Ketogenic low-carbohydrate diets have no metabolic advantage over nonketogenic low-carbohydrate diets1–3

Carol S Johnston, Sherrie L Tjonn, Pamela D Swan, Andrea White, Heather Hutchins, and Barry Sears

ABSTRACT
Background: Low-carbohydrate diets may promote greater weight loss than does the conventional low-fat, high-carbohydrate diet. Objectives: 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/m²): 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/m²) > 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...
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 dietician 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 (EdTS/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—approximately 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 approximately 5% of energy), whereas the NLC diet was low in fat (30% of energy; saturated fat, 9% of energy) and carbohydrates (approximately 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 approximately 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 dietician 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 approximately 70% of that needed for weight maintenance.

**Metabolic and analytical 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.

**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 1**

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

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).
increase in 5 KLC dieters (0.08, 0.13, 0.41, 0.44, and 0.52
0.025). Compared with baseline, the 6-wk LDL 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 concentra-
tions 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).

**RESULTS**

One participant (KLC diet group) developed heart arrhyth-
mias 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 1A). The
mean change in total weight during the self-monitored diet ad-
herence phase (weeks 7–10) was also not significantly affected
by diet (−1.4 kg and 0.1 kg for NLC and KLC dieters, respec-
tively; 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)
in KLC and NLC dieters, respectively; P = 0.324; Figure 2A).
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 mea-
sure 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 tria-
cyglycerols (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 de-
creased 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
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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 choles-
terol. 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 indi-
cates that the protein content of the diet, rather than the severity
of the carbohydrate restriction, likely contributed to the eleva-
tion 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 metabol-
ism. Furthermore, exercise and activity levels remained con-
stant in all study participants during the trial. It is possible that the

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

<table>
<thead>
<tr>
<th>Variable</th>
<th>KLC diet group (n = 9)</th>
<th>NLC diet group (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men/women (n)</td>
<td>2/7</td>
<td>2/8</td>
</tr>
<tr>
<td>Age (y)</td>
<td>38.4 ± 3.9</td>
<td>37.2 ± 3.9</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>95.8 ± 5.7</td>
<td>99.4 ± 6.1</td>
</tr>
<tr>
<td>Fat mass (kg)</td>
<td>38.8 ± 3.1</td>
<td>41.9 ± 3.9</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>35.0 ± 1.6</td>
<td>34.6 ± 1.5</td>
</tr>
<tr>
<td>Percentage body fat (%)</td>
<td>40.3 ± 1.9</td>
<td>41.8 ± 2.2</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>107.0 ± 3.9</td>
<td>106.5 ± 5.0</td>
</tr>
<tr>
<td>Waist:hip ratio</td>
<td>0.90 ± 0.02</td>
<td>0.89 ± 0.02</td>
</tr>
<tr>
<td>Cholesterol (mmol/L)</td>
<td>5.67 ± 0.28</td>
<td>5.28 ± 0.30</td>
</tr>
<tr>
<td>Low-density lipoprotein</td>
<td>3.71 ± 0.27</td>
<td>3.38 ± 0.29</td>
</tr>
<tr>
<td>High-density lipoprotein</td>
<td>1.27 ± 0.10</td>
<td>1.33 ± 0.07</td>
</tr>
<tr>
<td>Triglycerols (mmol/L)</td>
<td>1.82 ± 0.19</td>
<td>1.48 ± 0.12</td>
</tr>
<tr>
<td>Fasting insulin (μU/mL)</td>
<td>25.6 ± 2.2</td>
<td>28.0 ± 3.9</td>
</tr>
<tr>
<td>Fasting glucose (mg/dL)</td>
<td>98.2 ± 4.4</td>
<td>94.0 ± 2.5</td>
</tr>
</tbody>
</table>

1 There were no significant differences between diet groups (repeated-
measures ANOVA).
2 ± SE (all such values).

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

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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
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 administrative 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 a stockholder and serves on the boards of directors of Zone Café and ZoneNet. None of the other authors had any personal or financial conflict of interest.

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).

REFERENCES


