent in the RGL group than in the control group ($-4.9 \pm 0.6$ and $-3.0 \pm 0.6$ kg, respectively). However, no significant difference between groups was present at week 36 ($-2.7 \pm 0.7$ and $-2.2 \pm 0.8$ kg for the RGL and control groups, respectively; $P = 0.684$).

As shown in Table 2, body fat and fat-free mass were lower in both groups at week 12, and the reductions in the RGL arm were significantly ($P = 0.016$ and < 0.001 for body fat and fat-free mass, respectively) greater in the RGL arm than in the control arm. A significant ($P = 0.004$) difference between groups in the loss of fat-free mass persisted at 36 wk, whereas changes in fat mass from baseline were no longer significantly different ($-2.0$ and $-1.3$ kg for the RGL and control groups, respectively; $P = 0.333$). No significant difference in the loss of fat-free mass at week 12 was seen between groups after adjustment for body weight loss by using multiple linear regression ($P = 0.162$). However, RGL treatment was associated with significantly ($P = 0.037$) greater loss of fat-free mass at week 36, after adjustment for the difference in body weight response, than was the control diet. Waist circumference also declined in both groups, but the difference in response between groups was not significant at week 12 ($P = 0.082$) or week 36 ($P = 0.783$).

Physical activity and dietary composition

No significant differences between groups were observed in physical activity at baseline (Table 1) or at any timepoint during treatment (data not shown). Estimates of dietary composition

![Figure 2](image_url)
Body composition and waist circumference values by time point and treatment group

<table>
<thead>
<tr>
<th>Variable</th>
<th>RGL group</th>
<th>Control group</th>
<th>Time</th>
<th>Treatment × time</th>
<th>Pairwise P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fat mass (kg)</td>
<td>n</td>
<td>n</td>
<td></td>
<td></td>
<td></td>
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<tr>
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</tr>
<tr>
<td>Δ at week 36</td>
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<td>37</td>
<td></td>
<td>0.016</td>
<td>0.333</td>
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<td>Fat-free mass (kg)</td>
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<td></td>
</tr>
<tr>
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<tr>
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<td>37</td>
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<td>&lt;0.001</td>
</tr>
<tr>
<td>Δ at Week 36</td>
<td>37</td>
<td>37</td>
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<td>0.004</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>n</td>
<td>n</td>
<td></td>
<td></td>
<td></td>
</tr>
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<td>37</td>
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<td>0.082</td>
</tr>
<tr>
<td>Δ at Week 36</td>
<td>37</td>
<td>37</td>
<td></td>
<td>0.783</td>
<td></td>
</tr>
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</table>

1 RGL, reduced glycemic load.
2 P values from repeated-measures ANOVA models with treatment, time, and treatment × time interaction as factors.
3 P values from ANOVA models comparing treatments at each timepoint.
4 ± SEM (all such values).

from analysis of 3-d food records and Willett Food-Frequency Questionnaires (for GI and load) are shown in Table 3. The groups did not differ significantly at baseline in any variable except alcohol intake, which was higher in the RGL group than in the control group (6 and 2 g/d, respectively; P = 0.010).

Reported energy consumption was reduced from baseline in both groups throughout the treatment period. Differences between treatment arms did not reach significance, although mean values were 4.7% to 10.5% lower in the RGL group than in the control group at each timepoint after randomization. Consistent with the treatment plan, dietary carbohydrate and sugars (fructose and fructose) were markedly reduced at week 2 in the RGL group (P < 0.001 versus control group). Reported intakes of carbohydrate and sugars increased above the week 2 values in the RGL group but remained substantially below those intakes in the control group (for both dietary carbohydrate and sugars, P ≤ 0.005 at weeks 12 and 36).

Mean GI in the RGL group declined from 52 at baseline to 46 at week 12 and 48 at week 36 (P ≤ 0.001 versus control group at both timepoints) and remained essentially unchanged from baseline in the control group (52, 51, and 51 at baseline, week 12, and week 36, respectively). The combination of lower GI and reduced carbohydrate consumption produced reductions of 43% to 49% in mean GL in the RGL group but reductions of 12% to 16% in the control group (P ≤ 0.002 at weeks 12 and 36).

Alcohol was not allowed during the first 2 wk of the RGL treatment plan, which resulted in a significant difference in intake between groups at week 2 (P < 0.001), but intake did not differ at weeks 12 and 36. Reported protein intake was higher in the RGL group at all timepoints during treatment, but the treatment × time interaction was not significant (P = 0.067). Intakes of total, saturated, and unsaturated fats were also higher in the RGL group than in the control group, but differences did not reach significance. Mean dietary cholesterol intake was higher (122–259 mg/d) in the RGL group than in the control group at all timepoints during the treatment (P < 0.001).

Dietary fiber, expressed in g/1000 kcal, did not differ between groups. No significant differences between groups were observed in calcium, magnesium, potassium, or sodium intakes during treatment.

Cardiovascular disease risk markers, ketones, and quality of life

Mean values for CVD risk markers by group at baseline and changes from baseline are shown in Table 4. No significant differences between groups were present at baseline. The only significant difference in lipid responses between the RGL and control diet groups was in the increase in HDL cholesterol at week 36 (3.8 and 1.9 mg/dL, respectively; P = 0.037).

The RGL dietary regimen was designed to have sufficient carbohydrate to prevent significant ketonemia, even during the initial period of more severe carbohydrate restriction. At baseline, 4 subjects—1 in the RGL group and 3 in the control group—had measurable concentrations of urinary ketones (P = 0.270). At week 2, 12 subjects (29%) in the RGL group and 1 subject (3%) in the control group had urinary ketones (P = 0.001). Of the 12 subjects with urinary ketones in the RGL group, 6 were classified as having trace amounts and 6 as having small-to-moderate concentrations. At weeks 12 (14.6% in the RGL group and 7.1% in the control group; P = 0.273) and 36 (12.2% in the RGL group and 2.4% in the control group; P = 0.084), the prevalence of subjects with urinary ketones in the 2 groups did not differ significantly, but it tended to be higher in the RGL group.

No differences between groups at baseline or subsequent timepoints were observed for any domain in the SF-36 quality-of-life questionnaire (data not shown).

DISCUSSION

This randomized, controlled trial showed that an ad libitum RGL diet produced significantly greater losses of body weight and fat during an initial weight-loss period than did a traditional,
TABLE 3
Dietary composition, including dietary supplements, from analyses of 3-d diet records and Willett food-frequency questionnaires by timepoint and treatment group

<table>
<thead>
<tr>
<th>Variable</th>
<th>RGL group</th>
<th>Control group</th>
<th>Time$^2$</th>
<th>Treatment × time$^2$</th>
<th>Pairwise$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy (kcal/d)</td>
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<td>n</td>
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<td></td>
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</tr>
<tr>
<td>Week 12</td>
<td>41</td>
<td>41</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Week 36</td>
<td>41</td>
<td>41</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Carbohydrate (g/d)</td>
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<tr>
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<td>42</td>
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<td>&lt;0.001</td>
<td>&lt;0.001</td>
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<tr>
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<td></td>
<td></td>
<td>0.696</td>
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<tr>
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<tr>
<td>Week 36</td>
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<td>41</td>
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<td></td>
<td></td>
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<tr>
<td>Sucrose + fructose (g/d)</td>
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<tr>
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<td>&lt;0.001</td>
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<td>Week 36</td>
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<td>41</td>
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<td></td>
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<tr>
<td>Glycemic index$^a$</td>
<td></td>
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<td>Week 2</td>
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<td>Week 36</td>
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<tr>
<td>Total fat (g/d)</td>
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(Continued)
portion-controlled diet. No evidence was observed of any adverse effects on CVD risk markers.

Participants transitioned from the initial weight-loss period to a weight-maintenance phase by week 24. Subjects in both groups regained a portion of the maximum amount of weight lost: 1.9 and 1.8 kg in the RGL and control diets, respectively. At the end of the weight-maintenance period (week 36), differences between group losses of body weight and fat were no longer significant. In addition, no significant differences were observed in CVD risk markers, except for a larger increase in HDL cholesterol at week 36 in subjects in the RGL group than in the control group (3.8 and 1.9 mg/dL, respectively; \( P = 0.037 \)). These findings suggest that, whereas the RGL diet produced greater initial losses of body weight and fat than did the portion-controlled diet, it showed no clear superiority with respect to its influence on CVD risk markers or maintenance of changes in body weight and composition.

The differential losses of body weight and fat during the weight-loss phase indicate that subjects in the RGL group experienced greater negative energy balance than did those in the control group. This difference must be explained by greater EE, lower energy intake, or some combination of these factors. The decline in resting EE during weight loss may be attenuated with an RGL diet (3, 5). Rats and mice fed an RGL diet, achieved by use of a low-GI chow (made with amylose), required more energy to maintain the same body weight than did animals fed high-GI chow (made with amylopectin) (27). Despite higher energy intake, animals fed the RGL diet had lower adiposity after 9–18 wk than did those fed the control diet (27). These findings support the view that an RGL diet may affect EE and partitioning in ways that would favor negative energy balance.

Dietary GL, insulin secretion, and substrate oxidation may interact to influence appetite. An RGL diet is likely to produce a lower average daylong insulin concentration (3, 28–30). This is especially true for persons with insulin resistance and compensatory hyperinsulinemia, both of which are characteristic features of obesity (31–33).

In persons with excess adiposity, the ability of insulin to promote glycogenesis is impaired to a greater extent than is its ability to promote glucose oxidation (31). In an insulin-resistant person, a high-GL diet would be expected to produce extended periods of hyperinsulinemia that would, in turn, increase whole-body carbohydrate oxidation and depress fat oxidation (34). Because it has been shown that increased hepatic fat oxidation is associated with lower hunger and food intake in animals and humans (7, 35–37), the reduced fat oxidation associated with hyperinsulinemia may lead to an increase in food intake.

Protein consumption tended to be higher in the RGL group than in the control group. Protein appears to have greater ability than does carbohydrate to promote satiety and reduce subsequent food intake (38–40). In addition, numerous studies have shown elevated thermic responses to meals and higher 24-h EE with increased protein intake (40). Diets with higher protein content have also been found to produce greater weight loss in some trials, which may be accounted for by these effects (40–42).

Previous studies showed that 20–30% of weight lost by dieting is typically fat-free mass (43). In this study, loss of fat-free mass was significantly larger in the RGL group at week 36 (\( \approx 51\% \) and 41% of weight lost in the RGL and control groups, respectively), even after statistical adjustment for total weight loss (\( P = 0.037 \)). The greater reduction in fat-free mass is of potential concern, because this reduction could result in attenuation of total daily EE if attributable to a greater loss of lean tissue (44). Because DXA cannot distinguish between changes in nonbone lean tissue and those in fluid, the degree to which fluid loss may have contributed to the loss of fat-free mass is unclear.

### TABLE 3 (Continued)

<table>
<thead>
<tr>
<th>Variable</th>
<th>RGL group</th>
<th>Control group</th>
<th>Time</th>
<th>Treatment × time</th>
<th>Pairwise</th>
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<tr>
<td>Baseline</td>
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<td>0.583</td>
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<td>361 ± 16</td>
<td>342 ± 14</td>
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<td>Week 12</td>
<td>353 ± 11</td>
<td>347 ± 18</td>
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<tr>
<td>Week 36</td>
<td>360 ± 14</td>
<td>376 ± 23</td>
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<td>Potassium (mg/d)</td>
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<td>Baseline</td>
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<td>2467 ± 160</td>
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<td>Sodium (mg/d)</td>
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<tr>
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<td>Week 36</td>
<td>3217 ± 159</td>
<td>3226 ± 181</td>
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</table>

1 RGL, reduced glycemic load. Results for all variables except glycemic index and glycemic load are from analyses of 3-d food records; glycemic index and glycemic load results were derived from analyses of Willett food-frequency questionnaires.

2 \( \times \) values from repeated-measures ANOVA models with treatment, time, and treatment \( \times \) time interaction as factors.

3 \( \times \) values from ANOVA models comparing treatments at each timepoint.

4 \( \times \) SEM (all such values).

5 Calculated as the weighted average glycemic index value for all carbohydrate-containing foods in the diet.

6 Calculated as each food’s carbohydrate quantity (in g) multiplied by the respective glycemic index.
Because insulin stimulates renal sodium and water reabsorption, an RGL diet may be expected to produce fluid loss (10, 45–47). However, insulin is also a growth factor that enhances protein synthesis and inhibits protein catabolism in muscle tissues (48, 49), and thus some greater loss of lean tissue may also have occurred if total circulating insulin exposure was reduced. Additional research will be needed to differentiate between changes in the masses of fluid and those in lean tissue with consumption of RGL diets.

A common concern expressed regarding carbohydrate-restricted diets is that they may be associated with higher consumption of saturated fatty acids and cholesterol, which could lead to higher LDL cholesterol. In a meta-analysis comparing low-carbohydrate with low-fat weight-loss diets, Nordmann et al (19) found that both HDL (4.6 mg/dL) and LDL (5.4 mg/dL) cholesterol were higher after 6 mo in subjects assigned to the low-carbohydrate diet. In the current study, reported saturated fat and cholesterol intakes were...
higher in the RGL diet group than in the control group. Whereas the increase in HDL cholesterol at 36 wk was greater in the RGL diet group than in the control group (3.8 and 1.9 mg/dL, respectively; \( P = 0.037 \)), a finding that is consistent with the results of the meta-analysis, no difference was found between the groups in the mean change in LDL cholesterol (−2.8 and −1.9 mg/dL, respectively; \( P = 0.836 \)).

Jenkins et al (50) showed that, under conditions of identically matched food intake, a lower rate of carbohydrate absorption, elicited by consumption of 17 snacks as opposed to 3 larger meals, was associated with a 28% lower average insulin concentration and a mean reduction of 13.5% in LDL-cholesterol concentrations. Sloth et al (14) also found that ad libitum consumption of a low-GI diet resulted in a 10% decrease in LDL cholesterol, whereas consumption of a high-GI diet matched for macronutrient and fiber content per 1000 kcal resulted in a slight (2%) rise in LDL cholesterol.

Insulin has a stimulatory effect on VLDL synthesis (32). Therefore, a smaller integrated insulin response may reduce VLDL synthesis and entry into the circulation (5, 51). In the absence of changes in the rates of VLDL conversion to LDL or of LDL removal from the circulation (or both), a reduction in the concentration of LDL cholesterol would be expected. However, greater intakes of saturated fats and cholesterol can suppress hepatic LDL uptake (52), which may explain the absence of a larger reduction in LDL cholesterol in subjects consuming the RGL diet than in those consuming the control diet (53).

In summary, the results of the current trial showed that, in free-living, overweight and obese subjects, an ad libitum RGL diet produced greater losses of body weight and fat than did a traditional, portion-controlled diet during an initial weight-loss period. Weight regain from the point of maximal weight loss did not differ between treatments. However, the differences in body weight and body fat responses between groups were no longer significant at the end of the weight-maintenance phase of the trial (week 36). No evidence was present of any adverse effects of the RGL diet on CVD risk factors. Therefore, the results of the current study suggest that an ad libitum RGL diet is a reasonable alternative to a low-fat, portion-controlled weight-loss diet. Additional research is warranted to clarify the mechanisms responsible for the greater initial losses of body weight and fat associated with the RGL diet, to evaluate the persistence of those losses over longer treatment periods, and to obtain greater insight into strategies that would improve long-term weight-loss maintenance.

The authors thank Denise Umporowicz, Kimberly Oldham, and Marjorie Bell for assistance with data management and statistical analyses. All authors were responsible for the design of the study; KCM was responsible for the statistical analyses; all authors contributed to the final interpretation of the data; KCM wrote the draft of the manuscript, and all authors participated in revising the manuscript. TMR and KRR were employed by Kraft Foods at the time the trial was conducted. None of the other authors had any personal or financial conflict of interest.

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