Ketogenic low-carbohydrate diets have no metabolic advantage over nonketogenic low-carbohydrate diets[1–3]

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ABSTRACT

Background: Low-carbohydrate diets may promote greater weight loss than does the conventional low-fat, high-carbohydrate diet.

Objective: We compared weight loss and biomarker change in adults adhering to a ketogenic low-carbohydrate (KLC) diet or a nonketogenic low-carbohydrate (NLC) diet.

Design: Twenty adults [body mass index (in kg/m^2): 34.4 ± 1.0] were randomly assigned to the KLC (60% of energy as fat, beginning with ≈5% of energy as carbohydrate) or NLC (30% of energy as fat; ≈40% of energy as carbohydrate) diet. During the 6-wk trial, participants were sedentary, and 24-h intakes were strictly controlled.

Results: Mean (±SE) weight losses (6.3 ± 0.6 and 7.2 ± 0.8 kg in KLC and NLC dieters, respectively; $P = 0.324$) and fat losses (3.4 and 5.5 kg in KLC and NLC dieters, respectively; $P = 0.111$) did not differ significantly by group after 6 wk. Blood β-hydroxybutyrate in the KLC dieters was 3.6 times that in the NLC dieters at week 2 ($P = 0.018$), and LDL cholesterol was directly correlated with blood β-hydroxybutyrate ($r = 0.297$, $P = 0.025$). Overall, insulin sensitivity and resting energy expenditure increased and serum γ-glutamyltransferase concentrations decreased in both diet groups during the 6-wk trial ($P < 0.05$). However, inflammatory risk (arachidonic acid:eicosapentaenoic acid ratios in plasma phospholipids) and perceptions of vigor were more adversely affected by the KLC than by the NLC diet.

Conclusions: KLC and NLC diets were equally effective in reducing body weight and insulin resistance, but the KLC diet was associated with several adverse metabolic and emotional effects. The use of ketogenic diets for weight loss is not warranted. *Am J Clin Nutr* 2006;83:1055–61.

KEY WORDS Ketogenic low-carbohydrate diets, nonketogenic low-carbohydrate diets, weight loss, adults, insulin resistance

INTRODUCTION

Investigations reported over the past several years indicate that low-carbohydrate (LC) diets promote a greater degree of weight loss in the short term than does the conventional high-carbohydrate low-fat (HC) diet (1–4). Moreover, reductions in fasting blood lipids and insulin concentrations are comparable, and in some instances are greater, with an LC than with an HC diet (4–6). However, LC diets can vary, from the popular high-fat, ketogenic "Atkins diet" to low-fat, nonketogenic diets, and only the trials in which dietary intake is strictly controlled can confidently examine the metabolic effects of a particular LC diet.

In one randomized trial, 40% of subjects instructed to adhere to the high-fat, ketogenic Atkins diet did not test positive for urinary ketones at trial weeks 2, 4, or 8 (4); hence, the investigators' conclusion, that the high-fat, ketogenic Atkins diet produced greater weight loss than did the conventional HC diet, was inaccurate. McAuley et al (3) reported that subjects instructed to follow either an Atkins LC diet, a low-fat LC diet, or the conventional HC diet lost more body weight with consumption of the LC than of the HC diet. However, LDL cholesterol was significantly lower in the low-fat LC dieters after 24 wk than in the Atkins dieters. Hence, differentiating between ketogenic and nonketogenic LC diets is an important consideration for clinical practice. Furthermore, because the success of LC diets for weight loss has been attributed to the maintenance of subjects' pre-diet 24-h energy expenditure (EE) during active weight loss (7, 8), increased diet-induced thermogenesis (9), or reduced hunger (10, 11)—or all 3—it is important to ascertain whether these factors vary between ketogenic and nonketogenic LC diets.

We designed our study to compare weight loss and the metabolic effects of a ketogenic LC diet (beginning with <20 g carbohydrates) and of a nonketogenic, low-fat LC diet (40% energy as carbohydrate). All food and drink were provided to subjects, and energy intake was strictly controlled.

SUBJECTS AND METHODS

Participants and study design

Sedentary, overweight men and women [aged 20–60 y; body mass index (BMI; in kg/m^2) > 25] were screened for diagnosed disease and use of prescription medications. Participants (n = 20) were stratified by age, sex, and BMI and randomly assigned to 1 of 2 experimental diets: the ketogenic LC (KLC) diet or the low-fat, nonketogenic LC (NLC) diet.

All participants gave written informed consent. The Institutional Review Board of Arizona State University approved the study protocol.

During the 6-wk feeding trial, all food and beverages were provided to participants, who remained sedentary. Hot lunches

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[2] Supported by a grant from the Inflammation Research Foundation.

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Received August 16, 2005.

Accepted for publication February 3, 2006.

were prepared and served to participants Monday through Friday at the test site. Breakfast, dinner, and weekend meals were prepared and packaged for participants to take home. After the 6-wk trial, participants were instructed to continue following their diet plan (KLC or NLC) on their own for 4 wk. A registered dietitian discussed the diet details with each participant and provided daily meal plans and recipes for these 4 wk.

On day 1 of each week of the 6-wk trial, body weight and fat mass were recorded (Tanita Body Composition Analyzer TBF-300A; Tanita, Arlington Heights, IL) before lunch, and participants indicated on a 7-point Likert scale (range: extremely hungry to extremely full) how they had generally felt over the past week. The Profile of Mood States (POMS) questionnaire (EdiTS/Educational and Industrial Testing Service, San Diego, CA) that assessed 6 distinct mood states (ie, tension-anxiety, depression-dejection, anger-hostility, vigor-activity, fatigue-inertia, and confusion-bewilderment) was also completed. Body weight and fat mass were also recorded at week 10 (ie, after 4 wk self-monitored diet adherence).

Before the start of the trial and at weeks 2 and 6, participants provided a 24-h urine sample; the next morning, resting energy expenditure (REE) was measured after a 12-h fast and a 24-h avoidance of light-to-heavy activity. A fasting blood sample was collected from participants at trial weeks 0, 2, and 6.

Experimental diets

The protein content of the 2 experimental diets was comparable—≈30% energy—but the KLC diet was high in fat (60% of energy; saturated fat, 21% of energy) and very low in carbohydrates (beginning with ≈5% of energy), whereas the NLC diet was low in fat (30% of energy; saturated fat, 9% of energy) and carbohydrates (≈40% energy). The carbohydrate content of the KLC diet was increased by 5 g/wk in weeks 3–6, and subjects following this diet were instructed to consume ≈40 g carbohydrates/d during the self-monitored phase of the trial. The NLC diet had ≥ 67% of the recommended dietary intakes for the micronutrients; the KLC diet was less nutritious: fiber, vitamin E, folate, iron, magnesium, and potassium were <67% of recommended dietary intakes (**Table 1**). All participants were provided a daily multivitamin and mineral tablet beginning at the second week of the 6-wk trial.

Diets were developed by a registered dietitian with the use of FOOD PROCESSOR for WINDOWS nutrition analysis software (version 7.71; ESHA Research, Salem, OR), and only common food combinations were used. A 14-d rotating menu was devised for each diet plan. Foods were prepared by using scales and liquid measures. Within diet groups, participants consumed similar meal plans, but daily energy intakes were individually adjusted by altering portion size to provide ≈70% of that needed for weight maintenance.

Metabolic and analytic measurements

Metabolic measurements were recorded by using a respiratory mask with a 2-way, nonrebreathing valve (Hans-Rudolph Inc, Kansas City, MO) interfaced with a MAX-2 metabolic cart (Physiodyne Instrument Corp, Quogue, NY). Participants were habituated to the mask for 30 min in a quiet, darkened, temperature-controlled (25–27 °C) room. REE was then estimated from a mean of 20 min of continuous gas sampling via indirect calorimetry by using the formula of Weir (12) and adjusted for body mass.

TABLE 1
Nutrient composition of the ketogenic low-carbohydrate (KLC) and nonketogenic low-carbohydrate (NLC) diets[1]

Nutrients	KLC diet	NLC diet
Energy [mJ (kcal)]	6.25 (1500)	6.25 (1500)
Carbohydrate [g (% of energy)]	33[2] (9)	157[2] (42)
Sugar (g)	10	85
Protein [g (% of energy)]	125 (33)	117 (31)
Fat [g (% of energy)]	100 (60)	50 (30)
Saturated fat [g (% of energy)]	35 (21)	13[2] (8)
Monounsaturated fat [g (% of energy)]	34 (20)	16 (10)
Polyunsaturated fat [g (% of energy)]	14 (8)	7 (4)
Cholesterol (mg)	620	230
Fiber (g)	15[2]	30
Vitamin A (RE)	860	1910
Thiamin (mg)	1.10	1.50
Riboflavin (mg)	1.40	2.30
Niacin (mg)	23.5	16.9
Vitamin B-6 (mg)	1.80	2.15
Vitamin C (mg)	100	310
Vitamin E (mg)[3]	5.90[2]	10.20
Folate (μg)	220[2]	440
Calcium (mg)	715	1110
Iron (mg)	10[2]	15
Magnesium (mg)	190[2]	315
Potassium (mg)	1935[2]	3535
Zinc (mg)	10.9	11.3

[1] RE, retinol equivalents.
[2] Values ≤67% of daily recommendations for 31–50-y-old women.
[3] Vitamin E reported as alpha equivalents.

Serum concentrations of glucose; creatinine; total, HDL, and LDL cholesterol; and triacylglycerols were measured at Sonora Quest Laboratories (Tempe, AZ). Plasma insulin was measured by radioimmunoassay (ICN Diagnostics, Costa Mesa, CA), and insulin sensitivity was assessed by using the homeostasis model assessment (HOMA) index for insulin resistance: [(mmol fasting glucose/L) × (μU fasting insulin/mL)]/22.5 (13). Urinary creatinine was measured by using colorimetric procedures (procedure no. 0420; Stanbio Laboratory, Boerne, TX). Plasma uric acid, C-reactive protein, liver enzymes, and urinary calcium were measured at Sonora Quest Laboratories. Blood β-hydroxybutyrate was measured enzymatically by using an autoanalyzer (Precision Xtra; Abbott Laboratories, Bedford, MA). The fatty acid composition of isolated serum phospholipids, reported as the ratio of arachidonic acid to eicosapentaenoic acid, was analyzed by gas chromatography (Nutrasource Diagnostics, Guelph, Canada).

Statistical analysis

Data are reported as mean (±SE), and statistical analyses were performed by using SPSS for WINDOWS software (version 12; SPSS Inc, Chicago, IL). The repeated-measures analysis of variance, with main effects of time and group × time interaction, was used to assess differences in metabolic data. To assess change in body mass at week 6 by group or to ascertain whether a significant group × time interaction was observed for metabolic parameters, an unpaired Student's *t* test was performed. Although the study was limited by the small sample size, power calculations did indicate a 70% power to detect a change of 0.6 mmol/L

TABLE 2
Baseline characteristics of ketogenic low-carbohydrate (KLC) and nonketogenic low-carbohydrate (NLC) diet groups[1]

Variable	KLC diet group ($n = 9$)	NLC diet group ($n = 10$)
Men/women (n)	2/7	2/8
Age (y)	38.4 ± 3.9[2]	37.2 ± 3.9
Weight (kg)	95.8 ± 5.7	99.4 ± 6.1
Fat mass (kg)	38.8 ± 3.1	41.9 ± 3.9
BMI (kg/m^2)	35.0 ± 1.6	34.6 ± 1.5
Percentage body fat (%)	40.3 ± 1.9	41.8 ± 2.2
Waist circumference (cm)	107.0 ± 3.9	106.5 ± 5.0
Waist:hip ratio	0.90 ± 0.02	0.89 ± 0.02
Cholesterol (mmol/L)		
Total	5.67 ± 0.28	5.28 ± 0.30
Low-density lipoprotein	3.71 ± 0.27	3.38 ± 0.29
High-density lipoprotein	1.27 ± 0.10	1.33 ± 0.07
Triacylglycerols (mmol/L)	1.82 ± 0.19	1.48 ± 0.12
Fasting insulin (μU/mL)	25.6 ± 2.2	28.0 ± 3.9
Fasting glucose (mg/dL)	98.2 ± 4.4	94.0 ± 2.5

[1] There were no significant differences between diet groups (repeated-measures ANOVA).
[2] $\bar{x}$ ± SE (all such values).

in LDL cholesterol. Pearson's correlation was used to identify relations between variables. Significance was set at $P \leq 0.05$.

RESULTS

One participant (KLC diet group) developed heart arrhythmias during the first week and was dropped from the study. Baseline indexes did not vary by group (**Table 2** and **Table 3**). At the end of the 6-wk trial, the total weight loss did not differ significantly between diet groups (6.3 ± 0.6 and 7.2 ± 0.8 kg for KLC and NLC dieters, respectively; $P = 0.324$; **Figure 1**A). The mean change in total weight during the self-monitored diet adherence phase (weeks 7–10) was also not significantly affected by diet (−1.4 kg and 0.1 kg for NLC and KLC dieters, respectively; $P = 0.114$). Moreover, the reduction in fat mass over the 6-week trial was not significantly affected by diet (5.5 and 3.4 kg for NLC and KLC dieters, respectively; $P = 0.111$). Fat-free mass did not change significantly during the 6-wk trial, but BMI was significantly lower after 6 wk in both diet groups (−7%; $P < 0.05$; Table 3).

Hunger ratings tended to improve over the 6-wk trial in both diet groups, from "no particular feeling" (the middle of the range) to "satisfied" ($P = 0.078$), and hunger ratings did not differ significantly between diet groups. Feelings of vigor-activity as measured by the POMS questionnaire were significantly greater for NLC compared with KLC during the trial ($P = 0.025$; **Figure 2**). (Because of the way that this questionnaire was administered, data were not collected for trial week 6.) No other POMS measure varied significantly between diet groups during the trial.

The group × time interactions were not significant for total cholesterol ($P = 0.185$), LDL cholesterol ($P = 0.168$), or triacylglycerols ($P = 0.484$), as shown in **Figure 3**; however, over the course of the trial, LDL cholesterol was directly correlated with blood β-hydroxybutyrate concentrations ($r = 0.297$, $P = 0.025$). Compared with baseline, the 6-wk LDL concentrations increased in 5 KLC dieters (0.08, 0.13, 0.41, 0.44, and 0.52 mmol/L, respectively) and decreased in the remaining 4 KLC dieters (0.57 ± 0.18 mmol/L). In comparison, LDL cholesterol was raised in 2 NLC dieters (0.05 and 0.13 mmol/L) and decreased in the remaining 8 NLC dieters (0.78 ± 0.21 mmol/L). HDL cholesterol concentrations fell 9% during the 6-wk trial in both diet groups (data not shown).

The mean fasting blood β-hydroxybutyrate concentration in the KLC dieters was 3.6 times that in the NLC dieters at week 2 ($P = 0.018$), but this parameter did not vary by group at week 6 (Table 3). In both diet groups, weight-adjusted REE and fat oxidation (as indicated by respiratory quotient) increased, whereas insulin resistance decreased during the 6-wk trial ($P < 0.01$; Table 3). Moreover, blood β-hydroxybutyrate concentrations were inversely related to RQ ($r = -0.287$, $P = 0.031$) and insulin resistance ($r = -0.316$, $P = 0.017$). The mean serum phospholipid AA:EPA was nearly 90% higher in the KLC than in the NLC dieters at week 6 ($P = 0.038$; Table 3). Serum γ-glutamyltransferase concentrations fell in both diet groups during the trial ($P = 0.029$; Table 3). C-reactive protein and 24-h urinary calcium concentrations were not significantly affected by either diet treatment (Table 3). Although creatinine clearance and plasma uric acid concentrations fluctuated significantly over time, mean values at week 6 were below baseline values for both groups (Table 3).

DISCUSSION

These data show that, under isocaloric conditions, total weight loss and fat loss did not differ significantly by diet treatment. Yet, according to weight-loss averages during the "self-monitored" follow-up period, dietary compliance may be more easily achieved with NLC than with KLC diets. Reductions in total and LDL-cholesterol concentrations did not differ significantly by group, but 9% of the variation in LDL cholesterol was directly related to blood ketone concentrations, and several participants following the KLC diet had marked increases in LDL cholesterol. In a recent trial, McAuley et al (3) also noted that LDL cholesterol increased > 10% in 25% of subjects following an Atkins diet compared with 10% of subjects who were following a nonketogenic LC diet. Hence, blood lipid concentrations should be monitored in persons who are following ketogenic diets. As in other weight-loss trials (14–16), insulin resistance (HOMA index units) decreased in both diet groups (30%; $P < 0.05$), and body mass explained nearly 20% of the variance in insulin resistance.

The greater success of LC diets than of the conventional low-fat HC diet with respect to weight loss has been attributed to the maintenance of previous REE during active weight loss and to reduced hunger (17), but it is unclear whether these factors are related to dietary carbohydrate restriction or to increased dietary protein. Weight-adjusted REE increased in both diet groups over the 6-wk trial, but blood β-hydroxybutyrate concentrations were not correlated with REE ($r = -0.014$, $P = 0.921$), which indicates that the protein content of the diet, rather than the severity of the carbohydrate restriction, likely contributed to the elevations in REE. These data support the contention that calorie-reduced diets high in protein facilitate weight loss, in part, by preserving the metabolic rate (7, 8, 18). Fat-free mass, the major determinant of REE (19), was not correlated with REE in the present trial and cannot explain the observed increases in metabolism. Furthermore, exercise and activity levels remained constant in all study participants during the trial. It is possible that the

TABLE 3
Metabolic and physiologic indexes for ketogenic low-carbohydrate (KLC) and nonketogenic low-carbohydrate (NLC) diet groups during the 6-wk feeding trial[1]

				P[2]	
	Baseline	Week 2	Week 6	Time	Group × time
BMI (kg/m^2)					
KLC diet group	34.9 ± 1.6[3]	33.5 ± 1.6	32.5 ± 1.6		
NLC diet group	34.6 ± 1.5	33.2 ± 1.4	31.9 ± 1.3	<0.001	NS
Fat-free mass (kg)					
KLC diet group	54.9 ± 3.7	53.9 ± 3.5	53.2 ± 3.9		
NLC diet group	56.5 ± 3.5	54.6 ± 3.2	54.3 ± 3.4	NS	NS
Resting energy expenditure (kcal/kg)					
KLC diet group	5.80 ± 0.30	6.41 ± 0.46	7.24 ± 0.43		
NLC diet group	6.64 ± 0.46	6.79 ± 0.55	7.51 ± 0.33	0.004	NS
Respiratory quotient					
KLC diet group	0.75 ± 0.02	0.67 ± 0.01	0.72 ± 0.01		
NLC diet group	0.75 ± 0.02	0.66 ± 0.01	0.73 ± 0.01	<0.001	NS
Blood β-hydroxybutyrate (mmol/L)					
KLC diet group	0.089 ± 0.20	0.722 ± 0.177[4]	0.333 ± 0.078		
NLC diet group	0.100 ± 0.021	0.200 ± 0.030	0.200 ± 0.026	0.003	0.041
HOMA					
KLC diet group	6.24 ± 0.65	4.04 ± 0.53	4.38 ± 0.39		
NLC diet group	6.50 ± 0.91	4.70 ± 0.60	4.32 ± 0.37	<0.001	NS
AA:EPA					
KLC diet group	21.4 ± 2.3	29.3 ± 4.1	39.2 ± 7.8[5]		
NLC diet group	23.8 ± 2.9	25.1 ± 4.2	20.9 ± 2.9	0.007	0.005
γ-Glutamyltransferase (IU/L)					
KLC diet group	22.3 ± 5.5	17.2 ± 4.4	17.7 ± 4.2		
NLC diet group	20.7 ± 2.4	20.0 ± 2.7	19.2 ± 2.7	0.029	NS
C-reactive protein (mg/L)					
KLC diet group	7.50 ± 2.07	6.93 ± 2.06	6.39 ± 1.65		
NLC diet group	4.12 ± 0.78	4.48 ± 1.27	4.60 ± 1.40	NS	NS
Plasma uric acid (mmol/L)					
KLC diet group	0.36 ± 0.04	0.42 ± 0.05	0.32 ± 0.04		
NLC diet group	0.37 ± 0.04	0.41 ± 0.04	0.34 ± 0.03	0.001	NS
Urinary calcium (mmol/d)					
KLC diet group	3.22 ± 0.52	4.72 ± 0.52	4.13 ± 0.51		
NLC diet group	4.72 ± 1.07	2.34 ± 0.36	3.96 ± 0.43	NS	NS
Creatinine clearance (mL · s^{-1} · m^{-2})					
KLC diet group	1.21 ± 0.10	1.47 ± 0.11	1.18 ± 0.16		
NLC diet group	1.34 ± 0.11	1.31 ± 0.12	1.20 ± 0.12	0.044	NS

[1] $n = 9$ and 10 for the KLC and NLC groups, respectively. HOMA, homeostasis model assessment [(fasting glucose/L) × (μU fasting insulin/mL)/22.5]; AA, arachidonic acid; EPA, eicosapentaenoic acid. Baseline values did not differ significantly between groups.
[2] ANOVA.
[3] $\bar{x}$ ± SE (all such values).
[4,5] Significantly different from NLC group (unpaired Student's t test): [4]$P = 0.018$, [5]$P = 0.038$.

high-protein diets increased body protein turnover, which increased peptide bond synthesis as well as hydrolysis, processes that require ATP (20).

Although mean creatinine clearance values did not exceed baseline values at week 6, creatinine clearance did fluctuate significantly during the trial, and values for KLC at week 2 were 20% above baseline. A higher creatinine clearance rate exemplifies the renal functional reserve and is considered a normal physiologic response, but in persons with compromised renal function [11% of the US adult population (21) and 30–40% of diabetic patients (22)], renal hyperfiltration, which potentially leads to glomerulosclerosis (23), may occur. Thus, persons at risk of kidney disease should carefully consider KLC diets. Moreover, because inflammation is associated with faster rates of kidney function loss (24), it is important to note that AA:EPA in serum phospholipids was higher after 6 wk on the KLC diet (90% higher than that in NLC dieters; $P = 0.038$). These fatty acids affect prostanoid metabolism and function, and an elevated ratio has been associated with increased inflammation and tumorigenesis in rat models (25).

Plasma uric acid and urinary calcium, metabolic markers that typically are substantially higher with high-protein diets (26, 27), were not significantly higher at trial week 6 than at baseline, which supports the contention that these fluctuations are transient (28). In addition, hepatic function, as indicated by the serum γ-glutamyltransferase concentration, was favorably affected by the dietary treatments. Serum γ-glutamyltransferase concentrations have been directly related to impaired glucose tolerance (29), possibly as a result of greater amounts of intrahepatic lipids and greater hepatic insulin resistance (30). Insulin sensitivity was significantly

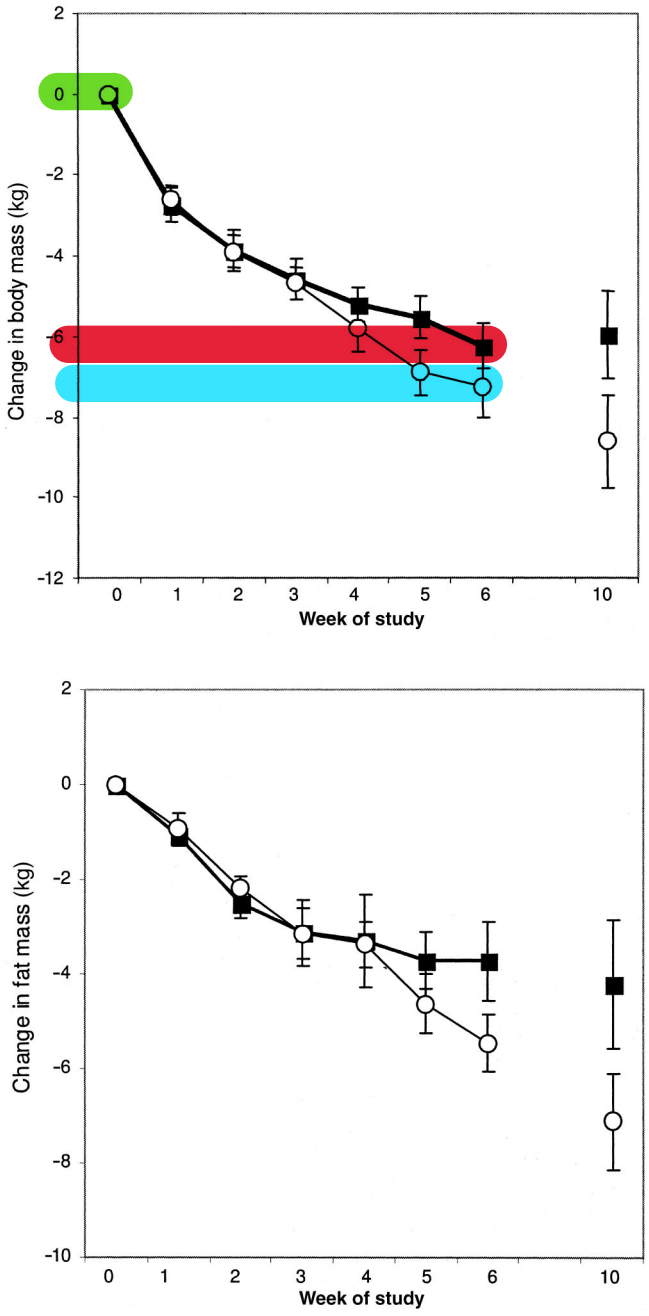

FIGURE 1. Mean (±SE) change in body mass and fat mass in ketogenic low-carbohydrate (KLC, ■; $n = 9$) and nonketogenic low-carbohydrate (NLC, ○; $n = 10$) diet groups during the 6-wk feeding trial and at the week 10 follow-up. Weight loss among participants was significant after 6 wk (6.3 ± 0.6 and 7.2 ± 0.8 kg for KLC and NLC dieters, respectively; both: $P < 0.001$), but group × time effects were not significant for total body mass or fat mass ($P = 0.324$ and 0.111, respectively; repeated-measures ANOVA).

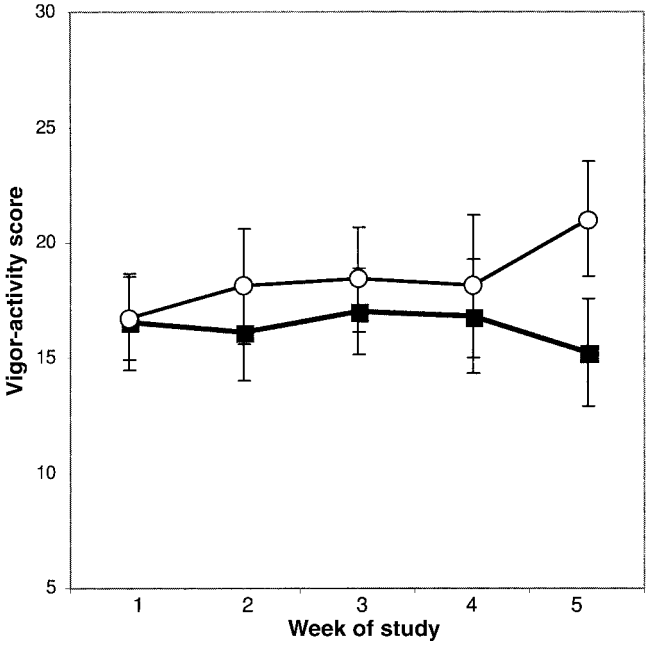

FIGURE 2. Mean (±SE) vigor-activity scores from the Profile of Mood States questionnaire for ketogenic low-carbohydrate (KLC, ■; $n = 9$) and nonketogenic low-carbohydrate (NLC, ○; $n = 10$) diet groups during the 6-wk feeding trial. The time effect was not significant ($P = 0.711$); the group × time interaction was significant ($P = 0.025$, repeated-measures ANOVA).

improved by both LC diets, and γ-glutamyltransferase was directly related to fasting insulin concentrations ($r = 0.457$, $P < 0.001$) and insulin resistance ($r = 0.522$, $P < 0.001$).

Weekly ratings of perceived hunger did not differ by diet group during the trial, which suggests, as discussed by others (31, 32), that it is the protein content of the diet and not the severity of dietary carbohydrate restriction that affects perceived hunger. Carbohydrate-restricted diets have been associated with fatigue and reduced vigor in response to exercise significantly more than have high-carbohydrate diets (33, 34). In the current study, weekly fatigue-inertia scores, representing a mood of weariness, inertia, and low energy level, did not differ significantly by diet treatment or time; however, vigor-activity scores, representing a mood of vigorousness, ebullience, and high energy, were significantly higher in NLC dieters than in KLC dieters. These data suggest that, in the context of high-protein diets, small differences (as little as 50–60 g/d) in dietary carbohydrate may affect emotion, mood state, and, potentially, the desire to be physically active. Bandini et al (35) reported substantial reductions in total daily EE (365 kcal) by subjects when they switched from a high-carbohydrate diet to a very-low-carbohydrate diet. Because REE and food-induced thermogenesis did not change in these subjects, the decrease in EE was likely due to reduced physical activity.

Although dietary intake was controlled during the 6-wk trial, which is a study strength, our study was limited by the small sample size. Nonetheless, these data offer important insights regarding the metabolic consequences associated with severe restriction of carbohydrates while dieting.

In summary, differentiating between ketogenic and nonketogenic LC diets is an important consideration for clinical practice because ketogenic diets have been associated with adverse metabolic events including elevated LDL (26) and cardiac complications (36, 37). In the current study, the KLC diet did not offer any significant metabolic advantage over the NLC diet. Both diets were effective at reducing total body mass and insulin resistance, but, because blood ketones were directly related to LDL-cholesterol concentrations and because inflammatory risk was elevated with adherence to the KLC diet, severe restrictions in dietary carbohydrate are not warranted. Furthermore, the NLC diet was associated with feelings of high energy and a more

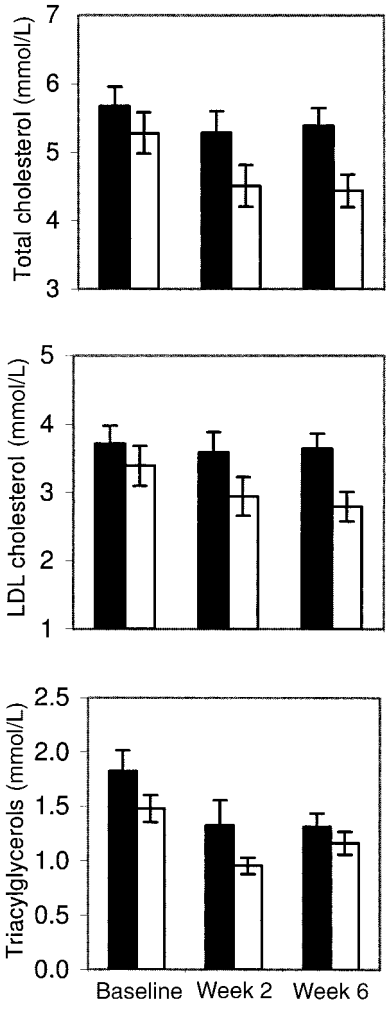

FIGURE 3. Mean (±SE) total cholesterol, LDL-cholesterol, and triacylglycerol concentrations in the ketogenic low-carbohydrate (KLC, ■; $n = 9$) and nonketogenic low-carbohydrate (NLC, □; $n = 10$) diet groups during the 6-wk feeding trial. Time effects were significant ($P < 0.001$, $P = 0.027$, and $P = 0.003$, respectively), and group × time interactions were not significant ($P > 0.05$, repeated-measures ANOVA).

favorable mood profile than was the KLC diet. Practitioners should advise patients who wish to follow an LC diet to choose low-fat meats and dairy products, 8–9 daily servings of fruit and vegetables, and a dietary carbohydrate limit near 100–125 g/d. Patients should know that there is no apparent metabolic advantage associated with ketosis during dieting.

We are grateful to the nutrition students who prepared and packaged meals; to Greg Trone for operating the metabolic cart; and to Michael Stroup for excellent technical assistance and for performing the phlebotomies.

HH and BS contributed to study design, AW provided technical and dietary assistance, PDS contributed to study design and provided technical assistance, SLT formulated the diet plans and prepared all meals and food packages, and CSJ contributed to study design, performed the statistical analyses, and wrote the manuscript. All authors made intellectual contributions to the manuscript. SLT received consulting fees from the Inflammation Research Foundation for participation in the research presented here. HH is an employee of Zone Labs Inc. BS is a stockholder and serves on the boards of directors of Zone Labs Inc and Zone Cuisine Inc; he is also on the boards of directors of Zone Café and ZoneNet. None of the other authors had any personal or financial conflict of interest.

REFERENCES

1. Brehm BJ, Seeley RJ, Daniels SR, D'Alessio DA. 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. J Clin Endocrinol Metabol 2003;88:1617–23.
2. Yancy WS, Olsen MK, Guyton JR, Bakst RP, Westman EC. A low-carbohydrate, ketogenic diet to treat obesity and hyperlipidemia. Ann Intern Med 2004;140:769–77.
3. McAuley KA, Hopkins CM, Smith KJ, et al. Comparison of high-fat and high-protein diets with a high carbohydrate diet in insulin-resistant obese women. Diabetologia 2005;48:8–16.
4. Foster GD, Wyatt HR, Hill JO, et al. A randomized trial of a low-carbohydrate diet for obesity. N Engl J Med 2003;348:2082–90.
5. Stern L, Iqbal N, Seshadri P, et al. The effects of low-carbohydrate versus conventional weight loss diets in severely obese adults: one-year follow-up of a randomized trial. Ann Intern Med 2004;140:778–85.
6. Samaha FF, Iqbal N, Seshadri P, et al. A low-carbohydrate as compared with a low-fat diet in severe obesity. N Engl J Med 2003;348:2074–81.
7. Whitehead JM, McNeill G, Smith JS. The effect of protein intake on 24-h energy expenditure during energy restriction. Int J Obes Relat Metab Disord 1996;20:727–32.
8. Baba NH, Sawaya S, Torbay N, Habbal Z, Azar S, Hashim SA. High protein vs high carbohydrate hypoenergetic diet for the treatment of obese hyperinsulinemic subjects. Int J Obes Relat Metab Disord 1999; 23:1202–6.
9. Johnston CS, Day CS, Swan PD. Postprandial thermogenesis is increased 100% on a high-protein, low-fat diet versus a high-carbohydrate, low-fat diet in healthy, young women. J Am Coll Nutr 2002;21:55–61.
10. Poppitt SD, McCormack D, Buffenstein R. Short-term effects of macronutrient preloads on appetite and energy intake in lean women. Physiol Behav 1998;64:279–85.
11. Latner JD, Schwartz M. The effects of a high-carbohydrate, high-protein or balanced lunch upon later food intake and hunger ratings. Appetite 1999;33:119–28.
12. Weir JB. New methods for calculating metabolic rate with special reference to protein. J Physiol 1949;109:1–49.
13. Keskin M, Kurtoglu S, Kendirci M, Atabek E, Yazici C. Homeostasis model assessment is more reliable than the fasting glucose/insulin ratio and quantitative insulin sensitivity check index for assessing insulin resistance among obese children and adolescents. Pediatrics 2005;115: e500–3. Epub 2005 Mar 1.
14. Johnston CS, Tjonn SL, Swan PD. High-protein, low-fat diets are effective for weight loss and favorably alter biomarkers in healthy adults. J Nutr 2004;134:588–91.
15. Sharman MJ, Gomez AL, Kraemer WJ, Volek JS. Very low-carbohydrate and low-fat diets affect fasting lipids and postprandial lipemia differently in overweight men. J Nutr 2004;134:880–5.
16. O'Brien KD, Brehm BJ, Seeley RJ, et al. Diet-induced weight loss is associated with decreases in plasma serum amyloid A and C-reactive protein independent of dietary macronutrient composition in obese subjects. J Clin Endocrinol Metab 2005;90:2244–9.
17. Schoeller DA, Buchholz AC. Energetics of obesity and weight control: does diet composition matter? J Am Diet Assoc 2005;105:S24–8.
18. Mikkelsen PB, Toubro S, Astrup A. Effect of fat-reduced diets on 24-h energy expenditure: comparisons between animal protein, vegetable protein, and carbohydrates. Am J Clin Nutr 2000;72:1135–41.
19. Ravussin E, Bogardus C. Relationship of genetics, age, and physical fitness to daily energy expenditure and fuel utilization. Am J Clin Nutr 1989;49:968–75.
20. van Milgen J, Noblet J, Dubois S. Energetic efficiency of starch, protein and lipid utilization in growing pigs. J Nutr 2001;131:1309–18.
21. Coresh J, Astor BC, Greene T, Eknoyan G, Levey AS. Prevalence of chronic kidney disease and decreased kidney function in the adult US population: third National Health and Nutrition Examination Survey. Am J Kidney Dis 2003;41:1–12.
22. Schena FP, Gesualdo L. Pathogenetic mechanisms of diabetic nephropathy. J Am Soc Nephrol 2005;16(suppl):S30–3.
23. Hellerstein S, Berenbom M, Erwin P, Wilson N, DiMaggio S. Measurement of renal functional reserve in children. Pediatr Nephrol 2004;19: 1132–6.
24. Tonelli M, Sacks F, Pfeffer M, Jhangri GS, Curhan G, Cholesterol and Recurrent Events (CARE) Trial Investigators. Biomarkers of inflammation and progression of chronic kidney disease. Kidney Int 2005;68:237–45.

25. Smith WL. Cyclooxygenases, peroxide tone and the allure of fish oil. Curr Opin Cell Biol 2005;17:174–82.
26. Larosa JC, Fry AG, Muesing R, Rosing DR. Effects of high-protein, low-carbohydrate dieting on plasma lipoproteins and body weight. J Am Diet Assoc 1980;77:264–70.
27. Schuette SA, Zemel MB, Linkswiler HM. Studies on the mechanism of protein induced hypercalciuria in older men and women. J Nutr 1980; 110:305–15.
28. Roughead ZK, Johnson LK, Lykken GI, Hunt JR. Controlled high meat diets do not affect calcium retention or indices of bone status in healthy postmenopausal women. J Nutr 2003;133:1020–6.
29. Nannipieri M, Gonzales C, Baldi S, et al. Liver enzymes, the metabolic syndrome, and incident diabetes: the Mexico city diabetes study. Diabetes Care 2005;28:1757–62.
30. Thamer C, Tschritter O, Haap M, et al. Elevated serum GGT concentrations predict reduced insulin sensitivity and increased intrahepatic lipids. Horm Metab Res 2005;37:246–51.
31. Westerterp-Plantenga MS. The significance of protein in food intake and body weight regulation. Curr Opin Clin Nutr Metab Care 2003;6:635–8.
32. Weigle DS, Breen PA, Matthys CC, et al. A high-protein diet induces sustained reductions in appetite, ad libitum caloric intake, and body weight despite compensatory changes in diurnal plasma leptin and ghrelin concentrations. Am J Clin Nutr 2005;82:41–8.
33. Butki BD, Baumstark J, Driver S. Effects of a carbohydrate-restricted diet on affective responses to acute exercise among physically active participants. Percept Mot Skills 2003;96:607–15.
34. Keith RE, O'Keeffe KA, Blessing DL, Wilson GD. Alterations in dietary carbohydrate, protein, and fat intake and mood state in trained female cyclists. Med Sci Sports Exerc 1991;23:212–6.
35. Bandini LG, Schoeller DA, Dietz WH. Metabolic differences in response to a high-fat vs. a high-carbohydrate diet. Obes Res 1994;2:348–54.
36. Best TH, Franz DN, Gilbert DL, Nelson DP, Epstein MR. Cardiac complications in pediatric patients on the ketogenic diet. Neurology 2000;54:2328–30.
37. Stevens A, Robinson DP, Turpin J, Groshong T, Tobias JK. Sudden cardiac death of an adolescent during dieting. South Med J 2002;95: 1047–9.