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The Role of Energy Expenditure in the Differential Weight Loss in Obese Women on Low-Fat and Low-Carbohydrate Diets

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We have recently reported that obese women randomized to a low-carbohydrate diet lost more than twice as much weight as those following a low-fat diet over 6 months. The difference in weight loss was not explained by differences in energy intake because women on the two diets reported similar daily energy consumption. We hypothesized that chronic ingestion of a low-carbohydrate diet increases energy expenditure relative to a low-fat diet and that this accounts for the differential weight loss. To study this question, 50 healthy, moderately obese (body mass index, 33.2 ± 0.28 kg/m^2) women were randomized to 4 months of an *ad libitum* low-carbohydrate diet or an energy-restricted, low-fat diet. Resting energy expenditure (REE) was measured by indirect calorimetry at baseline, 2 months, and 4 months. Physical activity was estimated by pedometers. The thermic effect of food (TEF) in response to low-fat and low-carbohydrate breakfasts was assessed over 5 h in a subset of subjects. Forty women completed the trial. The low-carbohydrate group lost more weight (9.79 ± 0.71 *vs.* 6.14 ± 0.91 kg; $P < 0.05$) and more body fat (6.20 ± 0.67 *vs.* 3.23 ± 0.67 kg; $P < 0.05$) than the low-fat group. There were no differences in energy intake between the diet groups as reported on 3-d food records at the conclusion of the study (1422 ± 73 *vs.* 1530 ± 102 kcal; 5954 ± 306 *vs.* 6406 ± 427 kJ). Mean REE in the two groups was comparable at baseline, decreased with weight loss, and did not differ at 2 or 4 months. The low-fat meal caused a greater 5-h increase in TEF than did the low-carbohydrate meal (53 ± 9 *vs.* 31 ± 5 kcal; 222 ± 38 *vs.* 130 ± 21 kJ; $P = 0.017$). Estimates of physical activity were stable in the dieters during the study and did not differ between groups. These results confirm that short-term weight loss is greater in obese women on a low-carbohydrate diet than in those on a low-fat diet even when reported food intake is similar. The differential weight loss is not explained by differences in REE, TEF, or physical activity and likely reflects underreporting of food consumption by the low-fat dieters. (*J Clin Endocrinol Metab* 90: 1475–1482, 2005)

THE INCIDENCE OF obesity in the United States has escalated along with its physiological and psychological comorbidities (1–3). The imperative for effective weight loss methods has stimulated the promotion of numerous alternative diet plans, most of which are based on some modification of macronutrient content (*i.e.* low-carbohydrate and high-carbohydrate diets). The low-carbohydrate, high-protein diet, promoted extensively by Atkins and others, is one of the most popular weight loss approaches (4). Although adopted by millions of Americans yearly, the efficacy of this diet has only recently been studied in a systematic manner (5–7).

We previously performed a randomized, controlled trial that compared the effects of a low-carbohydrate diet with a low-fat control diet on weight loss and commonly studied cardiovascular risk factors (5). In this study, healthy obese women on the low-carbohydrate diet lost 8.5 kg, more than twice the amount of weight lost by women on the control diet, over a 6-month period. Loss of fat mass was also significantly greater in the low-carbohydrate group, but the diets had similar effects on blood pressure, blood lipids, and plasma glucose and insulin. Other recent studies of short-term weight loss using low-carbohydrate diets reported comparable results (6, 7).

In our previous study, subjects on the low-carbohydrate diet did not have restrictions in energy intake (5). They were instructed only to limit their carbohydrate intake and were allowed primarily protein- and fat-containing foods *ad libitum*. In contrast, subjects in the low-fat control group were asked to limit their intake to approximately 1200 kcal/d (5024 kJ/d). Despite these differences in prescribed energy intake, the two groups reported similar amounts of energy consumption on their weekly 3-d food records. Based on these results, we could not ascribe the significantly greater weight loss in the low-carbohydrate group to differences in energy intake between the two groups. One possible explanation for the greater weight loss in the low-carbohydrate group is that they had greater energy expenditure than the low-fat group. Although never formally tested, the possibility that low-carbohydrate diets promote increased energy expenditure is touted by advocates of this diet (8). To evaluate the hypothesis that low-carbohydrate diets increase energy expenditure, we randomized 50 healthy obese women to 4 months of a low-carbohydrate diet or an energy-restricted, low-fat diet conforming to the guidelines currently recommended by

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Abbreviations: DEXA, Dual-energy x-ray absorptiometry; GCRC, General Clinical Research Center; HDL, high-density lipoprotein; LDL, low-density lipoprotein; REE, resting energy expenditure; RQ, respiratory quotient; TEF, thermic effect of food; VCO_2, carbon dioxide production; VO_2, oxygen consumption.

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the American Heart Association and measured the effects on resting energy expenditure (REE) and physical activity. Thermic effect of food (TEF) was measured in a subset of subjects.

Subjects and Methods

Subjects

Fifty obese females were recruited by advertisement according to the following inclusion criteria: age at least 18 yr, moderate obesity with a body mass index (BMI) of 30–35, and a stable weight over the preceding 6 months (no weight loss or gain of >10% of their body weight). Exclusion criteria were the presence of cardiovascular disease, untreated hypertension, diabetes, hypothyroidism, substance abuse, pregnancy, or lactation. All subjects gave informed consent for the study, which was approved by the University of Cincinnati and Cincinnati Children's Hospital Medical Center Institutional Review Boards. The procedures followed were in accordance with the ethical standards of the involved institutions.

Assessments

Subject screenings and assessments were conducted at the General Clinical Research Center (GCRC) of Cincinnati Children's Hospital Medical Center by trained research nurses. At the initial screening visit, each subject's height, weight, blood pressure, and fasting glucose were measured, a medical history was taken, and an electrocardiogram was performed. Individuals meeting the criteria for study participation were enrolled in the study and returned to the GCRC for a baseline assessment.

At the baseline assessment, after an overnight fast of 12 h and a normal pattern of activity and sleep on the previous day, subjects relaxed for 30 min in a bed in a darkened room before undergoing an assessment of their REE using a computerized, open-circuit indirect calorimeter (Vmax 29N indirect calorimeter, Sensormedics Corp., Yorba Linda, CA). The instrument was calibrated before each test using reference gases, and respiratory gas exchange was measured over 30 min using a ventilated hood. Oxygen consumption (VO_2), carbon dioxide production (VCO_2), and a calculation of energy expenditure were reported every 20 sec; REE was computed as the mean of the values reported after steady-state rates of VO_2 and VCO_2 were maintained for a minimum of 5 min. After the REE testing, subjects' height, weight, and blood pressure were measured and a fasting blood sample was drawn. Each subjects' body fat was measured by dual-energy x-ray absorptiometry (DEXA) using a Hologic 4500A total body scanner. DEXA scans were conducted at the Body Composition Core Laboratory of the GCRC by trained technicians.

After 2 and 4 months of dieting, subjects returned to the GCRC for follow-up assessments that included the same measures and procedures described for the baseline assessment (*i.e.* REE, height, weight, blood pressure, fasting blood sample, and DEXA scans).

Diets/activity

The primary objective of the study was to compare the effects of a low-carbohydrate diet and an energy-restricted, low-fat diet on energy balance; the secondary objective was to confirm the results of our previous study by examining the diets' effects on body composition and cardiovascular risk factors. We designed this study identically to our previous one in which groups of subjects were recruited and studied sequentially (5). After each block of subjects was enrolled, the principal investigator used a computerized randomization program to randomly assign those subjects to one of two diets. One group of dieters was instructed to follow an *ad libitum* diet with a maximum intake of 20 g of carbohydrate per day, with the intent of producing ketosis. After 2 wk of dieting, subjects were permitted to increase their intake of carbohydrate to 40–60 g/d only if self-testing of urinary ketones continued to indicate ketosis. The other group of dieters was instructed to follow an energy-restricted, moderately low-fat diet with a recommended macronutrient distribution of 55% carbohydrate, 15% protein, and 30% fat. Energy prescriptions were based on body size and calculated using the Harris-Benedict equation plus an activity factor. All subjects were advised to continue their baseline level of physical activity. During the first 2 months of the study, subjects were required to complete weekly 3-d food records and pedometer records (number of steps per day) as well as during the week before their 4-month counseling session.

Two registered dietitians delivered a 2-month intervention that included weekly counseling, either one-on-one or in a group, on the University of Cincinnati campus. To control for possible bias, each dietitian was assigned subjects from each diet group for counseling and alternated as the meeting facilitator for both groups of dieters. Group meetings with subjects on the same diet were held biweekly and addressed cooking tips, stress management, behavior modification, and relapse prevention. On alternating weeks, subjects met for individual counseling sessions during which their assigned dietitian reviewed their 3-d food records and pedometer records from the previous week and provided dietary recommendations and positive reinforcement. Before each weekly session, subjects were weighed on a single electronic scale (Tanita, Arlington Heights, IL) and assessment of urinary ketones was performed using Ketostix (Bayer, Elkhart, IN). All food records were analyzed by Nutritionist Pro software (First Data Bank, San Bruno, CA).

At the end of the 2-month intervention, subjects were instructed to continue with their weight loss efforts, but without scheduled contact with the dietitians or researchers, until the 4-month assessment.

Determination of the TEF

The thermic effects of low-fat and low-carbohydrate meals were tested in eight obese women who had completed our current or previous (5) low-carbohydrate *vs.* low-fat diet trials. Subjects (BMI, 32.96 ± 0.76 kg/m^2) reported to the GCRC on two mornings after an overnight fast. REE was determined as described above, except in this set of experiments, calculated REE values were reported at 1-min intervals. Subjects were then given either a low-carbohydrate or low-fat breakfast of approximately 540 kcal (2261 kJ), distributed as 5% carbohydrate, 26% protein, and 69% fat (for the low-carbohydrate meal) or as 69% carbohydrate, 11% protein, and 20% fat (for the low-fat meal). To control for other dietary factors that have the potential to influence hunger and satiety, the breakfast meals were similar in weight, fiber, fluid, variety, and palatability. The low-carbohydrate breakfast included pork sausage links (39 g), liquid eggs scrambled (150 g), margarine (5 g), shredded cheddar cheese (28 g), nonfat milk (61 g), and water (237 g); the low-fat breakfast included sugar-free maple-flavored syrup (52.5 g), three pancakes (116 g), margarine (9 g), banana (100 g), and nonfat milk (245 g). The order of the two meals was randomized. Subjects were asked to consume the meal within 30 min. Postprandial energy expenditure was measured for 300 min by indirect calorimetry. Subjects remained supine in bed for this period under the calorimetry hood except for one to three short breaks. The values of energy expenditure and respiratory quotient (RQ) were averaged for each 30-min period after meal completion. TEF was calculated as the area under the curve of the postprandial energy expenditure above the REE.

Analyses

Rates of energy expenditure were determined from the respiratory gas exchange as calculated by proprietary software provided by the manufacturer of the calorimeter. Values of RQ do not include correction for estimates of protein oxidation. Determination of total cholesterol, low-density lipoprotein (LDL)-cholesterol, high-density lipoprotein (HDL)-cholesterol, triglycerides, glucose, insulin, and β-hydroxybutyrate in fasting plasma was made using conventional methods (5). The DEXA scan readings and biochemical analyses were conducted by personnel blinded to the group assignment of the subjects.

Statistics

Baseline characteristics were compared between the two groups using *t* tests. To assess the effects of the diets, two-way repeated-measures ANOVA, with time as the repeated factor, was performed using the software package SAS, version 8.2. The level of significance was set at 0.05 for testing the main effects of diet and time, and the interaction effect. If the main effect was significant, the Bonferroni multiple comparison was implemented to determine the specific differences. If the interaction was significant, the Bonferroni adjustment was used to keep the overall level of significance at 0.05. Differences between the groups are indicated only when there is a significant interaction between diet and time. Body weight, DEXA measurements, biochemical parameters, REE measurements, and pedometer readings were analyzed for the 40 subjects who completed the study. Comparisons of TEF between the two diets were made using paired *t* tests for eight subjects. Data are presented as mean and SE, unless designated otherwise.

Results

Subjects

Fifty obese females (10 African-Americans and 40 Caucasians) were enrolled in the study. Volunteers were enrolled in four successive groups of 8, 13, 10, and 19 subjects at 3- to 4-month intervals. Forty of the 50 subjects (80%) completed the 4-month study, with an equal number of dropouts from each diet group. The majority of dropouts (eight subjects) occurred during the first month of the intervention; two subjects dropped out during the second month. The most common reason for discontinuing the study was the inability to commit to weekly counseling sessions. Other reasons included pregnancy, new out-of-state job, dislike of the low-carbohydrate diet, and advice against following the low-carbohydrate diet by family physician. Age and anthropometric characteristics of those subjects completing the study are included in Table 1.

Nutrient intake

Subjects randomized to the low-fat (n = 20) and the low-carbohydrate (n = 20) groups reported similar energy intake at the initiation of the diets, 2176 ± 118 kcal and 2166 ± 128 kcal (9111 ± 494 and 9069 ± 536 kJ), respectively, per day, with comparable distributions of macronutrients (Figs. 1 and 2). During the first 2-month phase of the study, subjects complied with their assigned diets as reflected on their 3-d food records. At 2 months, both diet groups reported similar decreases in energy intake of approximately 850 kcal (3559 kJ) per day compared with baseline. Although energy intake in the two groups was similar in the low-fat and low-carbohydrate groups (1339 ± 72 and 1288 ± 104 kcal/d, respectively; 5606 ± 301 *vs.* 5393 ± 435 kJ/d, respectively; Fig. 1), the proportion of carbohydrate, protein, and fat consumed differed dramatically. Compared with baseline, the low-carbohydrate group decreased their carbohydrate intake from 48 to 15% of total energy and increased their fat intake from 36 to 57% of total energy at 2 months. In the low-fat group, the distribution of macronutrients as a percentage of total energy was relatively unchanged from baseline to 2 months (Fig. 2). At 2 months, the low-carbohydrate group consumed significantly less carbohydrate, vitamin C, and fiber and significantly more total fat, saturated fat,

TABLE 1. Age and anthropometric characteristics before diet initiation of subjects who completed the 4-month study

	Low-fat diet group (n = 20) mean (SEM)	Low-carbohydrate diet group (n = 20) mean (SEM)	*P* value
Age (yr)	41.4 (3.2)	44.8 (2.4)	0.41
Height (m)	1.6 (0.01)	1.7 (0.01)	0.61
Weight (kg)	90.9 (2.1)	90.6 (2.4)	0.91
BMI[a]	33.5 (0.5)	32.8 (0.5)	0.23
Body fat (%)	41.0 (0.7)	42.0 (0.7)	0.25

[a] Body mass index (BMI) = weight (kg)/height (m)^2.

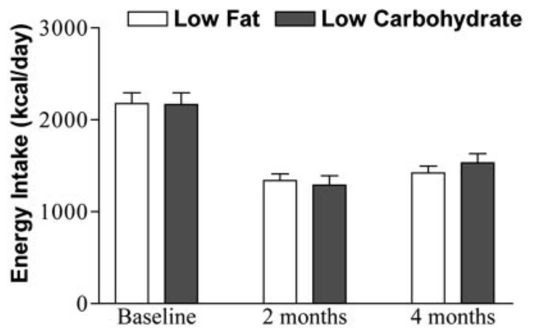

FIG. 1. Self-reported energy intake of women randomized to low-carbohydrate and low-fat diets before dieting and after 2 and 4 months of dieting. Data are presented as mean ± SEM. To convert to SI units (kJ), multiply kcal × 4.187.

monounsaturated fat, polyunsaturated fat, and cholesterol than the low-fat group ($P < 0.05$ for all comparisons; data not shown). At 4 months, the two groups still differed significantly for most of these measures but continued to report similar levels of energy intake (low-fat, 1422 ± 73 kcal/d, and low-carbohydrate, 1531 ± 102 kcal/d; low-fat, 5954 ± 306 kJ/d, and low-carbohydrate, 6410 ± 427 kJ/d; Fig. 2).

Weight and body composition

Body weight and body fat in the low-fat and low-carbohydrate groups were similar at baseline (Table 1). The women in the low-carbohydrate group lost an average of 6.69 ± 0.50 kg after 2 months and 9.79 ± 0.71 kg after 4 months of diet. Women following the low-fat diet lost 4.79 ± 0.58 kg and 6.14 ± 0.91 kg at two and four months, respectively (Fig. 3). Both fat mass and fat-free mass decreased significantly in the two groups over the course of the trial ($P < 0.001$; Table 2). However, fat mass decreased significantly more in the low-carbohydrate group compared with the low-fat group at 4 months ($P < 0.001$). There were no significant changes in bone mineral content noted in either diet group over the course of the study.

Energy expenditure

REE. REE was similar in the low-carbohydrate and low-fat dieters at the onset of the study, 1388 ± 37 kcal (5812 ± 155 kJ) and 1479 ± 34 kcal (6193 ± 142 kJ) per 24 h, respectively. REE decreased in both groups over the course of the study by an average of 82 kcal (343 kJ) per 24 h ($P < 0.001$). There were no differences between the two diet groups in REE over the course of the study, whether analyzed as total kcal REE or expressed as a function of body weight or lean body mass (Table 3). The RQ in the low-fat group was 0.87 ± 0.03 at baseline; the RQ did not change at the 2- or 4-month assessments. The RQ in the low-carbohydrate group was 0.88 ± 0.02 at baseline and decreased to 0.82 ± 0.02 and 0.81 ± 0.02 after 2 and 4 months of diet. Although 70% of the women in the low-carbohydrate group had a decrease in RQ during the trial, this change did not reach statistical significance.

Physical activity. Mean pedometer readings for the low-fat group and the low-carbohydrate group were similar at baseline, 6786 ± 811 and 6327 ± 686 steps per day, respectively. Physical activity as estimated by pedometer readings did not

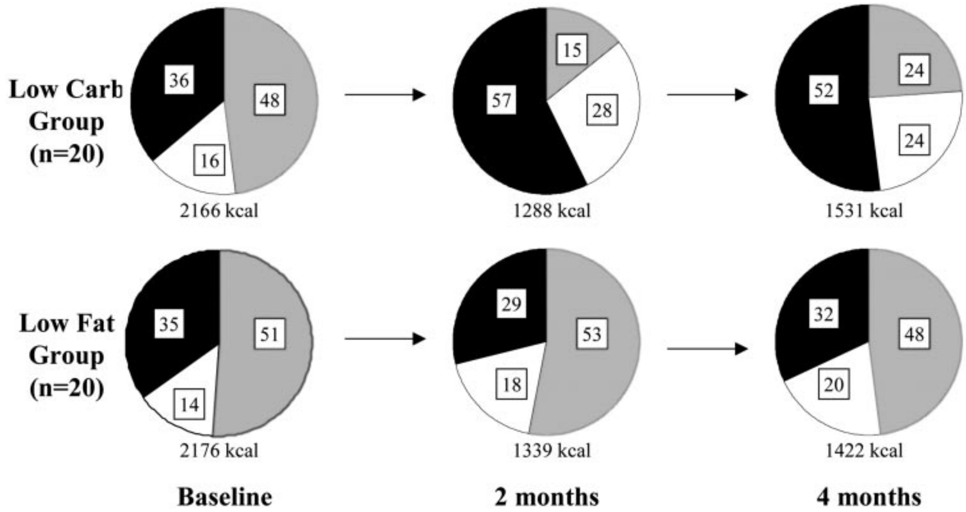

FIG. 2. Distribution of macronutrients as a percentage of total energy in the diets of women randomized to low-carbohydrate and low-fat diets before dieting and after 2 and 4 months of dieting. *Gray*, Carbohydrate; *white*, protein; *black*, fat. To convert to SI units (kJ), multiply kcal × 4.187.

change significantly over time or between groups ($P <$ 0.9992; Fig. 4). These data indicate that both groups maintained their baseline level of physical activity, as instructed at the initiation of the study.

TEF. REE did not differ in the women on the mornings they consumed the low-fat or low-carbohydrate breakfasts (1404 ± 61 *vs.* 1420 ± 78 kcal/24 h; 5879 ± 255 *vs.* 5946 ± 327 kJ/24 h). Similarly, the RQ values did not differ before the two meals (0.82 ± 0.02 and 0.86 ± 0.01). After the meal, energy expenditure and RQ increased within the first 30 min and remained elevated for the next 5 h (Fig. 5). Energy expenditure peaked at 60–90 min after the low-fat meal and 180–210 min after the low-carbohydrate meal. By 300 min post-meal consumption, energy expenditure had decreased to similar levels after both test meals and RQ had returned to near basal levels (0.86 ± 0.03 and 0.87 ± 0.01 for the low-fat and low-carbohydrate meals, respectively). The TEF after the low-fat meal was significantly greater than the TEF after the low-carbohydrate meal (53 ± 9 *vs.* 31 ± 5 kcal; 222 ± 38 *vs.* 130 ± 21 kJ; $P = 0.017$).

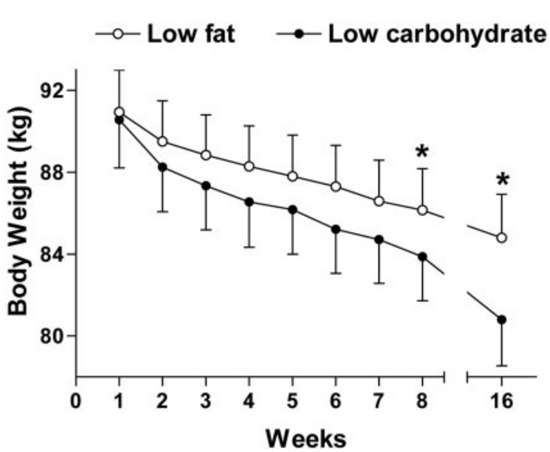

FIG. 3. Mean body weight of women randomized to low-carbohydrate and low-fat diets over the course of the 4-month trial. The first time point (wk 1) represents the subjects' body weights immediately before randomization. Follow-up for the two groups included 18–20 subjects in each group. For subjects missing a follow-up visit, their last recorded weight is included in the calculation of the group mean. Data are presented as mean ± SEM. *, Value different from low-carbohydrate diet group (*i.e.* significant interaction of time and diet); $P < 0.01$.

Fasting hormones and substrates

Fasting glucose levels were normal in all subjects at baseline, 90 ± 0.2 mg/dl (5 ± 0.01 mmol/liter), and were not significantly different at the 2- and 4-month assessments. Plasma insulin levels were also similar in both groups at baseline, 19 ± 2 and 22 ± 3 μU/ml (135 ± 12 and 151 ± 22 pmol/liter) for the low-carbohydrate and low-fat groups, respectively, and decreased in both groups after 2 and 4 months of dieting to 14 ± 1 and 12 ± 1 μU/ml (97 ± 8 and 86 ± 10 pmol/liter) in the low-carbohydrate group and 19 ± 2 and 19 ± 3 μU/ml (131 ± 12 and 133 ± 18 pmol/liter) in the low-fat group. There was a significant time effect for fasting insulin levels in both groups over the course of the study ($P < 0.01$) but no interaction with diet. There was a significant increase in fasting plasma β-hydroxybutyrate in the women on the low-carbohydrate diet over the course of the study. Before randomization, fasting levels were .57 ± 0.1 mg/dl (55 ± 7 μmol/liter) but increased to 2.8 ± 0.3 and 2.0 ± 0.4 mg/dl (270 ± 31 and 190 ± 38 μmol/liter) after 2 and 4 months dieting ($P < 0.01$). There was no change in

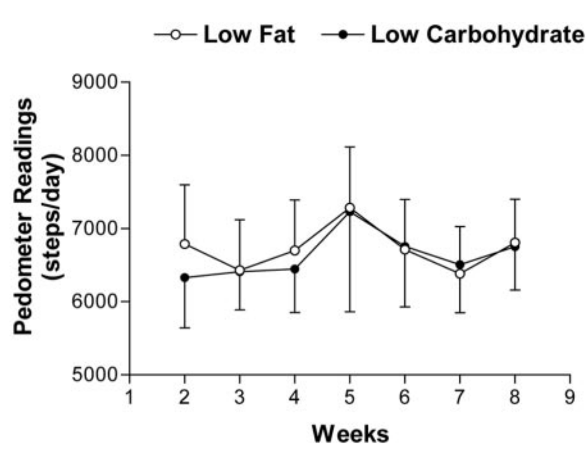

FIG. 4. Pedometer readings of women randomized to low-carbohydrate and low-fat diets. Data are presented as mean ± SEM.

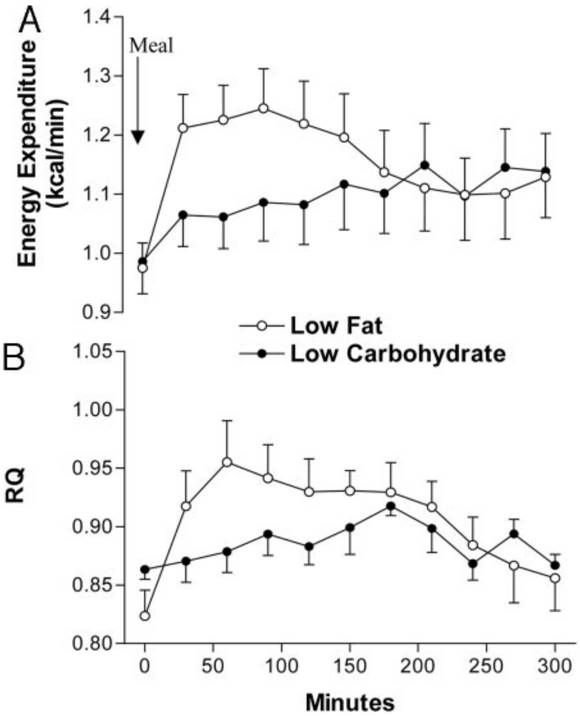

FIG. 5. Energy expenditure (A) and respiratory quotient (RQ) (B) before and after consumption of a 540-kcal (2261 kJ) low-fat or low-carbohydrate meal. Data are presented as mean ± SEM. To convert to SI units (kJ) multiply kcal × 4.187.

fasting plasma β-hydroxybutyrate in the low-fat dieters from baseline to 2 months or 4 months, 0.75 ± 0.12, 0.57 ± 0.05, and 0.7 ± 0.1 mg/dl, respectively (72 ± 12, 55 ± 5, and 67 ± 10 μmol/liter, respectively).

Blood pressure and plasma lipids

Blood pressure and plasma lipids were normal at the outset of the study. Significant time effects ($P < 0.05$) were noted, indicating small improvements in systolic blood pressure, total cholesterol, triglycerides, and HDL-cholesterol over the 4 months (Table 4). Differences between the groups were not detected in total cholesterol, LDL-cholesterol, and triglycerides at the 2- or 4-month assessments. However, similar to the findings of other researchers (6), HDL-cholesterol increased significantly more in the low-carbohydrate group compared with the low-fat group at 2 months and 4 months ($P < 0.001$).

Discussion

The results of this study confirm those of our prior clinical trial and the work of other investigators, showing that low-carbohydrate diets are effective for loss of weight and body fat over periods of 4–6 months (5–7). In the current study, the low-carbohydrate dieters lost over 10% of their body weight, whereas the low-fat dieters lost approximately 7% of their body weight, robust results for a 4-month period. Similar to our previous trial, we could not explain this differential weight loss by the subjects' reported energy intake. This study was designed primarily to determine whether a difference in energy expenditure could explain the greater weight loss in the low-carbohydrate group. Our results demonstrate that the primary components of daily energy expenditure do not differ substantially between healthy women on low-fat and low-carbohydrate diets and cannot account for significant differences in weight loss. This raises the possibility that there were, in fact, significant differences in energy intake in the two groups that were not detected in the 3-d food records.

We embarked on this study in an attempt to determine whether the greater weight loss observed in women on low-carbohydrate diets compared with those on low-fat diets could be the result of greater energy expenditure. In our previous trial, food records of subjects on these regimens showed differences in the reported intake of macronutrients but not in energy intake (5). Therefore, holding strictly to the reported intake data, we could not ascribe the greater amounts of weight loss in the low-carbohydrate group to a greater restriction of food intake. In the present study, the subjects in both groups reported similar energy intake before initiating the diet and throughout the intervention. Again, we did not predict a similarity in energy consumption, because the low-carbohydrate dieters were given no restrictions in energy intake, whereas the low-fat dieters were instructed to limit their intake to approximately 1200 kcal (5024 kJ) per day. Based on the subjects' food records, there was a reduction in energy of approximately 850 kcal (3559 kJ) per day at 2 months and 700 kcal (2931 kJ) per day at 4 months in both the low-fat and low-carbohydrate groups. To account for the approximately 3.6 kg difference in weight loss between the groups over 4 months, with similar energy intake, the low-carbohydrate group would have to expend approximately 225 kcal (942 kJ) per day more than the low-fat group (9, 10). However, we could not account for differences of this magnitude in measurements of REE or TEF or estimates of physical activity.

REE was determined by indirect calorimetry after an overnight fast, using standard assumptions and extrapolated over 24 h (11). Our results showed a reduction in REE in both groups over the course of the study, as expected with the loss of fat and fat-free mass (12). REE did not differ between the groups at baseline or at the 2- and 4-month assessments, whether expressed as absolute energy expenditure or as a function of body size. In the women studied in this trial, we

TABLE 2. Means (SEM) of body composition measures of women before dieting and after 2 and 4 months of dieting

	Low-carbohydrate diet group (n = 20)			Low-fat diet group (n = 20)		
	Baseline	2 months	4 months	Baseline	2 months	4 months
Body fat (kg)	37.89 (1.27)	33.71 (1.16)	31.70[a] (1.41)	37.15 (0.92)	34.51 (1.10)	33.91 (1.29)
Bone mineral content (kg)	2.70 (0.10)	2.70 (0.10)	2.71 (0.10)	2.65 (0.09)	2.67 (0.09)	2.68 (0.09)
Lean body mass (kg)	49.56 (1.17)	47.48 (1.17)	46.22 (1.73)	50.77 (1.40)	49.12 (1.26)	48.83 (1.25)

[a] Value different from the low-fat group (*i.e.*, significant interaction of time and diet); $P < 0.01$.

TABLE 3. REE (SEM) of women randomized to low-carbohydrate (n = 20) and low-fat (n = 20) diets before dieting and after 2 and 4 months of dieting

	Low-carbohydrate diet group (n = 20)			Low-fat diet group (n = 20)		
	Baseline	2 months	4 months	Baseline	2 months	4 months
REE (kcal)	1388.21 (36.76)	1277.32 (43.55)	1306.37 (48.97)	1478.63 (33.97)	1448.90 (49.22)	1396.89 (43.63)
REE/kg body weight	15.41 (0.42)	15.26 (0.41)	16.25 (0.46)	16.45 (0.31)	16.86 (0.49)	16.64 (0.42)
REE/kg lean body mass	28.12 (0.69)	26.98 (0.72)	29.04 (1.51)	29.64 (0.42)	29.51 (0.68)	28.70 (0.46)

To convert to SI units (kJ), multiply kcal × 4.187.

have observed day-to-day variability in REE of 4–5%, similar to what we reported previously for obese men (13). Using this value of variance for the measurement of REE, this study had more than 95% power to detect a systematic difference in REE of more than 225 kcal (942 kJ) between the two diet groups. The lack of significant differences between the groups in terms of REE does not support the hypothesis, or the claim by proponents of low-carbohydrate diets (8), that an enhanced metabolic rate is responsible for the increased weight loss associated with this dietary strategy.

To assess potential differences in physical activity that could systematically alter energy balance in the two groups, subjects kept weekly 3-d pedometer records that were reviewed by the dietitians. Pedometers have been used to measure physical activity in free-living humans, especially when walking is the primary form of physical activity, and have been shown to be valid and reliable instruments that provide a useful indicator of daily step counts (14, 15). There was variable compliance with pedometer use/recording in our subjects between months 2 and 4 of the study. However, complete data were available on all subjects at the end of the first 2 months of the study, showing no significant differences in pedometer readings between the two diet groups. Because the relative differences in weight loss between the two groups were similar at 2 and 4 months, we think that it is unlikely that there were any systematic differences in activity in the latter part of the trial that could account for the final changes in body weight.

The TEF includes energy expended in the absorption and assimilation of nutrients and comprises 10% or less of daily energy consumption (13). Diets high in protein have been reported to induce greater TEF because assimilation of protein is an energetically costly process. However, over the 5 h we assessed TEF in obese women after breakfasts that were matched in calories but with different macronutrient content, we found significantly higher energy expenditure for the low-fat meal compared with the low-carbohydrate meal. The patterns of energy expenditure after the meal suggest that the low-carbohydrate meal was absorbed more slowly than the low-fat meal, a reasonable assumption given the known effects of the nutrient fat to slow gastric emptying (16, 17). Thus, it is plausible that the 5-h period we used to measure TEF may have underestimated the full TEF of the low-carbohydrate meal to a greater extent than the low-fat meal. However, it has been demonstrated that measurement of TEF for at least 5 h, in response to meals that were equal to or greater than the breakfasts used in this study, is sufficient to detect the majority of TEF (18). Previous studies indicate that diet-induced thermogenesis is unlikely to result in expenditure of greater than 15% of the energy content of the nutrients (13, 16, 19, 20), which, in the case of our 540-kcal (2261 kJ) meals, would account for a maximum of approximately 80 kcal (335 kJ). For TEF to account for an energy differential sufficient for a 3- to 4-kg difference in weight loss over 4 months, an 80-kcal (335 kJ) increase of TEF in the low-carbohydrate over the low-fat diet group would be required at three meals per day. Yet, even if we had underestimated TEF in the low-carbohydrate group by 100% in this study, we would not have approached the amount of energy needed to account for the greater weight loss in this group.

We did not measure TEF in women while they were enrolled in our weight loss studies, so as to limit the intensity of intervention and maximize subject retention. Instead, we made comparisons of low-fat and low-carbohydrate meals in subjects who had completed the trials. Acheson and colleagues (21) reported that in healthy adults, 3–6 d of a low-carbohydrate diet decreased the thermic effect of ingested glucose by 40% compared with several days of low-fat, high-carbohydrate intake. We cannot exclude the possibility that our subjects would have had systematically different TEF responses had we studied them during the active diet intervention. However, if a low-carbohydrate diet for several months has the same effect on TEF as short-term low-carbohydrate intakes (21), the postprandial energy expenditure would have been even lower in this group, and certainly not consistent with their greater weight loss.

TABLE 4. Means (SEM) of blood pressure and plasma lipid concentrations of women before dieting and after 2 and 4 months of dieting

	Low-carbohydrate diet group (n = 20)			Low-fat diet group (n = 20)		
	Baseline	2 months	4 months	Baseline	2 months	4 months
Blood pressure (mm Hg)	119/76 (3.5/1.7)	114/73 (3.8/2.4)	110/71 (3.4/2.1)	119/77 (2.9/1.7)	116/74 (2.8/2.0)	116/75 (3.5/2.8)
Total cholesterol (mg/dl)	205.05 (9.58)	193.90 (7.07)	199.70 (10.36)	196.21 (7.93)	180.65 (8.74)	188.85 (9.59)
Triglycerides (mg/dl)	128.85 (13.44)	78.80 (4.82)	80.75 (6.11)	145.63 (19.95)	129.45 (10.30)	130.65 (13.41)
LDL (mg/dl)	134.85 (8.26)	130.10 (7.16)	131.90 (9.93)	125.28 (5.95)	111.15 (7.35)	116.60 (8.08)
HDL (mg/dl)	44.40 (2.11)	48.10[a] (2.71)	51.65[a] (2.55)	44.21 (1.69)	43.50 (2.02)	46.20 (2.08)

To convert to SI units (mmol/liter), multiply total cholesterol, LDL-cholesterol, HDL-cholesterol (mg/dl) × 0.0259; multiply triglycerides (mg/dl) × 0.1129.

[a] Value different from the low-fat group (*i.e.*, significant interaction of time and diet); $P < 0.01$.

Although each of the measurements of energy expenditure that were used in this study has limitations, there was no evidence of even a trend for greater energy expenditure in the low-carbohydrate group. It is possible that there were differences in physical activity and REE between the groups that were not detected by our assessments. Although pedometers have been shown to be useful in assessing physical activity in free-living populations (15, 22), limitations of pedometers include their inability to assess the intensity or duration of the activity. A limitation of indirect calorimetry for measuring REE is the assumption that a relatively short assessment time can be projected throughout the day. Ultimately this question might best be addressed using more sophisticated assessment methods that can integrate total energy expenditure over longer time periods, such as the doubly labeled water method (23) or whole room calorimetry (24). Nonetheless, we believe that even with these techniques, it is unlikely that the difference in short-term weight loss between the low-carbohydrate and low-fat diet groups can be explained by energy expenditure.

Another possible explanation of the results of our two trials comparing low-carbohydrate and low-fat diets is reporting bias. We propose that the women randomized to the low-fat diet systematically underreported their energy intake. Such an error could account for the apparent paradox in the estimates of energy balance in groups of subjects with significantly different amounts of weight loss. Based on the low-carbohydrate dieters' reported energy intake at baseline, 2 months, and 4 months, the expected weight loss was 6.8 kg and 11.8 kg at 2 and 4 months, not substantially different from their actual weight loss of 6.7 kg and 9.8 kg, respectively. In contrast, the weight loss predicted from the diet records of the low-fat group was 6.5 kg and 12.4 kg at 2 and 4 months, overestimates compared with the measured results of 4.8 kg and 6.1 kg. Thus, actual weight loss approximates the expected weight loss for the low-carbohydrate group but is less than expected for the low-fat group. One reason for underreporting by the low-fat dieters may have been that they were following a prescribed energy restriction and so were faced with a limit in daily energy intake. Because we did not restrict energy intake in the low-carbohydrate group, it is plausible that they felt less pressure to meet any goals for energy intake. If we had given a prescribed energy restriction to the low-carbohydrate group, they too might have underreported their daily intake. In addition, because the low-carbohydrate group followed a diet that differed dramatically from their usual intake, with more limited food choices that were likely easier to catalogue and record, we think that it is probable that their reporting was more accurate. Consistent underreporting of energy intake by nonobese subjects, and even greater underreporting by obese subjects, has been noted in previous studies (25–27), and we believe this is the most likely explanation for our results even though we cannot directly prove it. To our knowledge, this would be the first report of biased reporting of intake because of differences in macronutrient content of the diet and instructions regarding energy restriction. These results have important implications for future clinical research in that randomization of subjects with similar BMIs is not sufficient to ensure equivalent reporting of energy intake between diet groups.

Despite questions related to the accuracy of the amount of energy consumed, we have confidence that the two groups consumed qualitatively different diets. Similar to our first trial comparing low-fat and low-carbohydrate diets, the plasma levels of β-hydroxybutyrate were consistent with the assigned diets in the two groups. As expected, the low-fat dieters had plasma β-hydroxybutyrate levels that remained static throughout the study, whereas the low-carbohydrate group had significantly increased ketones at 2 and 4 months. To maintain significant plasma ketosis requires very limited carbohydrate intake, and this measure has been the hallmark of adherence to these diets.

In summary, we have demonstrated that women consuming a low-carbohydrate diet lose more weight than women consuming a low-fat diet over several months. The more pronounced weight loss in the low-carbohydrate dieters is not explained by increased REE, TEF, or physical activity and cannot be accounted for by their reported energy intakes. However, we believe that the best explanation for the difference in weight loss between the groups is a difference in energy intake that was not apparent in their self-reported 3-d food records. The reason for decreased energy intake in the low-carbohydrate group, even in the face of no restrictions on energy, remains to be explained. Some have speculated that this self-restriction is a result of the effect of circulating ketones on appetite or other satiating effects of low-carbohydrate diets, but this remains unproven. The major point is that the principal means of voluntarily shifting energy balance to promote weight loss is restriction of intake and increase in expenditure. At present, the best methods for accomplishing these lifestyle changes for prolonged periods of time remain elusive.

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