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A Randomized Trial Comparing a Very Low Carbohydrate Diet and a Calorie-Restricted Low Fat Diet on Body Weight and Cardiovascular Risk Factors in Healthy Women

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Untested alternative weight loss diets, such as very low carbohydrate diets, have unsubstantiated efficacy and the potential to adversely affect cardiovascular risk factors. Therefore, we designed a randomized, controlled trial to determine the effects of a very low carbohydrate diet on body composition and cardiovascular risk factors. Subjects were randomized to 6 months of either an *ad libitum* very low carbohydrate diet or a calorie-restricted diet with 30% of the calories as fat. Anthropometric and metabolic measures were assessed at baseline, 3 months, and 6 months. Fifty-three healthy, obese female volunteers (mean body mass index, 33.6 ± 0.3 kg/m^2) were randomized; 42 (79%) completed the trial. Women on both diets reduced calorie consumption by comparable amounts at 3 and 6 months. The very low carbohydrate diet group lost more weight (8.5 ± 1.0 *vs.* 3.9 ± 1.0 kg; $P < 0.001$) and more body fat (4.8 ± 0.67 *vs.* 2.0 ± 0.75 kg; $P < 0.01$) than the low fat diet group. Mean levels of blood pressure, lipids, fasting glucose, and insulin were within normal ranges in both groups at baseline. Although all of these parameters improved over the course of the study, there were no differences observed between the two diet groups at 3 or 6 months. β-Hydroxybutyrate increased significantly in the very low carbohydrate group at 3 months ($P = 0.001$). Based on these data, a very low carbohydrate diet is more effective than a low fat diet for short-term weight loss and, over 6 months, is not associated with deleterious effects on important cardiovascular risk factors in healthy women. (*J Clin Endocrinol Metab* 88: 1617–1623, 2003)

THE INCIDENCE OF obesity in the United States has risen continuously over the last several decades, and the associated medical and economic costs to society are substantial (1–3). Despite considerable desire on the part of obese individuals to lose weight (4) and the clear health benefits of doing so (5), there are currently no proven, effective approaches for meaningful and long-term weight loss for most overweight individuals (2). Dietary strategies supported by the majority of physicians and dietitians, which emphasize restriction of fat intake, are associated with only modest weight loss and poor long-term compliance (6, 7). Given these difficulties and the popular demand for effective weight loss methods, it is not surprising that a number of diet plans have been developed outside the medical and nutritional mainstream that are marketed directly to the public as weight loss strategies.

The very low carbohydrate, high protein diet, promoted extensively by Atkins and others, is one of the most popular of the alternative weight loss approaches (8). The central rationale of this diet is that severe restriction of dietary carbohydrate (<10% of daily caloric intake), with its resulting ketosis, promotes lipid oxidation, satiety, and increased energy expenditure, factors that should promote negative energy balance and weight loss (8). However, these purported responses to very low carbohydrate feeding have not been established. Furthermore, as studies that severely restrict carbohydrate intake have all been of short duration (*i.e.* <6 wk) (9–16), the clinical benefits of ketogenic diets are unproven.

Because low carbohydrate diets derive large proportions of calories from protein and fat, there has been considerable concern for their potentially detrimental impact on cardiovascular risk (17). Increased consumption of fat, particularly saturated fat, has been linked to increased plasma concentrations of lipids (18), insulin resistance, glucose intolerance (19, 20), and obesity (21, 22). Therefore, it is possible that many Americans could actually suffer adverse health effects by using very low carbohydrate diets in an attempt to lose weight. To evaluate the effects of a very low carbohydrate diet on weight loss and cardiovascular risk factors, we randomized 53 healthy obese women to 6 months of a very low carbohydrate diet or a calorie-restricted, low fat diet conforming to the guidelines currently recommended by the American Heart Association and other expert panels (23).

Subjects and Methods

Subjects

Fifty-three obese females were recruited by advertisement and randomized to the 2 diets based on a prior estimate that 20–25 subjects/group would be sufficient to demonstrate a 25% difference in weight loss and a 30% difference in low density lipoprotein (LDL) cholesterol levels between the 2 regimens. Inclusion criteria were age at least 18 yr, moderate obesity (body mass index, 30–35), and a stable weight over the preceding 6 months (no weight loss or gain >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.

Abbreviations: DEXA, Dual energy x-ray absorptiometry; HDL, high density lipoprotein; LDL, low density lipoprotein.

Assessments

Subject assessments were conducted at the General Clinical Research Center of Cincinnati Children's Hospital Medical Center by trained research nurses. Subjects were screened by medical history and measurements of height, weight, blood pressure, and fasting glucose, and each was given an electrocardiogram. Blood pressure measurements were made by auscultation using an appropriate size cuff with the subject seated quietly. Individuals meeting the criteria for study participation were enrolled in the study by the research assistant or the principal investigator. Subjects gave a sample of fasting blood and had body fat measured by dual energy x-ray absorptiometry (DEXA) using a total body scanner (4500A, Hologic, Inc., San Francisco, CA). DEXA scans were conducted at the body composition core laboratory of the General Clinical Research Center by trained technicians. Each of these measures was repeated after 3 and 6 months of diet.

Study diets

The primary objective of the study was to compare the effects of a very low carbohydrate diet and a calorie-restricted, low fat diet on body composition and cardiovascular risk factors. Therefore, after each block of subjects was assessed, the principal investigator used a random number table 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 carbohydrate/d (8). It was anticipated that this diet would induce 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 on a calorie-restricted, moderately low fat diet with a recommended macronutrient distribution of 55% carbohydrate, 15% protein, and 30% fat. Calorie prescriptions were based on body size and calculated using the Harris-Benedict equation (24).

Two registered dietitians delivered a 3-month intervention aimed at promoting dietary compliance. Group meetings with subjects on the same diet were held biweekly on the University of Cincinnati campus 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 from the previous week, analyzed by Nutritionist V (First Data Bank, San Bruno, CA), and provided dietary recommendations and positive reinforcement. Subjects were advised to continue their baseline level of activity. 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. Before each weekly session, subjects submitted 3-d food records and were weighed on a single electronic scale (Tanita, Arlington Heights, IL). Blood pressure was measured, and assessment of urinary ketones was performed using Ketostix (Bayer Corp., Elkhart, IN). At the end of the 3-month intervention, subjects were instructed to continue with their weight loss efforts, but without scheduled contact with the dietitians until the 6-month assessment.

Analyses

Determination of total cholesterol, LDL cholesterol, high density lipoprotein (HDL) cholesterol, glucose, insulin, leptin, β-hydroxybutyrate, and triglycerides in fasting plasma were made using conventional methods (25–27). The results of DEXA and biochemical analyses were made 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, SAS Institute, Inc., Cary, NC). 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 groups are indicated only when there is a significant interaction between diet and time. Body weight, biochemical parameters, and DEXA measurements were analyzed for the 42 subjects who completed the study (*i.e.* those for whom follow-up data were available). Body weight was also analyzed for the entire randomized cohort. In this intention to treat analysis, the initial weights for the subjects who withdrew from the study were used as their follow-up weights at 3 and 6 months (*i.e.* an assumption of 0 kg of weight loss). Data are presented as the mean and SE unless designated otherwise.

Results

Subjects

Subjects were recruited through advertisements from May 2000 through January 2001. Fifty-three obese females (13 African-Americans and 40 Caucasians) were enrolled in the study. Volunteers were enrolled in 3 successive groups of 14, 20, and 19 subjects at 3- to 4-month intervals. Forty-two of the 53 subjects (79%) completed the 6-month study, with 4 dropouts from the very low carbohydrate diet group and 7 dropouts from the low fat diet group (Fig. 1). The majority of subjects discontinuing the study cited difficulty maintaining the scheduled visits as the primary reason, and follow-up measurements were obtained for only 1 of the these women. One subject from each diet group dropped out due to dislike for their assigned diet. 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 very low carbohydrate (n = 22) diet groups consumed similar amounts of calories at the initiation of the diets (1707 ± 104 and 1608 ± 123 kcal respectively) with similar distribution of macronutrients (Fig. 2). Based on the results of the weekly food records, subjects complied with their assigned diets. Although subjects on the carbohydrate-restricted diet were

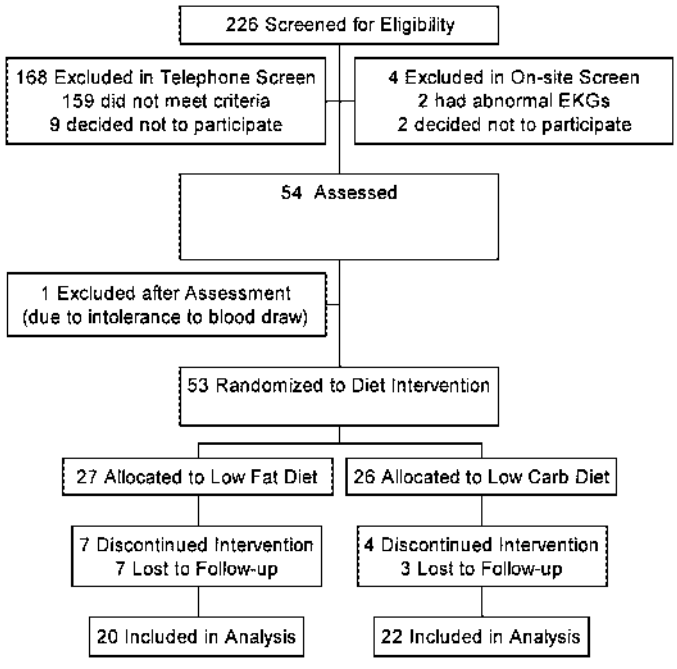

FIG. 1. Flow chart of subjects in the controlled, randomized weight loss trial.

not specifically asked to limit caloric intake as were those on the low fat diet, both groups reported a decrease in caloric intake of approximately 450 calories compared with baseline. Although caloric intakes in the two groups were similar, the proportions of carbohydrate, protein, and fat consumed differed dramatically. At 3 months, caloric intake in the very low carbohydrate diet group was distributed as 15% carbohydrate, 28% protein, and 57% fat. In contrast, the low fat diet group had daily calories distributed as 54% carbohydrate, 18% protein, and 28% fat. At 3 months, the very low carbohydrate diet group consumed significantly less carbohydrate, vitamin C, and fiber and significantly more protein, total fat, saturated fat, monounsaturated fat, polyunsaturated fat, and cholesterol than the low fat diet group ($P < 0.01$ for all comparisons). At 6 months, the two groups still differed significantly for most of these measures (Table 2).

Weight and body composition

Body weight and body fat in the low fat and very low carbohydrate groups were similar at baseline (Table 1). After the initiation of the diets, both groups had a decrease in body weight that was more rapid in the earlier weeks of observation and became less pronounced as the study progressed (Fig. 3). The women in the very low carbohydrate group lost an average of 7.6 ± 0.7 kg after 3 months and 8.5 ± 1.0 kg after 6 months of diet. Women following the low fat diet lost 4.2 ± 0.8 and 3.9 ± 1.0 kg at 3 and 6 months, respectively. The amount of weight lost was significantly greater in the very low carbohydrate group compared with the low fat group, whether analyzed as intention to treat with all randomized subjects in the analysis ($P < 0.001$ at 3 and 6 months) or with only the subjects who completed the trial (Fig. 3; $P < 0.001$ at 3 and 6 months).

Body composition data for the two groups of women are shown in Table 3. Both fat mass and fat-free mass decreased significantly ($P < 0.001$) in the two groups over the course of the trial. However, similar to body weight, fat mass and lean body mass decreased significantly more in the very low carbohydrate group compared with the low fat group at both 3 and 6 months ($P < 0.01$). The reduced fat mass comprised 50–60% of the weight lost in both groups. There were no changes in bone mineral content over the course of the study.

TABLE 1. Age and anthropometric characteristics before diet initiation of subjects who completed the 6-month study

	Low fat diet group (n = 20)		Very low carbohydrate diet group (n = 22)		
	Mean (SD)	Range	Mean (SD)	Range	*P*
Age (yr)	43.10 (8.56)	31.08–58.55	44.22 (6.84)	29.01–53.49	0.64
Height (m)	1.65 (0.05)	1.58–1.75	1.66 (0.07)	1.54–1.79	0.58
Weight (kg)	92.31 (6.0)	83.4–105.2	91.20 (8.4)	76.9–113.7	0.61
BMI[a]	34.04 (1.83)	29.57–36.05	33.17 (1.83)	30.87–37.03	0.13
Body fat (%)	41.34 (2.70)	37.3–47.6	41.26 (3.67)	36.2–50.1	0.93

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

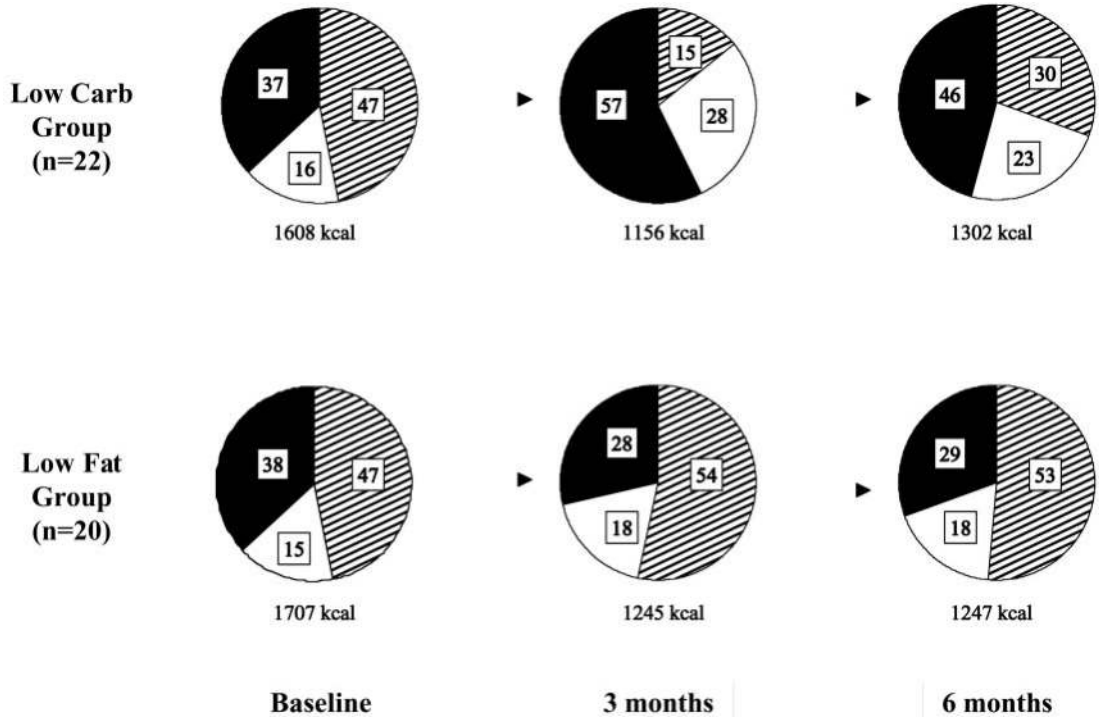

FIG. 2. Mean caloric intake and distribution of macronutrients (as percentage of total kilocalories) of women before and at 3 and 6 months of either very low carbohydrate or low fat diets. *Gray lines*, Carbohydrate; *white*, protein; *black*, fat.

TABLE 2. Mean nutrient intake of women before and after 3 and 6 months of dieting

	Baseline	3 months	6 months	Recommended intake[a]
Very low carbohydrate diet group (n = 22)				
Carbohydrate (g)	188.92	41.13[c]	96.98[c]	≥55% total kcal
Protein (g)	63.32	78.15[c]	74.13[c]	10–15% total kcal
Total fat (g)	65.79	71.32[c]	65.45[c]	≤30% total kcal
Saturated fat (%)	12.4	20.7[c]	17.4[b]	≤10% total kcal
Monounsaturated fat (%)	10.1	20.6[c]	15.8[c]	10% total kcal
Polyunsaturated fat (%)	6.2	9.0[c]	8.2[c]	10% total kcal
Cholesterol (mg)	215.25	460.87[c]	285.44[b]	<300
Vitamin C (mg)	70.28	35.65[c]	58.46	75
Folate (μg)	155.14	139.65	195.89	400
Calcium (mg)	590.81	444.20	739.01	1000
Fiber (g)	12.03	5.27[c]	8.40[c]	20–35
Low fat diet group (n = 20)				
Carbohydrate (g)	200.06	169.40	162.88	≥55% total kcal
Protein (g)	66.06	55.93	54.74	10–15% total kcal
Total fat (g)	71.60	39.77	43.13	≤30% total kcal
Saturated fat (%)	12.3	9.9	11.1	≤10% total kcal
Monounsaturated fat (%)	10.1	9.0	7.3	10% total kcal
Polyunsaturated fat (%)	5.8	4.5	3.7	10% total kcal
Cholesterol (mg)	273.51	169.00	182.21	<300
Vitamin C (mg)	76.92	94.18	53.14	75
Folate (μg)	170.95	221.72	193.90	400
Calcium (mg)	607.25	567.19	662.62	1000
Fiber (g)	12.48	13.31	12.35	20–35

[a] Recommended intake for females, 19–50 yr of age.
[b] Denotes values different from the low fat diet group, $P \leq 0.05$.
[c] Denotes values different from the low fat diet group, $P \leq 0.01$.

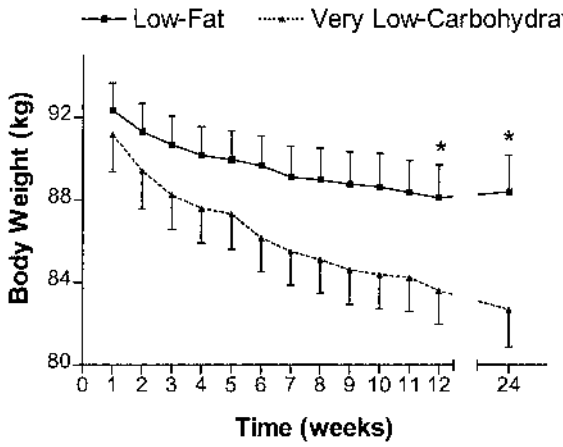

FIG. 3. Mean body weight of women randomized to very low carbohydrate and low fat diets over the course of the 6-month trial. The first time point (wk 1) represents the subjects' body weights immediately before randomization. Follow-up for the 2 groups included 17–20 subjects in the low fat group and 19–22 subjects in the very low carbohydrate group. For subjects missing a follow-up visit, their last recorded weight is included in the calculation of the group mean. *, Value different from very low carbohydrate diet group (*i.e.* significant interaction of time and diet), $P < 0.001$.

Cardiovascular risk factors

EKG. There were no electrocardiographic abnormalities in any of the subjects during the study.

Blood pressure. The blood pressures in the two groups were within the normal range at the outset of the study and remained so throughout the study (Table 4). Significant differences in blood pressure were not found between the groups during the study.

Plasma lipids. Mean plasma concentrations of total cholesterol, triglycerides, LDL cholesterol, and HDL cholesterol were normal in each of the two groups before starting the diets. A significant interaction ($P < 0.05$) was found for plasma triglycerides, but this was probably due to a difference between the groups at baseline. Differences in plasma lipids between the groups were not detected at the 3- or 6-month assessments (Table 4). Significant time effects ($P < 0.01$) for all of the plasma lipids indicated that the subjects improved their lipid profiles during the course of the study, with significant decreases in total cholesterol, LDL cholesterol, and triglycerides at 3 months and significant increases in HDL cholesterol at 6 months (Table 4).

Fasting hormones and substrates. Fasting glucose and insulin did not differ between the two groups at the 3- or 6-month assessments. However, significant time effects for glucose ($P < 0.001$) and insulin ($P < 0.0001$) indicate that the glucose and insulin levels decreased significantly in the women on both diets over the 6-month study (Table 5). There were no differences in leptin levels between the two groups (Table 5). Yet a significant time effect ($P < 0.0001$) shows that plasma leptin levels decreased significantly in both groups of subjects at 3 months (Table 5). A significant difference between the groups was detected for plasma β-hydroxybutyrate, with this ketone increasing significantly more in the very low carbohydrate group at 3 months ($P = 0.0005$; Table 5). Weekly testing of urinary ketones was positive in the majority of subjects on the very low carbohydrate diet and negative in those on the low fat diet.

Discussion

The results of this study demonstrate that a very low carbohydrate diet, taken without a specified restriction of

caloric intake, is effective for weight loss over a 6-month period in healthy, obese women. Compared with the low fat group, who followed a diet conforming to currently recommended distributions of macronutrient calories, the very low carbohydrate group lost significantly more weight, a finding that was apparent both when the women completing the diet were considered alone and when the data were analyzed using intent to treat principles. In addition, despite eating a high percentage of calories as fat and having relatively high intakes of saturated fat and cholesterol, the women in the very low carbohydrate group maintained normal levels of blood pressure, plasma lipids, glucose, and insulin. These data suggest that the deleterious effects of diets containing a high percentage of fat on body weight and cardiac risk factors are mitigated by restriction of caloric intake and associated weight loss.

The subjects recruited for this study were healthy adult women who were moderately obese by current standards. As such they were representative of many American women who embark on weight loss efforts each year using the alternative dietary plans currently marketed in this country. Although compliance with the diets was assessed primarily by dietary records, these data are supported by more objective measures. For example, the average 3-month weight loss in the low fat diet group (~4 kg) is what would be expected for individuals decreasing their daily caloric consumption by about 400 kcal (28), approximately the restriction these women reported making. In addition, there was a significant correlation between reported changes in caloric intake and weight loss ($r = 0.41$; $P < 0.001$). Finally, the presence of measurable ketonemia and ketonuria in the very low carbohydrate group is consistent with severe carbohydrate restriction and was not seen in the low fat dieters. Thus, we believe that the outcomes of this study can be attributed primarily to differences in the prescribed diets of the two groups and are applicable to the large number of obese, but otherwise healthy, American women exploring very low carbohydrate diets.

One conclusion of previous reports on low carbohydrate diets was that the increased weight loss was due to the diuresis that accompanies severe caloric restriction or was due to decreased body water, presumably accompanying depletion of stored glycogen (29, 30). However, these studies were of very short duration, from 1–2 wk in length. Most diets that have a significant restriction of calories cause a sodium diuresis that occurs over the first wk or 2 of their use, and in fact, we noted the most rapid weight loss in both groups over this period. The low fat diet group lost 1.6 kg in the first 2 wk, representing 38% of their mean weight loss during the first 3 months of the study. The very low carbohydrate group lost 3.0 kg during the first 2 wk, or 39% of their mean 3-month weight loss. We analyzed body composition at 3 and 6 months of dieting, well after the expected period of diuresis. Our analysis of body composition showed that the weight lost in the very low carbohydrate diet group consisted of a similar percentage of fat mass as in the low fat diet group. Thus, we think it is very unlikely that differences in weight between the two groups at 3 and 6 months are a result of disproportionate changes in body water in the very low carbohydrate dieters.

The mechanism of the enhanced weight loss in the very low carbohydrate diet group relative to the low fat diet group is not clear. Based on dietary records, the reduction in daily caloric intake was similar in the two groups. For the greater weight loss in the very low carbohydrate group to be strictly a result of decreased caloric consumption, they would have had to consume approximately 300 fewer calories/d over the first 3 months relative to the low fat diet group (28). Although the inaccuracy of dietary records for obese individuals is well documented (31, 32), it seems unlikely that a systematic discrepancy of this magnitude occurred between groups of subjects who were comparably overweight. Therefore, it is difficult to explain the differences in weight loss between the two groups primarily as a function of differing caloric intake. Despite instructions to maintain baseline levels of activity, it is possible that the women in the very low carbohydrate diet group exercised more than those in the low fat diet group. Additionally, it is possible that consuming a very low carbohydrate diet increases resting or postprandial energy expenditure. The possibility that differences in the macronutrient composition of the diet alter energy expenditure is an interesting question that bears further investigation.

Another unexplained, but important, observation was the spontaneous restriction of food intake in the very low carbohydrate diet group to a level equal to that of the control subjects who were following a prescribed restriction of calories. This raises the possibility that the very low carbohydrate diet may have been more satiating. Previous studies have suggested that, calorie for calorie, protein is more satiating than either carbohydrate or fat (33, 34), and it may be that the higher consumption of protein in the very low carbohydrate diet group played a role in limiting food intake. Another explanation for restricted food intake in the very low carbohydrate group is that food choices were probably greatly limited by the requirements of minimizing carbohydrate intake, and that dietary adherence *per se* may have forced caloric restriction due to practical factors. Although it has been proposed that ketosis developing from severe carbohydrate intake contributes to a decrease in appetite (8), this does not seem likely based on our data. Although the women

TABLE 3. Means (and SD) of body composition measures of women before and after 3 and 6 months of dieting

	Very low carbohydrate diet group (n = 22)			Low fat diet group (n = 20)		
	Baseline	3 months	6 months	Baseline	3 months	6 months
Body fat (g)	37,327.0 (4,787.7)	33,035.2[a] (4,756.9)	32,554.0[a] (5,170.5)	37,827.9 (2,651.8)	35,305.5 (3,602.4)	35,853.3 (4,125.2)
Bone mineral content (g)	2,782.8 (321.2)	2,799.2 (313.7)	2,775.7 (312.7)	2,819.7 (284.7)	2,827.7 (288.2)	2,792.8 (296.7)
Lean body mass (g)	50,385.9 (5,999.9)	47,565.3[a] (5,922.0)	48,418.0[a] (5,871.5)	51,026.8 (5,010.4)	50,181.3 (5,124.9)	50,295.9 (5,197.5)

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

TABLE 4. Means (and SE) of blood pressure and plasma lipid concentrations of women before and after 3 and 6 months of dieting

	Very low carbohydrate diet group (n = 22)			Low fat diet group (n = 20)		
	Baseline	3 months	6 months	Baseline	3 months	6 months
Blood pressure (mm Hg)	116/79 (3.23/2.69)	112/72 (2.36/2.06)	114/74 (2.82/2.23)	115/75 (2.47/1.99)	116/75 (2.01/1.79)	113/74 (2.41/1.62)
Total cholesterol (mg/dl)	206.32 (6.63)	185.68 (5.64)	205.46 (6.79)	184.45 (6.07)	176.25 (5.87)	182.85 (6.21)
Triglycerides (mg/dl)	148.73[a] (13.41)	92.41 (8.74)	113.86 (15.25)	109.25 (9.49)	101.80 (6.71)	111.00 (12.37)
LDL (mg/dl)	124.86 (5.39)	113.00 (5.34)	124.00 (5.81)	113.80 (6.36)	104.90 (5.97)	107.80 (5.86)
HDL (mg/dl)	51.77 (2.82)	54.09 (2.77)	58.73 (2.57)	48.75 (2.23)	51.05 (3.49)	52.85 (2.58)

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

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

following the very low carbohydrate diet developed significant ketonemia, the elevation of circulating β-hydroxybutyrate was mild, well below what is seen in other clinical states of ketosis, such as starvation and diabetic ketoacidosis (26, 35), and was noted only at 3 months. In addition, there was no correlation between the level of plasma β-hydroxybutyrate and weight loss ($r = 0.29$; $P = 0.43$).

This study provides a surprising challenge to prevailing dietary practice. The current standards for healthy eating include reducing total fat intake to less than 30% of total calories and decreasing saturated fat intake to less than 10%. This recommendation is based on a large body of primarily epidemiological data and is intended to lower plasma cholesterol (23), but has been extended by some experts as a means to decrease the risk of obesity. However, the subjects on the very low carbohydrate diet experienced significantly more weight loss than the low fat group and maintained comparable levels of plasma lipids and other cardiovascular risk factors while consuming more than 50% of their calories as fat and 20% as saturated fat. These data indicate that the role of macronutrient distribution in individuals who are on weight loss diets needs to be further investigated. In particular, it seems likely that in the short term, a decrease in total caloric intake with accompanying weight loss has a greater impact on nutritionally sensitive parameters such as plasma lipids than do the macronutrient constituents of the diet.

The results of this study are applicable to healthy persons, but extension of our findings to subjects with established cardiovascular risk factors should not be made without further careful investigation. The mean levels of blood pressure, glucose, and plasma lipids in our subjects were normal and, in fact, lower than the average values for American adults (36). It is possible that very low carbohydrate diets, with high relative intakes of protein and fat, would have deleterious effects in subjects with hyperlipidemia, diabetes, or other metabolic disorders.

Although advocates for very low carbohydrate diets are likely to embrace the results of this study, several points of caution need to be emphasized. First, a single study of a specific dietary regimen cannot provide a full assessment of safety and efficacy. Despite this study being the longest randomized, controlled trial of a very low carbohydrate diet reported, our results are still limited by the 6-month time frame. Whether the very low carbohydrate diet will produce sustained weight loss and continued improvement in cardiovascular risk factors over longer periods of time remains to be determined; the gradual increase in carbohydrate consumption in the final 3 months of the study suggests that some degree of recidivism is likely in persons on this diet. In addition, increased dietary fat has been linked to certain types of cancer (37) and may have effects on cardiovascular health beyond the risk factors assessed in this study. There was also a low intake of calcium and fiber in the very low carbohydrate group that would need to be addressed if this diet were to be used for longer periods. Finally, long-standing ketosis has been associated with myocardial dysfunction in children after a ketogenic diet to treat intractable seizures (38). Despite these concerns, the present results indicate that there are important, interesting, and poorly understood effects of severe carbohydrate restriction that warrant further

TABLE 5. Means (and SE) of substrate and hormone concentrations of women before and after 3 and 6 months of dieting

	Very low carbohydrate diet group (n = 22)			Low fat diet group (n = 20)		
	Baseline	3 months	6 months	Baseline	3 months	6 months
Glucose (mg/dl)	99.1 (2.6)	93.8 (2.7)	90.1 (2.1)	91.1 (2.1)	90.5 (2.5)	87.5 (2.0)
Insulin (μU/ml)	16.9 (1.8)	11.6 (1.2)	14.4 (1.4)	23.9 (2.34)	18.1 (2.5)	18.4 (2.1)
Leptin (ng/ml)	25.43 (1.49)	16.23 (1.09)	21.68 (1.49)	30.08 (1.88)	25.35 (1.82)	29.40 (2.58)
β-hydroxybutyrate (mg/dl)	1.04 (0.31)	4.30[a] (1.10)	1.52 (0.51)	1.01 (0.40)	1.17 (0.27)	1.14 (0.44)

To convert to SI units, multiply glucose (mg/dl) $\times$ 0.0555 = mmol/liter; multiply insulin (μU/ml) $\times$ 6.945 = pmol/liter; multiply β-hydroxybutyrate (mg/dl) $\times$ 96.05 = μmol/liter.

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

investigation as we seek effective therapeutic strategies to manage the epidemic of obesity.

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