Annals of Internal Medicine | ARTICLE

A Low-Carbohydrate, Ketogenic Diet versus a Low-Fat Diet To Treat Obesity and Hyperlipidemia

A Randomized, Controlled Trial

William S. Yancy Jr., MD, MHS; Maren K. Olsen, PhD; John R. Guyton, MD; Ronna P. Bakst, RD; and Eric C. Westman, MD, MHS

Background: **Low-carbohydrate diets remain popular despite a paucity of scientific evidence on their effectiveness.**

Objective: **To compare the effects of a low-carbohydrate, ketogenic diet program with those of a low-fat, low-cholesterol, reduced-calorie diet.**

Design: **Randomized, controlled trial.**

Setting: **Outpatient research clinic.**

Participants: **120 overweight, hyperlipidemic volunteers from the community.**

Intervention: **Low-carbohydrate diet (initially, <20 g of carbohydrate daily) plus nutritional supplementation, exercise recommendation, and group meetings, or low-fat diet (<30% energy from fat, <300 mg of cholesterol daily, and deficit of 500 to 1000 kcal/d) plus exercise recommendation and group meetings.**

Measurements: **Body weight, body composition, fasting serum lipid levels, and tolerability.**

Results: **A greater proportion of the low-carbohydrate diet group than the low-fat diet group completed the study (76% vs. 57%; $P = 0.02$). At 24 weeks, weight loss was greater in the low-carbohydrate diet group than in the low-fat diet group (mean change, −12.9% vs. −6.7%; $P < 0.001$). Patients in both groups lost substantially more fat mass (change, −9.4 kg with the low-carbohydrate diet vs. −4.8 kg with the low-fat diet) than fat-free mass (change, −3.3 kg vs. −2.4 kg, respectively). Compared with recipients of the low-fat diet, recipients of the low-carbohydrate diet had greater decreases in serum triglyceride levels (change, −0.84 mmol/L vs. −0.31 mmol/L [−74.2 mg/dL vs. −27.9 mg/dL]; $P = 0.004$) and greater increases in high-density lipoprotein cholesterol levels (0.14 mmol/L vs. −0.04 mmol/L [5.5 mg/dL vs. −1.6 mg/dL]; $P < 0.001$). Changes in low-density lipoprotein cholesterol level did not differ statistically (0.04 mmol/L [1.6 mg/dL] with the low-carbohydrate diet and −0.19 mmol/L [−7.4 mg/dL] with the low-fat diet; $P = 0.2$). Minor adverse effects were more frequent in the low-carbohydrate diet group.**

Limitations: **We could not definitively distinguish effects of the low-carbohydrate diet and those of the nutritional supplements provided only to that group. In addition, participants were healthy and were followed for only 24 weeks. These factors limit the generalizability of the study results.**

Conclusions: **Compared with a low-fat diet, a low-carbohydrate diet program had better participant retention and greater weight loss. During active weight loss, serum triglyceride levels decreased more and high-density lipoprotein cholesterol level increased more with the low-carbohydrate diet than with the low-fat diet.**

Ann Intern Med. 2004;140:769-777. www.annals.org

For author affiliations, see end of text.

See related article on pp 778-785 and editorial comment on pp 836-837.

As the prevalence of obesity has increased over the past 20 years (1), the difficulties faced by overweight patients and their health care practitioners have become apparent. Fewer than 25% of Americans who attempt to lose weight actually reduce caloric intake and increase exercise as currently recommended (2). Persons who successfully lose weight have difficulty maintaining their weight loss (3). Therefore, it is not surprising that consumers spend $33 billion yearly on weight loss products and services in search of effective therapies (2). Because many weight loss interventions are unproven and untested, practitioners often lack information with which to recommend a certain therapy or to monitor a patient once a therapy is chosen.

One approach to weight loss that has gained recognition in the face of modest supportive scientific evidence is the low-carbohydrate diet. A popular version of this diet recommends extreme restriction of carbohydrate intake to less than 20 g/d initially (4). This level of carbohydrate restriction can induce serum and urinary ketones and weight loss (5, 6). However, until recently, available data on low-carbohydrate diets came from small studies of short duration, most of which were uncontrolled (5, 7–10).

We examined body weight, body composition, serum lipid levels, and adverse effects over 24 weeks in hyperlipidemic persons who were randomly assigned to follow a low-carbohydrate, ketogenic diet or a low-fat, low-cholesterol, reduced-calorie diet commonly used to induce weight loss and decrease serum lipid levels.

METHODS

Participants

Generally healthy persons were recruited from the community. Inclusion criteria were age 18 to 65 years, body mass index of 30 to 60 kg/m^2, desire to lose weight, elevated lipid levels (total cholesterol level > 5.17 mmol/L [>200 mg/dL], low-density lipoprotein [LDL] cholesterol level > 3.36 mmol/L [>130 mg/dL], or triglyceride level > 2.26 mmol/L [200 mg/dL]), and no serious medical condition. Exclusion criteria were use of any prescription medication in the previous 2 months (except for oral contraceptives, estrogen therapy, and stable thyroid medication), pregnancy or breastfeeding, use of any weight loss diet or diet pills in the previous 6 months, and baseline

Context

Low-carbohydrate weight reduction diets are popular despite a dearth of data on long-term efficacy and adverse effects.

Contribution

Community-dwelling hyperlipidemic persons were randomly assigned to either a low-carbohydrate, ketogenic diet or a low-fat, low-cholesterol, reduced-calorie diet for 24 weeks. Compared to the low-fat group, patients in the low-carbohydrate group lost more weight, had a greater decrease in triglyceride levels, and had higher high-density lipoprotein cholesterol levels. Levels of low-density lipoprotein cholesterol remained stable in both groups. Side effects were more common in the low-cholesterol group but were generally mild.

Cautions

While the study suggests the efficacy and relative safety of the low-cholesterol diet, the high dropout rate, self-directed adherence to the diet, and relatively short observation period challenge the generalizability of the findings.

–The Editors

ketonuria. All participants provided written informed consent, and the institutional review board of Duke University Health System approved the study. Participants received no monetary incentive.

Interventions

By using a computer-generated simple randomization list, participants were allocated to receive the low-carbohydrate diet or low-fat diet. The intervention for both groups included group meetings, diet instruction, and an exercise recommendation. Group meetings took place at an outpatient research clinic twice monthly for 3 months, then monthly for 3 months. These meetings typically lasted 1 hour and consisted of diet instruction, supportive counseling, questionnaires, and biomedical measurements. During the study, participants selected their own menus and prepared or bought their own meals according to the guidelines presented to them. Participants were encouraged to exercise for 30 minutes at least 3 times weekly, but no formal exercise program or incentives were provided.

Low-Carbohydrate Diet

Using a popular diet book published by a lay press and additional handouts, trained research staff instructed participants to restrict intake of carbohydrates to less than 20 g/d (4). Participants were permitted unlimited amounts of animal foods (meat, fowl, fish, and shellfish), unlimited eggs, 4 oz of hard cheese, 2 cups of salad vegetables (such as lettuce, spinach, or celery), and 1 cup of low-carbohydrate vegetables (such as broccoli, cauliflower, or squash) daily. Participants were encouraged to drink 6 to 8 glasses of water daily. When participants were halfway to their goal body weight (determined at the week 10 visit with assistance from research personnel), they were advised to add approximately 5 g of carbohydrates to their daily intake each week until they reached a level at which body weight was maintained. To simulate the practice of the study sponsor, the low-carbohydrate diet group also received daily nutritional supplements (multivitamin, essential oils, diet formulation, and chromium picolinate; for a list of the composition of these supplements, see the Appendix, available at www.annals.org) (6).

Low-Fat Diet

Using a commonly available booklet and additional handouts, a registered dietitian instructed participants in a diet consisting of less than 30% of daily energy intake from fat, less than 10% of daily energy intake from saturated fat, and less than 300 mg of cholesterol daily (11, 12). The recommended energy intake was 2.1 to 4.2 MJ (500 to 1000 kcal) less than the participant's calculated energy intake for weight maintenance (body weight in pounds $\times$ 10) (13).

Primary Outcome Measure

Body weight and body mass index were the primary outcome measures. At each visit, participants were weighed on the same calibrated scale while wearing lightweight clothing and no shoes. Body mass index was calculated as body weight in kilograms divided by height in meters squared.

Secondary Outcome Measures

Adherence

Adherence to the diet was measured by self-report, food records, and, for the low-carbohydrate diet group, urinary ketone assessment.

Diet Composition

All participants completed a 24-hour recall of food intake at baseline and take-home food records (5 consecutive days, including a weekend) that were collected at each meeting during the study. Participants were instructed on how to document food intake and were given handouts with examples of how to complete the records. A sample of participants (13 in the low-carbohydrate diet group and 7 in the low-fat diet group) who completed the study was selected for food record analysis by the research staff on the basis of adequacy of detail in their records. A registered dietitian analyzed the food records by using a nutrition software program (Nutritionist Five, version 1.6 [First DataBank, Inc., San Bruno, California]).

Ketonuria

Restriction of dietary intake of carbohydrates to less than 40 g/d typically results in ketonuria that is detectable by dipstick analysis, which can be used to monitor adherence to the low-carbohydrate diet (14, 15). At each return

visit, participants provided a fresh urine specimen for analysis. The following semi-quantitative scale was used to categorize ketone content: none, trace (up to 0.9 mmol/L [5 mg/dL]), small (0.9 to 6.9 mmol/L [5 to 40 mg/dL]), moderate (6.9 to 13.8 mmol/L [40 to 80 mg/dL]), large80 (13.8 to 27.5 mmol/L [80 to 160 mg/dL]), and large160 (>27.5 mmol/L [>160 mg/dL]).

Body Composition

Body composition was estimated by using bioelectric impedance (model TBF-300A [Tanita Corp., Arlington Heights, Illinois]) at approximately the same time of day (afternoon or evening) at each return visit. In a subset of 33 participants, the percentage of body fat as measured by bioelectric impedance had excellent correlation with the percentage as measured by dual-energy x-ray absorptiometry ($r = 0.93$ [95% CI, 0.87 to 0.97]).

Vital Signs

Blood pressure and pulse rate were measured in the nondominant arm by using an automated digital cuff (model HEM-725C [Omron Corp., Vernon Hills, Illinois]) after the participant had been sitting for 3 minutes. Two measurements were taken at each visit and averaged for the analysis.

Serum Lipids and Lipoproteins

Serum specimens for lipid measurement were obtained in the morning after at least 8 hours of fasting at the screening visit and at 8, 16, and 24 weeks.

Other Metabolic Effects

Serum tests for sodium, potassium, chloride, urea nitrogen, creatinine, calcium, phosphorus, total protein, albumin, uric acid, total bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, thyroid-stimulating hormone, iron, hemoglobin, leukocyte count, and platelet count were obtained at the screening visit and at 8, 16, and 24 weeks. The glomerular filtration rate was estimated by using an equation that included age; sex; race; and serum levels of albumin, creatinine, and urea nitrogen (Modification of Diet in Renal Disease Study equation) (16).

Adverse Effects

At all return visits, participants completed an open-ended questionnaire on side effects. At the 20- and 24-week visits, participants completed a checklist of the side effects that were most often mentioned during the study.

Statistical Analysis

Analyses were performed by using S-PLUS software, version 6.1 (Insightful Corp., Seattle, Washington), or SAS software, version 8.02 (SAS Institute, Inc., Cary, North Carolina). For categorical outcomes, groups were compared by using the chi-square test or Fisher exact test, as appropriate. For all primary and secondary continuous outcomes, linear mixed-effects models (PROC MIXED procedure in SAS software) that included fixed and random effects were used to determine expected mean values at each time point and to test hypotheses of group differences. In most body weight and body composition models, time and group assignment were included as fixed effects with linear and quadratic time-by-group interaction terms. In the fat-free mass, total body water, and vital sign models, the time-by-group interaction was treated as a categorical variable. In all body weight and body composition models, random effects included intercept and linear slope terms. For the serum outcome measure models, the time-by-group interaction was treated as a categorical variable, and an unstructured covariance was used to account for within-patient correlation over time.

All available data, including those from participants who subsequently discontinued the study, were used for the longitudinal analyses. Mixed-effects models assume noninformative dropout, meaning that the probability of dropout may depend on covariates or a participant's previous responses but not on current or future responses (17). A P value of 0.05 or less was considered statistically significant.

Role of the Funding Source

Investigators at Duke University conducted the study and maintained exclusive control of all data and analyses. The funding source had no involvement in the recruitment of participants; study interventions; collection, analysis, or interpretation of the data; or preparation or review of the manuscript.

RESULTS

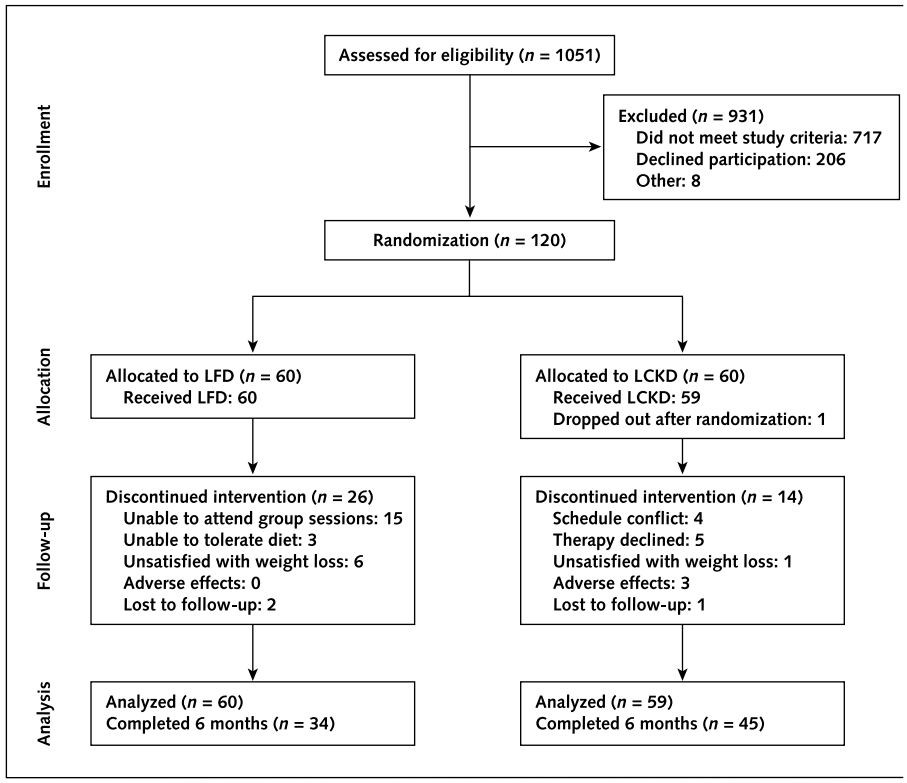
Participants

From July 2000 to July 2001, 1051 volunteers were screened for eligibility and 120 underwent randomization (**Figure 1**). One participant who was assigned to the low-carbohydrate diet group discontinued the study before receiving dietary instruction and was not included in analyses. **Table 1** shows baseline characteristics of the participants.

Retention

Forty-five (76%) of the 59 participants originally assigned to the low-carbohydrate diet group and 34 (57%) of the 60 participants assigned to the low-fat diet group completed the study ($P = 0.02$). In the low-carbohydrate diet group, 4 participants (7%) could not adhere to the group meeting schedule, 5 (8%) could not adhere to the diet, 1 (2%) was unsatisfied with weight loss, 3 (5%) dropped out because of adverse effects, and 1 (2%) was lost to follow-up. Of the 3 participants who dropped out because of adverse effects, 2 had increases in LDL cholesterol level, and 1 experienced shakiness and uneasiness. In the low-fat diet group, 15 participants (25%) could not adhere to the group meeting schedule, 3 (5%) could not adhere to the

Figure 1. **Flow of participants into the study.**



LCKD = low-carbohydrate, ketogenic diet; LFD = low-fat, low-cholesterol, reduced-calorie diet.

diet, 6 (10%) were unsatisfied with weight loss, and 2 (3%) were lost to follow-up (**Appendix Figure**, available at www.annals.org).

Body Weight

Over 24 weeks, the expected mean change in body weight was −12.0 kg (95% CI, −13.8 to −10.2 kg) in the low-carbohydrate diet group compared with −6.5 kg (CI, −8.4 to −4.6) in the low-fat diet group (mean difference, −5.5 kg [CI, −8.1 to −2.9 kg]) (**Figure 2**). **Figure 3** shows body weight trajectories for all participants, by diet group. The expected mean percentage change in body weight was −12.9% (CI, −14.8% to −10.9%) in the low-carbohydrate diet group and −6.7% (CI, −8.7% to −4.8%) in the low-fat diet group (mean difference, −6.2 percentage points [CI, −8.9 to −3.4 percentage points). In other terms, 61% ($n = 36$) of recipients of the low-carbohydrate diet and 23% ($n = 14$) of recipients of the low-fat diet completed the study and lost greater than 10% of their initial body weight ($P < 0.001$).

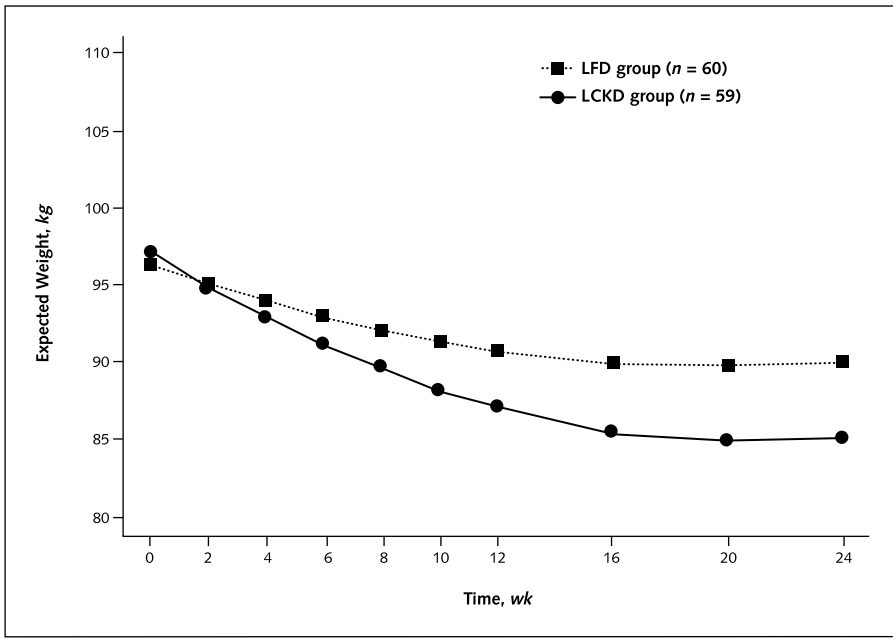
Diet Composition

Diet composition was measured on the basis of food records collected at each visit from a subsample of participants (13 from the low-carbohydrate diet group and 7 from the low-fat diet group.) The low-carbohydrate diet group consumed a mean (±SD) of 29.5 ± 11.1 g of carbohydrates (8% of daily energy intake), 97.9 ± 24.3 g of protein (26% of daily energy intake), and 110.6 ± 27.3 g

Table 1. **Baseline Characteristics**

Characteristic	Low-Fat Diet Group			Low-Carbohydrate, Ketogenic Diet Group		
	Enrollees (n = 60)	Completers (n = 34)	Noncompleters (n = 26)	Enrollees (n = 59)	Completers (n = 45)	Noncompleters (n = 14)
Mean age ± SD, *y*	45.6 ± 9.0	44.1 ± 8.7	47.6 ± 9.2	44.2 ± 10.1	45.3 ± 9.5	40.5 ± 11.3
Women, %	78	76	81	75	71	80
White, %	78	79	77	75	80	60
African-American, %	18	18	19	22	18	33
College degree, %	63	65	62	56	60	47
Mean body weight ± SD, *kg*	96.8 ± 19.2	95.7 ± 18.0	98.3 ± 20.9	97.8 ± 15.0	98.1 ± 15.2	96.5 ± 14.7
Mean body mass index ± SD, kg/m^2	34.0 ± 5.2	33.9 ± 5.3	34.5 ± 5.0	34.6 ± 4.9	34.6 ± 5.2	34.7 ± 4.0

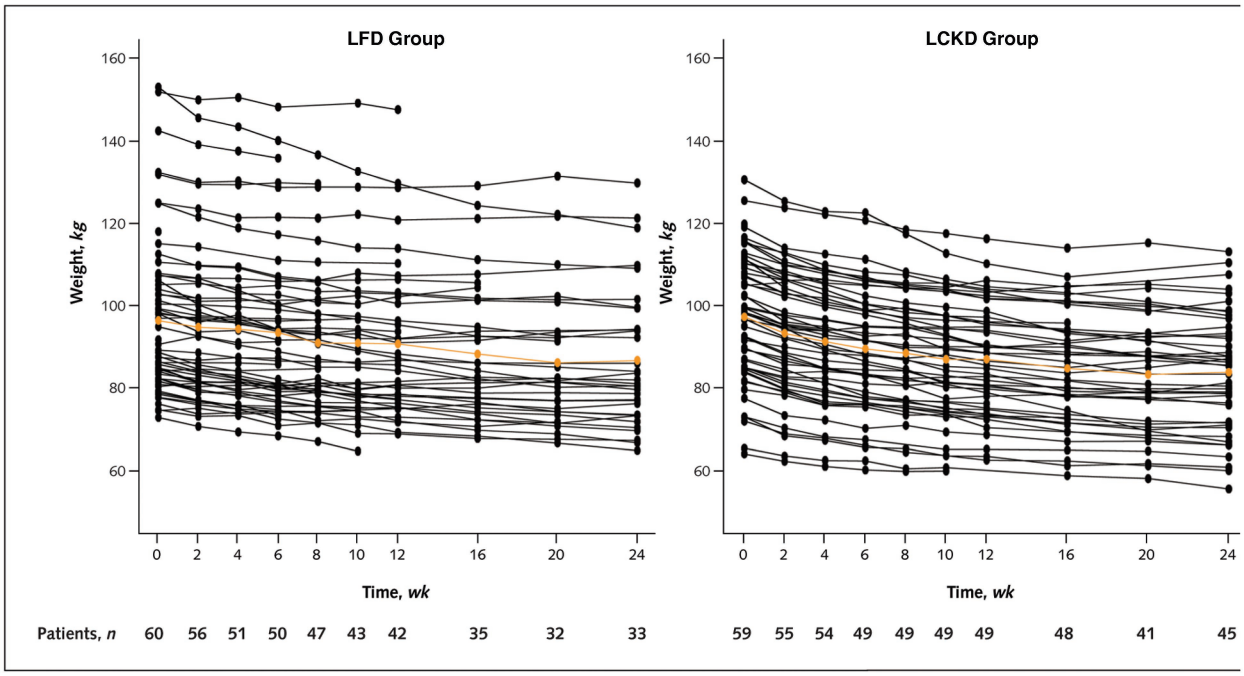
Figure 2. **Expected mean body weight over time, by diet group.**



Expected mean body weight determined by linear mixed-effects model analysis. $P < 0.001$ for linear and quadratic time-by-diet group interaction terms. LCKD = low-carbohydrate, ketogenic diet; LFD = low-fat, low-cholesterol, reduced-calorie diet.

of fat (68% of daily energy intake) daily. The low-fat diet group consumed 197.6 ± 34.2 g of carbohydrates (52% of daily energy intake), 70.5 ± 9.7 g of protein (19% of daily energy intake), and 48.9 ± 12.0 g of fat (29% of daily energy intake) daily. The estimated daily energy intake was 6.14 ± 1.37 MJ (1461.0 ± 325.7 kcal) in the low-carbohydrate diet group and 6.31 ± 0.68 MJ (1502.0 ± 162.1 kcal) in the low-fat diet group.

Figure 3. **Individual body weight trajectories, by diet group.**



The orange line represents the observed trajectory for mean body weight in the low-fat, low-cholesterol, reduced-calorie diet (*LCD*) group (*left*) or the low-carbohydrate, ketogenic diet (*LCKD*) group (*right*). At week 24, the low-fat diet group included 33 rather than 34 participants because 1 participant contributed a blood specimen, but not weight measurements, at that time point.

Table 2. **Effect of Diet Programs on Fasting Lipid Profiles***

Variable	Low-Fat Diet Group ($n = 60$)				Low-Carbohydrate, Ketogenic Diet Group ($n = 59$)				*P* Value for Between-Group Comparison
	Week 0	Week 24	Change	*P* Value	Week 0	Week 24	Change	*P* Value	
Total cholesterol level, *mmol/L (mg/dL)*	6.20 (239.9)	5.85 (226.2)	−0.35 (−13.7)	0.008	6.32 (244.5)	6.11 (236.4)	−0.21 (−8.1)	0.08	>0.2
Triglyceride level, *mmol/L (mg/dL)*	2.15 (190.7)	1.84 (162.7)	−0.31 (−27.9)	0.02	1.78 (157.8)	0.94 (83.6)	−0.84 (−74.2)	<0.001	0.004
LDL cholesterol level, *mmol/L (mg/dL)*	3.83 (148.0)	3.64 (140.6)	−0.19 (−7.4)	0.2	4.07 (157.2)	4.11 (158.8)	0.04 (1.6)	>0.2	0.2
HDL cholesterol level, *mmol/L (mg/dL)*	1.40 (54.1)	1.36 (52.5)	−0.04 (−1.6)	>0.2	1.43 (55.4)	1.57 (60.9)	0.14 (5.5)	<0.001	<0.001
Ratio of total cholesterol to HDL cholesterol	4.7	4.4	−0.3	0.09	4.7	4.1	−0.6	<0.001	0.09
Ratio of triglyceride to HDL cholesterol	4.1	3.4	−0.6	0.02	3.2	1.6	−1.6	<0.001	0.02

* Values are expected means by linear mixed-effects model analysis. HDL = high-density lipoprotein; LDL = low-density lipoprotein.

Ketonuria

The proportion of participants in the low-carbohydrate diet group whose level of urinary ketones was classified as trace or greater was 86% (47 of 55) at 2 weeks and decreased to 42% (19 of 45) at 24 weeks. The proportion of participants in this group who had urinary ketone levels classified as moderate or greater was 64% (35 of 55) at 2 weeks and decreased to 18% (8 of 45) at 24 weeks.

Body Composition

Over 24 weeks, participants in each group lost more fat mass than fat-free mass. The expected mean change in fat mass was −9.4 kg (CI, −10.9 to −7.9 kg) in the low-carbohydrate diet group and −4.8 kg (CI, −6.3 to −3.2 kg) for the low-fat diet group (mean difference, −4.6 kg [CI, −6.8 to −2.5 kg]). However, the percentage of total weight loss that was fat mass was similar in the 2 groups (78% in the low-carbohydrate diet group and 74% in the low-fat diet group). The expected mean percentage of body fat decreased from 41.0% to 35.2% (change, −5.8 percentage points [CI, −6.7 to −4.8 percentage points]) in the low-carbohydrate diet group and 41.1% to 38.3% (change, −2.8 percentage points [CI, −3.9 to −1.9 percentage points]) in the low-fat diet group (mean difference between groups, −3.0 percentage points [CI, −4.2 to −1.5 percentage points]). The expected mean change in fat-free mass was −3.3 kg (CI, −3.9 to −2.7 kg) in the low-carbohydrate diet group and −2.4 kg (CI, −3.1 to −1.7 kg) in the low-fat diet group (mean difference, −0.9 kg [CI, −1.8 to 0 kg]; $P = 0.054$). Changes in total body water explained most of the change in fat-free mass in both groups. The expected mean change in total body water was −2.4 kg (CI, −2.9 to −2.0 kg) in the low-carbohydrate diet group and −1.8 kg (CI, −2.3 to −1.3 kg) in the low-fat diet group (mean difference, −0.6 kg [CI, −1.3 to 0 kg]; $P = 0.052$). However, the low-carbohydrate diet group lost a greater amount of total body water in the first 2 weeks of the study than did the low-fat diet group (−1.1 kg versus −0.5 kg; mean difference, −0.6 kg [CI, −1.0 to −0.2 kg]).

Vital Signs

Over 24 weeks, systolic blood pressure in the low-carbohydrate diet group decreased by 9.6 mm Hg (CI, −13.3 to −6.0 mm Hg), diastolic blood pressure decreased by 6.0 mm Hg (CI, −8.0 to −3.9 mm Hg), and pulse rate decreased by 8.9 beats/min (CI, −12.1 to −5.8 beats/min). In the low-fat diet group, systolic blood pressure decreased by 7.5 mm Hg (CI, −11.6 to −3.5 mm Hg), diastolic blood pressure decreased by 5.2 mm Hg (CI, −7.5 to −2.9 mm Hg), and pulse rate decreased by 10.3 beats/min (CI, −13.7 to −6.8 beats/min). These changes did not statistically differ in between-group comparisons.

Serum Lipids and Lipoproteins

In between-group comparisons, the low-carbohydrate diet group had statistically greater changes in triglyceride level, high-density lipoprotein (HDL) cholesterol level, and ratio of triglycerides to HDL cholesterol ($P = 0.004$, $P < 0.001$, and $P = 0.02$, respectively) (**Table 2**). However, 2 participants in the low-carbohydrate diet group dropped out of the study because of concerns about elevated serum lipid levels. In 1 participant, the LDL cholesterol level increased from 4.75 mmol/L (184 mg/dL) at baseline to 7.31 mmol/L (283 mg/dL) at 3 months. One participant dropped out after a local physician measured her serum lipids 4 weeks into the study; her LDL cholesterol level was 4.70 mmol/L (182 mg/dL) at baseline and increased to 5.66 mmol/L (219 mg/dL). Among participants for whom data on LDL cholesterol were available at both baseline and week 24, the LDL cholesterol level increased by more than 10% in 13 (30%) of 44 recipients of the low-carbohydrate diet and 5 (16%) of 31 recipients of the low-fat diet ($P > 0.2$).

Other Metabolic Effects

In the low-carbohydrate diet group, the expected mean blood urea nitrogen level increased from 5.1 mmol/L (14.2 mg/dL) at baseline to 6.0 mmol/L (16.8 mg/dL) at 24 weeks. This change was statistically greater than that in the low-fat diet group ($P < 0.001$). The expected mean serum alkaline phosphatase level decreased from 1.45 μkat/L (85.3 U/L) at baseline to 1.35 μkat/L (79.6 U/L) at 24 weeks in the low-carbohydrate diet group, whereas it increased from 1.38 μkat/L (81.1 U/L) to 1.56 μkat/L (92.0 U/L) in the low-fat diet group ($P < 0.001$ for comparison). Changes in other serum measurements and estimated glomerular filtration rate did not differ between groups.

Adverse Effects

Several symptomatic adverse effects occurred more frequently in the low-carbohydrate diet group than in the low-fat diet group, including constipation (68% vs. 35%; $P < 0.001$), headache (60% vs. 40%; $P = 0.03$), halitosis (38% vs. 8%; $P < 0.001$), muscle cramps (35% vs. 7%; $P < 0.001$), diarrhea (23% vs. 7%; $P = 0.02$), general weakness (25% vs. 8%; $P = 0.01$), and rash (13% vs. 0%; $P = 0.006$). One participant sought medical attention for constipation but had no complications. One 53-year-old man in the low-carbohydrate diet group who had a family history of early heart disease developed chest pain near the end of the study, and coronary heart disease was subsequently diagnosed. During the study, this participant lost 16 kg, his serum LDL cholesterol level decreased by 0.75 mmol/L (29 mg/dL), and his serum HDL cholesterol level increased by 0.21 mmol/L (8 mg/dL).

DISCUSSION

Over 24 weeks, a low-carbohydrate diet program led to greater weight loss, reduction in serum triglyceride level, and increase in HDL cholesterol level compared with a low-fat diet. These effects on weight loss and serum triglyceride level are similar to those in 4 randomized, controlled trials of the low-carbohydrate diet (7–10). The serum HDL cholesterol level also increased in 1 of these studies (9). The magnitude of weight loss that we observed compares favorably with that achieved with use of weight loss medications approved by the U.S. Food and Drug Administration, such as orlistat (decrease of about 9% at 6 months) (18, 19) and sibutramine (decrease of about 8% at 6 months) (20).

Weight loss in both groups resulted predominantly from reduced energy intake; however, the method of reducing energy intake differed greatly. The low-fat diet group received counseling to restrict intake of fat, cholesterol, and energy, whereas the low-carbohydrate diet group received counseling to restrict intake of carbohydrates but not energy. The voluntary reduction in energy intake among recipients of the low-carbohydrate diet merits future research. These participants may have restricted intake because of limited food choices, or the low-carbohydrate diet may have appetite suppressant properties (21, 22). Other possible explanations for the discrepancy in weight loss between groups include loss of energy through ketonuria and the increased thermic effect of a high-protein diet (23). A study in which food intake is rigorously controlled will better determine what factors contribute to weight loss from the low-carbohydrate diet.

With regard to the composition of weight loss, both groups lost predominantly fat mass over 24 weeks, and the percentage of total weight loss that was fat was similar in both groups. The low-carbohydrate group lost a greater amount of water in the first 2 weeks than did the low-fat diet group; this finding confirms anecdotal reports of diuresis with the low-carbohydrate diet. After the first 2 weeks, however, estimations of total body water were similar in the low-carbohydrate diet group and the low-fat diet group. Moreover, the changes in fat-free mass in both groups were largely explained by changes in total body water, not lean tissue mass.

Perhaps the biggest concern about the low-carbohydrate diet is that the increase in fat intake will have detrimental effects on serum lipid levels (24). We found that the LDL cholesterol level did not change on average but did increase by more than 10% from baseline to week 24 in 30% of recipients of the low-carbohydrate diet who completed the study. In an uncontrolled trial of the low-carbohydrate diet, the LDL cholesterol level increased by 0.62 mmol/L (24 mg/dL) in 24 participants at 2 months (15). In another uncontrolled study, the LDL cholesterol level decreased by 0.26 mmol/L (10 mg/dL) in 41 participants at 6 months (6). Because the low-carbohydrate diet may adversely affect the LDL cholesterol level, it is prudent to monitor the serum lipid profiles of followers of this diet.

Our results confirm the decrease in serum triglyceride level seen in previous studies (5–10, 15, 25, 26). Our data are limited, however, to persons with normal or moderately elevated baseline triglyceride levels. Persons with fasting chylomicronemia (serum triglyceride level > 5.64 mmol/L [>500 mg/dL] and usually > 11.3 mmol/L [>1000 mg/dL]) may have fat-induced lipemia, meaning that high fat intake further increases serum triglyceride levels. In these persons, a low-fat diet is the standard of care for decreasing triglyceride levels and therefore preventing pancreatitis (27).

The low-carbohydrate diet group experienced an increase in HDL cholesterol level, which occurred concurrently with weight loss. Although this effect is uncommon in the setting of weight loss, the HDL cholesterol level is known to increase when dietary carbohydrate is replaced by saturated, monounsaturated, or polyunsaturated fat (28). With traditional low-fat diets, the HDL cholesterol level generally decreases from baseline during active weight loss and then increases during weight stabilization when the diet is maintained (29). Similarly, levels of LDL cholesterol and triglycerides decrease during active weight loss, then increase during weight stabilization but remain lower

than baseline levels if the low-fat diet is maintained. Because we did not follow participants beyond the period of active weight loss, we cannot state with certainty how levels of HDL cholesterol or other lipids might change during a weight maintenance phase.

The changes in body weight, blood pressure, and serum lipid levels that we observed suggest that research may be warranted on the effects of the low-carbohydrate diet in patients with the metabolic syndrome, which is characterized by increased blood pressure, hypertriglyceridemia, low HDL cholesterol levels, abdominal adiposity, and insulin resistance (30). We did not measure insulin sensitivity, but previous studies of the low-carbohydrate diet have shown that serum glucose and insulin levels decrease (8, 9, 31–33).

The rate of dropout and reasons for doing so differed between the two groups. Most of the participants in the low-fat diet group who dropped out because of schedule conflicts had less weight loss than their peers. We theorize that "unable to adhere to group meeting schedule" may have actually meant "unable to adhere to diet" or "unsatisfied with weight loss" for many of these participants. In that vein, participant dissatisfaction with weight loss may have been the underlying reason for the greater dropout rate in the low-fat diet group. To address the differential dropout rates, we used the mixed-effects model as our primary analysis tool. This analysis includes all enrolled participants and permits valid inferences when the probability of dropout depends on group assignment or previously observed weight values.

Recipients of the low-carbohydrate diet reported symptomatic adverse effects more frequently than did recipients of the low-fat diet, but only 1 participant dropped out as a result of symptoms. The difference in dropout rates may explain in part the difference in rates of adverse effects because more recipients of the low-carbohydrate diet had the opportunity to report adverse effects. Symptomatic adverse effects that typically occur at initiation of a low-carbohydrate diet (for example, weakness, orthostasis, headaches, constipation, and muscle cramps) are short-lived and may be reduced by copious fluid intake, consumption of the allowed amounts of vegetables, bouillon, and a daily multivitamin and mineral supplement.

Our study had limitations. First, we could not definitively distinguish effects of the low-carbohydrate diet and those of the nutritional supplements provided only to that group. Not only could the supplements have been an incentive for participants in the low-carbohydrate diet group to remain in the study, but they also may have increased weight loss in these participants. However, in a systematic review, the ingredients of the nutritional supplements were not shown to effectively induce weight loss (34). The essential oils supplement contained fish oils, which have been shown to decrease triglyceride levels and slightly increase HDL cholesterol and LDL cholesterol levels (35). The dose of fish oils was very low compared with the doses used to treat hypertriglyceridemia (36), but they may have contributed to the changes that occurred. It is also possible that the nutritional supplements helped to prevent potential adverse effects of the low-carbohydrate diet. For example, a recent study suggests that this type of diet at a daily energy intake of 8.40 MJ (2000 kcal) may increase the risk for kidney stones (37). Citric acid contained in the supplements may have helped to prevent the formation of kidney stones.

In addition, participants were healthy and were followed for only 24 weeks, factors that limit generalization of our results. The low-carbohydrate diet has not been studied extensively in patients with chronic illness, and certain patients may require close medical supervision when following this diet (8). Furthermore, weight loss resulting from the low-carbohydrate diet may be difficult to maintain after 24 weeks (9).

In summary, over 24 weeks, healthy hyperlipidemic persons who followed a low-carbohydrate diet lost more body weight and body fat than did those who followed a low-fat diet. Serum lipid profiles improved in both groups, but monitoring remains important because a small percentage of persons may experience adverse changes. Further research is needed in other groups and for longer periods to determine the safety of this dietary approach.

From the Center for Health Services Research in Primary Care, Department of Veterans Affairs Medical Center, and Duke University Medical Center, Durham, North Carolina.

Acknowledgments: The authors thank Keith Tomlin, Bill Bryson, Juanita Hepburn, Christine Perkins, and Angela Braswell for assistance with the interventions and data collection; David Simel and John Williams for manuscript review; and John J.B. Anderson, Howard Eisenson, Jarol Boan, Jim Lane, Truls Ostbye, and Robert Rosati, members of the Oversight Committee.

Grant Support: By the Robert C. Atkins Foundation, New York, New York. Dr. Yancy is supported by a Veterans Administration Health Services Research Career Development Award.

Potential Financial Conflicts of Interests: *Grants received:* E.C. Westman (Robert C. Atkins Foundation); *Grants pending:* E.C. Westman and W.S. Yancy Jr. (Robert C. Atkins Foundation).

Requests for Single Reprints: Eric C. Westman, MD, MHS, Duke University Medical Center, Box 50, Suite 200-B Wing, 2200 West Main Street, Durham, NC 27705; e-mail, ewestman@duke.edu.

Current author addresses and author contributions are available at www.annals.org.

References

1. **Flegal KM, Carroll MD, Kuczmarski RJ, Johnson CL.** Overweight and obesity in the United States: prevalence and trends, 1960-1994. Int J Obes Relat Metab Disord. 1998;22:39-47. [PMID: 9481598]

2. **Serdula MK, Mokdad AH, Williamson DF, Galuska DA, Mendlein JM, Heath GW.** Prevalence of attempting weight loss and strategies for controlling weight. JAMA. 1999;282:1353-8. [PMID: 10527182]

3. Methods for voluntary weight loss and control. NIH Technology Assessment

Conference Panel. Consensus Development Conference, 30 March to 1 April 1992. Ann Intern Med. 1993;119:764-70. [PMID: 8363212]

4. **Atkins RC.** Dr. Atkins' New Diet Revolution. New York: Simon & Schuster; 1998.

5. **Westman EC.** A review of very low carbohydrate diets. Journal of Clinical Outcomes Management. 1999;6:36-40.

6. **Westman EC, Yancy WS, Edman JS, Tomlin KF, Perkins CE.** Effect of 6-month adherence to a very low carbohydrate diet program. Am J Med. 2002; 113:30-6. [PMID: 12106620]

7. **Sondike SB, Copperman N, Jacobson MS.** Effects of a low-carbohydrate diet on weight loss and cardiovascular risk factor in overweight adolescents. J Pediatr. 2003;142:253-8. [PMID: 12640371]

8. **Samaha FF, Iqbal N, Seshadri P, Chicano KL, Daily DA, McGrory J, et al.** A low-carbohydrate as compared with a low-fat diet in severe obesity. N Engl J Med. 2003;348:2074-81. [PMID: 12761364]

9. **Foster GD, Wyatt HR, Hill JO, McGuckin BG, Brill C, Mohammed BS, et al.** A randomized trial of a low-carbohydrate diet for obesity. N Engl J Med. 2003;348:2082-90. [PMID: 12761365]

10. **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 Metab. 2003;88:1617-23. [PMID: 12679447]

11. Step by Step. Eating to Lower Your High Blood Cholesterol. Bethesda, MD: American Heart Association, U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Heart, Lung, and Blood Institute; 1994. NIH publication no. 94-2920.

12. The Practical Guide: Identification, Evaluation and Treatment of Overweight and Obesity in Adults. Bethesda, MD: National Institutes of Health, National Heart, Lung, and Blood Institute, North American Association for the Study of Obesity, U.S. Department of Health and Human Services, Public Health Service; 2000. NIH publication no. 00-4084.

13. **Duyff RL.** The American Dietetic Association's Complete Food and Nutrition Guide. Minneapolis: Chronimed; 1998.

14. **Free HM, Smeby RR, Cook MH, Free AH.** A comparative study of qualitative tests for ketones in urine and serum. Clin Chem. 1958;4:323-30. [PMID: 13561546]

15. **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. [PMID: 7410754]

16. **Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D.** A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med. 1999;130:461-70. [PMID: 10075613]

17. **Diggle PJ, Kenward MG.** Informative dropout in longitudinal data analysis (with discussion). Applied Statistics. 1994;43:49-94.

18. **Sjostrom L, Rissanen A, Andersen T, Boldrin M, Golay A, Koppeschaar HP, et al.** Randomised placebo-controlled trial of orlistat for weight loss and prevention of weight regain in obese patients. European Multicentre Orlistat Study Group. Lancet. 1998;352:167-72. [PMID: 9683204]

19. **Davidson MH, Hauptman J, DiGirolamo M, Foreyt JP, Halsted CH, Heber D, et al.** Weight control and risk factor reduction in obese subjects treated for 2 years with orlistat: a randomized controlled trial. JAMA. 1999;281:235-42. [PMID: 9918478]

20. **Bray GA, Ryan DH, Gordon D, Heidingsfelder S, Cerise F, Wilson K.** A double-blind randomized placebo-controlled trial of sibutramine. Obes Res. 1996;4:263-70. [PMID: 8732960]

21. **Arase K, Fisler JS, Shargill NS, York DA, Bray GA.** Intracerebroventricular infusions of 3-OHB and insulin in a rat model of dietary obesity. Am J Physiol. 1988;255(6 Pt 2):R974-R981. [PMID: 3059829]

22. **Stubbs J, Ferres S, Horgan G.** Energy density of foods: effects on energy intake. Crit Rev Food Sci Nutr. 2000;40:481-515. [PMID: 11186237]

23. **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. [PMID: 11838888]

24. **St Jeor ST, Howard BV, Prewitt TE, Bovee V, Bazzarre T, Eckel RH, et al.** Dietary protein and weight reduction: a statement for healthcare professionals from the Nutrition Committee of the Council on Nutrition, Physical Activity, and Metabolism of the American Heart Association. Circulation. 2001;104:1869-74. [PMID: 11591629]

25. **Rabast U, Kasper H, Schonborn J.** Comparative studies in obese subjects fed carbohydrate-restricted and high carbohydrate 1,000-calorie formula diets. Nutr Metab. 1978;22:269-77. [PMID: 662209]

26. **Golay A, Allaz AF, Morel Y, de Tonnac N, Tankova S, Reaven G.** Similar weight loss with low- or high-carbohydrate diets. Am J Clin Nutr. 1996;63: 174-8. [PMID: 8561057]

27. **Chait A, Brunzell JD.** Chylomicronemia syndrome. Adv Intern Med. 1992; 37:249-73. [PMID: 1557997]

28. **Mensink RP, Katan MB.** Effect of dietary fatty acids on serum lipids and lipoproteins. A meta-analysis of 27 trials. Arterioscler Thromb. 1992;12:911-9. [PMID: 1386252]

29. **Dattilo AM, Kris-Etherton PM.** Effects of weight reduction on blood lipids and lipoproteins: a meta-analysis. Am J Clin Nutr. 1992;56:320-8. [PMID: 1386186]

30. **Ford ES, Giles WH, Dietz WH.** Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. JAMA. 2002;287:356-9. [PMID: 11790215]

31. **Atkinson RL, Kaiser DL.** Effects of calorie restriction and weight loss on glucose and insulin levels in obese humans. J Am Coll Nutr. 1985;4:411-9. [PMID: 3900179]

32. **Langfort J, Pilis W, Zarzeczny R, Nazar K, Kaciuba-Uscilko H.** Effect of low-carbohydrate-ketogenic diet on metabolic and hormonal responses to graded exercise in men. J Physiol Pharmacol. 1996;47:361-71. [PMID: 8807563]

33. **Phinney SD, Bistrian BR, Wolfe RR, Blackburn GL.** The human metabolic response to chronic ketosis without caloric restriction: physical and biochemical adaptation. Metabolism. 1983;32:757-68. [PMID: 6865775]

34. **Yanovski SZ, Yanovski JA.** Obesity. N Engl J Med. 2002;346:591-602. [PMID: 11856799]

35. **Harper CR, Jacobson TA.** The fats of life: the role of omega-3 fatty acids in the prevention of coronary heart disease. Arch Intern Med. 2001;161:2185-92. [PMID: 11575974]

36. **Farmer A, Montori V, Dinneen S, Clar C.** Fish oil in people with type 2 diabetes mellitus. Cochrane Database Syst Rev. 2001:CD003205. [PMID: 11687050]

37. **Reddy ST, Wang CY, Sakhaee K, Brinkley L, Pak CY.** Effect of low-carbohydrate high-protein diets on acid-base balance, stone-forming propensity, and calcium metabolism. Am J Kidney Dis. 2002;40:265-74. [PMID: 12148098]

Appendix: Nutritional Supplement Ingredients

Supplements were provided by Atkins Nutritionals, Inc., New York, New York.

Multivitamin formula (administered daily as 6 capsules): vitamin A as acetate (3000 IU); vitamin A as β-carotene with mixed carotenoids (1200 IU); vitamin C (360 mg); vitamin D_3 (400 IU); vitamin E (300 IU); vitamin B_1 (50 mg); vitamin B_2 (50 mg); niacin (40 mg); vitamin B_6 (50 mg); folate (1600 mg); vitamin B_{12} (800 mcg); vitamin K (10 μg); biotin (600 μg); pantothenic acid (120 mg); calcium (500 mg); magnesium (250 mg); zinc (50 mg); selenium (200 μg); manganese (10 mg); chromium (600 μg); molybdenum (60 μg); potassium (20 mg); inositol hexanicotinate (100 mg); choline bitartrate (100 mg); para-amino benzoic acid (100 mg); vanadyl (80 μg); *N*-acetyl-L-cysteine (120 mg); pantethine (150 mg); quercetin (100 mg); boron (2 mg); grapeseed extract (40 mg); green tea (80 mg); and lecithin extracts, garlic, arginine, licorice, bromelain, pantethine, spirulina, inulin, lactoferrin, bioperine, and acidophilus, in unspecified amounts.

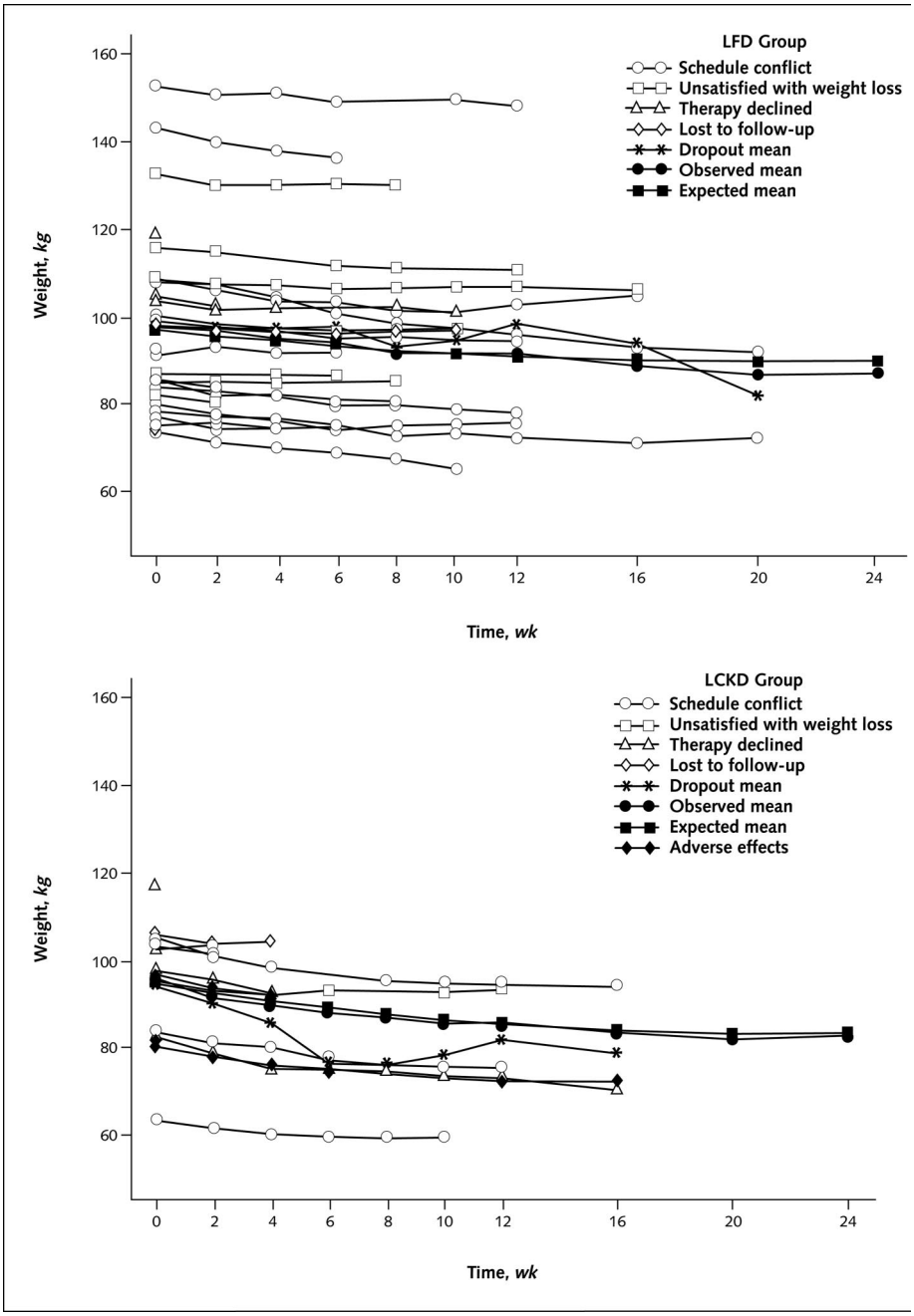
Essential oil formula (administered daily as 3 capsules): flaxseed oil (1200 mg), borage seed oil (1200 mg), fish oil (1200 mg), vitamin E (15 IU).

Diet formula (administered daily as 6 capsules): citrin (2700 mg), chromium (1200 μg), soy extract (9000 mg), methionine (1500 mg), L-carnitine (3000 mg), vitamin B_6 (120 mg), pantethine (120 mg), asparagus (300 mg), parsley (300 mg), kelp (120 mg), spirulina (300 mg), potassium citrate (594 mg), magnesium (360 mg), L-glutamine (450 mg), dl-phenylalanine (900 mg), L-tyrosine (450 mg), piperine (30 mg).

Current Author Addresses: Drs. Yancy and Olsen: Health Services Research and Development (152), Veterans Affairs Medical Center, 508 Fulton Street, Durham, NC 27705.
Dr. Guyton: Duke Lipid Clinic, Duke University Medical Center, Box 3510, Durham, NC 27710.
Ms. Bakst: Duke University Medical Center, Box 3921, Durham, NC 27710.
Dr. Westman: Duke University Medical Center, Box 50, Suite 200-B Wing, 2200 West Main Street, Durham, NC 27705.

Author Contributions: Conception and design: W.S. Yancy Jr., E.C. Westman.
Analysis and interpretation of the data: W.S. Yancy Jr., M.K. Olsen, J.R. Guyton, E.C. Westman.
Drafting of the article: W.S. Yancy Jr., J.R. Guyton, E.C. Westman.
Critical revision of the article for important intellectual content: W.S. Yancy Jr., M.K. Olsen. J.R. Guyton, R.P. Bakst, E.C. Westman.
Final approval of the article: W.S. Yancy Jr., M.K. Olsen, J.R. Guyton, R.P. Bakst, E.C. Westman.
Provision of study materials or patients: W.S. Yancy Jr., E.C. Westman.
Statistical expertise: W.S. Yancy Jr., M.K. Olsen, E.C. Westman.
Obtaining of funding: E.C. Westman.
Administrative, technical, or logistic support: R.P. Bakst, E.C. Westman.
Collection and assembly of data: W.S. Yancy Jr., R.P. Bakst, E.C. Westman.

Appendix Figure. **Reasons for discontinuation and individual weight trajectories for participants who dropped out, by diet group.**



Top. Low-fat, low-cholesterol, reduced-calorie diet (*LFD*) group. **Bottom.** Low-carbohydrate, ketogenic diet (*LCKD* group). At week 24, the low-fat diet group included 33 rather than 34 participants because 1 participant contributed a blood specimen, but not weight measurements, at that time point. The dropout mean is the mean weight loss for each diet group's dropouts who were still in the study at that time point. The observed mean is the mean weight loss for each diet group's participants who were still in the study at that time point. The expected mean is the mean weight loss for each diet group's participants at that time point, by linear mixed-effects model analysis.