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A Randomized Trial of a Low-Carbohydrate Diet vs Orlistat Plus a Low-Fat Diet for Weight Loss

William S. Yancy Jr, MD, MHS; Eric C. Westman, MD, MHS; Jennifer R. McDuffie, PhD, RD, MPH; Steven C. Grambow, PhD; Amy S. Jeffreys, MStat; Jamiyla Bolton, MS; Allison Chalecki, RD; Eugene Z. Oddone, MD, MHS

Background: Two potent weight loss therapies, a low-carbohydrate, ketogenic diet (LCKD) and orlistat therapy combined with a low-fat diet (O + LFD), are available to the public but, to our knowledge, have never been compared.

Methods: Overweight or obese outpatients (n = 146) from the Department of Veterans Affairs primary care clinics in Durham, North Carolina, were randomized to either LCKD instruction (initially, <20 g of carbohydrate daily) or orlistat therapy, 120 mg orally 3 times daily, plus low-fat diet instruction (<30% energy from fat, 500-1000 kcal/d deficit) delivered at group meetings over 48 weeks. Main outcome measures were body weight, blood pressure, fasting serum lipid, and glycemic parameters.

Results: The mean age was 52 years and mean body mass index was 39.3 (calculated as weight in kilograms divided by height in meters squared); 72% were men, 55% were black, and 32% had type 2 diabetes mellitus. Of the study participants, 57 of the LCKD group (79%) and 65 of the O + LFD group (88%) completed measurements at 48 weeks. Weight loss was similar for the LCKD (expected mean change, –9.5%) and the O + LFD (–8.5%) ($P = .60$ for comparison) groups. The LCKD had a more beneficial impact than O + LFD on systolic (–5.9 vs 1.5 mm Hg) and diastolic (–4.5 vs 0.4 mm Hg) blood pressures ($P < .001$ for both comparisons). High-density lipoprotein cholesterol and triglyceride levels improved similarly within both groups. Low-density lipoprotein cholesterol levels improved within the O + LFD group only, whereas glucose, insulin, and hemoglobin A_{1c} levels improved within the LCKD group only; comparisons between groups, however, were not statistically significant.

Conclusion: In a sample of medical outpatients, an LCKD led to similar improvements as O + LFD for weight, serum lipid, and glycemic parameters and was more effective for lowering blood pressure.

Trial Registration: clinicaltrials.gov Identifier: NCT00108524

Arch Intern Med. 2010;170(2):136-145

Author Affiliations: Center for Health Services Research in Primary Care, Department of Veterans Affairs Medical Center, Durham, North Carolina (Drs Yancy, McDuffie, Grambow, and Oddone and Mss Jeffreys, Bolton, and Chalecki); and Departments of Medicine (Drs Yancy, Westman, and Oddone) and Biostatistics and Bioinformatics (Dr Grambow), Duke University Medical Center, Durham, North Carolina.

STUDIES COMPARING LOW-carbohydrate diets with reduced-calorie diets have shown that weight loss can be greater with a low-carbohydrate diet for durations of 6 months or less and similar or greater for durations up to 2 years.[1-3] Likewise, the 2 weight loss medications approved for long-term use, orlistat and sibutramine, when paired with a reduced-calorie diet, have proved more effective than diet alone.[4] Yet, neither of these medications has been compared with a low-carbohydrate diet. Now that orlistat is available without prescription, it is appropriate to compare it with other readily available, potent interventions such as the low-carbohydrate diet.

See also pages 121, 126, and 146

In addition, low-carbohydrate diets have been studied infrequently in patients with chronic illnesses.[5-9] With treatment guidelines beginning to include the low-carbohydrate diet as an option for such patients, it is important to study the diet's effect on chronic illnesses using rigorous research methods.[10] For example, patients taking medications that lower blood glucose level and blood pressure may respond differently to diets compared with healthy volunteers.[5,8] In this way, low-carbohydrate diets may be like weight loss medications in that medical monitoring is required and empirical experience is needed to inform practitioners. If a low-carbohydrate diet is at least comparable to a weight loss medication, it may be an attractive alternative to practitioners because it is simpler and less expensive than a diet plus medication combination therapy.

The purpose of this study was to examine body weight, metabolic, and ad-

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verse effects over 48 weeks in outpatients randomized to follow a low-carbohydrate, ketogenic diet (LCKD) or orlistat therapy plus a low-fat, reduced-calorie diet (O + LFD). Our hypothesis was that weight loss would be greater in participants following the LCKD.

METHODS

PARTICIPANTS

Participants were recruited from outpatient clinics affiliated with the Department of Veterans Affairs Medical Center in Durham, North Carolina, between April 2005 and October 2006. The inclusion criteria were age between 18 and 70 years and a body mass index (BMI) between 27 and 30 (calculated as weight in kilograms divided by height in meters squared) plus an obesity-related disease or a BMI of 30 or higher regardless of comorbidity.[11] Exclusion criteria included weight loss in the past month; pregnancy, breastfeeding, or lack of birth control; type 1 diabetes mellitus; unstable heart disease; dementia, unstable psychiatric illness, or substance abuse; blood pressure higher than 160/100 mm Hg; serum creatinine level higher than 1.5 mg/dL (to convert to micromoles per liter, multiply by 88.4) in men and higher than 1.3 mg/dL in women; liver transaminase level higher than 2 times the upper limit of normal, alkaline phosphatase level higher than 120 U/L (to convert to microkatals, multiply by 0.0167), or total bilirubin level higher than 1.6 mg/dL (to convert to micromoles per liter, multiply by 17.104); hemoglobin A_{1c} level higher than 11% (to convert to a proportion of total hemoglobin, multiply by 0.01); and fasting serum triglyceride level higher than 600 mg/dL (to convert to millimoles per liter, multiply by 0.0113) or low-density lipoprotein cholesterol (LDL-C) level higher than 190 mg/dL (to convert to millimoles per liter, multiply by 0.0259). All participants provided written informed consent approved by the Durham VA Medical Center's institutional review board.

RANDOMIZATION AND INTERVENTION

Eligible participants were allocated to the LCKD or O + LFD using a computer-generated randomization list kept exclusively by the study statisticians (S.C.G. and A.S.J.). Randomization was stratified by sex and presence of type 2 diabetes mellitus.

Both interventions included small group meetings (6 to 12 participants) at an outpatient clinic every 2 weeks for 24 weeks, then every 4 weeks for 24 weeks. Meetings lasted 1 to 2 hours and consisted of study measurements followed by group counseling led by a registered dietitian (A.C.), a research assistant (J.B.), and a physician (W.S.Y.). The counseling sessions followed a predetermined syllabus of topics (eg, nutrition label reading, eating out) that were parallel between the 2 interventions but specific to diet. All participants were advised to exercise on their own for 30 minutes at least 3 times per week, take a multivitamin daily, drink 6 to 8 glasses of fluids daily, and minimize consumption of caffeine and alcohol. Participants and study personnel were not blinded to treatment assignment.

LOW-CARBOHYDRATE DIET

Participants were instructed to restrict carbohydrate intake initially to less than 20 g/d using pocket guides and handouts.[12,13] Participants could eat unlimited meat and eggs, 112 g of hard cheese, 0.48 L of low-carbohydrate vegetables (eg, leafy greens), and 0.24 L of moderate-carbohydrate vegetables (eg, broccoli, asparagus) daily; calorie intake was not restricted. As participants approached their goal weight or if cravings threatened their adherence to the diet, they were advised to add approximately 5 g of carbohydrates to their daily intake each week until weight was maintained or cravings diminished.

ORLISTAT PLUS LOW-FAT DIET

Participants were instructed to restrict intake of total fat (<30% of daily energy), saturated fat (<10% of daily energy), cholesterol (<300 mg daily), and calories using pocket guides, handouts, and individualized goals.[13,14] Recommended calorie intake was 500 to 1000 kcal below a participant's calculated weight maintenance intake.[15] In addition, a 30-day supply of orlistat (120 mg before meals 3 times a day) was provided monthly.

OUTCOME MEASURES

Outcome measures were performed by trained research personnel. Body weight was measured using the same calibrated scale (Tanita Corp, Arlington Heights, Illinois) at each visit at the same time of day, with the participant wearing light clothing and no shoes. Blood pressure and pulse were measured twice at each visit in the nondominant arm using an automated digital cuff (Omron Corp, Vernon Hills, Illinois) after the participant was sitting for 5 minutes. The mean of the 2 readings was used in analyses. Similarly, waist circumference was measured twice at the skin surface at the level of the umbilicus using a nonelastic tape. Urinary ketones were measured at each visit from a fresh urine specimen.

Diet adherence was measured using 4-day food records (including 2 weekend days) at baseline and weeks 2, 12, 24, 36, and 48. Participants were given verbal and written instructions regarding record completion. A registered dietitian (A.C. or J.R.M.) clarified ambiguous entries with the participant and input data using nutrition analysis software (ESHA Research, Salem, Oregon). Self-administered questionnaires were completed at group visits to assess medication changes, physical activity level, and adverse effects.[16]

Blood and urine samples were obtained after at least 8 hours of fasting at baseline and at weeks 2, 12, 24, 36, and 48. Processing and testing of samples were performed by the central laboratory of the medical center following standardized techniques; LDL-C level was calculated using the Friedewald equation.[17]

STATISTICAL ANALYSIS

The primary outcome was percentage change in body weight. The sample size estimate, however, was based on the secondary outcome of mean change in LDL-C level because it has been considered a safety concern for the LCKD and has more stringent sample size requirements. Based on previous data, a 2-sided type 1 error rate of 0.05 and 80% power, we estimated that 140 participants (70 in each treatment group) were needed to detect a 9-mg/dL absolute difference between the 2 interventions in mean LDL-C level change from baseline to 48 weeks.[18] This estimate provided greater than 95% power to detect a 3% absolute difference between the interventions in mean percentage weight change. Sample size calculations assumed a 30% final dropout rate and accounted for clustering due to small meeting groups within each treatment condition.[19]

Baseline variables of the 2 interventions were compared using unpaired t tests for continuous variables and χ^2 tests for categorical variables. The primary analysis for outcomes was performed according to intention-to-treat principles; all participants who were randomized and had at least 1 outcome data

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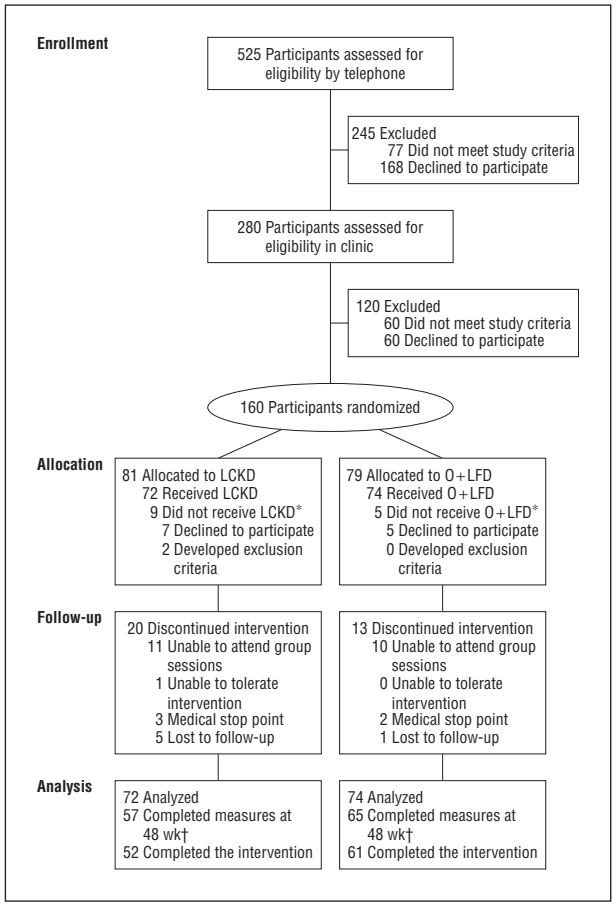

Figure 1. Participant flowchart. O + LFD indicates orlistat plus a low-fat, reduced-calorie diet; LCKD, low-carbohydrate, ketogenic diet. *Participants who withdrew after randomization but before receiving the intervention were unaware of their allocation. †Nine participants (LCKD, n=5; O + LFD, n=4) returned for measurements at week 48 despite discontinuing the intervention.

measurement collected were included in analyses according to their randomized allocation.[20] Subjects who failed to attend their initial small group visit were unaware of their randomization assignment, did not have outcome data collected, and therefore, were not included in analyses. To compare categorical outcomes between groups, we used the Pearson χ^2 test. For continuous, longitudinal outcomes, we used linear mixed models to test hypotheses of treatment differences over time.[21] For body measurement and vital sign models, we used a random coefficient approach with time and treatment group included as fixed effects with linear, quadratic, or cubic time-by-treatment group interaction terms as appropriate[22]; random effects included intercept and slope terms (percentage change in weight did not include a random intercept term because, by definition, percentage change must be zero at baseline). In addition, the proportions of participants in each intervention who achieved levels of weight loss (<5%, 5% to <10%, 10% to <20%, and ≥20%) were estimated using best linear unbiased predictors from the mixed model.[23] For serum tests (collected at 5 time points compared with 19 for body and vital sign measurements), we used a repeated-measures approach with the time-by-treatment group interaction as a categorical variable and an unstructured covariance to account for within-patient correlation over time. Longitudinal models used all available data, including data from participants who had missing observations and/or were lost to attrition; these models yield unbiased estimates of parameters when missing outcome data are assumed to be ignorable, ie, the missing values may be related to either observed covariates or response variables but not related to the unobserved values.[24] Because there were no estimable small group effects, the presented analyses do not incorporate adjustment for clustering. Statistical analyses were performed using SAS software version 9.1 (SAS Institute Inc, Cary, North Carolina) and S-PLUS version 7 (Insightful Corp, Seattle, Washington).

RESULTS

PARTICIPANTS AND RETENTION

During recruitment, 525 volunteers were screened for eligibility by telephone, 280 were subsequently screened in the clinic, and 160 were randomized (**Figure 1**). Of those, 14 did not attend the first intervention visit and therefore did not learn of their intervention assignments nor have baseline outcome measurements. Baseline characteristics for the 146 participants who initiated the intervention are given in **Table 1**.

Of the 33 participants (LCKD, n=20; O + LFD, n=13) who discontinued the intervention, 9 (LCKD, n=5; O + LFD, n=4) agreed to return for week 48 measurements (Figure 1). Five participants were discontinued for safety reasons (LCKD, 2 for LDL-C elevations and 1 for a kidney stone; O + LFD, 1 for pregnancy and 1 for a kidney stone).

DIET COMPOSITION AND ADHERENCE MEASURES

The 2 treatment groups had similar intakes of calories, macronutrients, and fiber at baseline (**Table 2**). Both groups had substantially reduced caloric intake over the course of the study compared with baseline. There were obvious differences in carbohydrate and fat intake between the groups during follow-up, as expected.

The presence of urinary ketones is a marker of adherence to the LCKD. The proportion of LCKD participants with urinary ketones present (≥5 mg/dL [≥0.9 mmol/L]) was 72% (50 of 69 participants) at 2 weeks and declined gradually to a low of 13% at 48 weeks. The proportion of O + LFD participants with urinary ketones remained below 15% with few exceptions.

We analyzed orlistat pill counts by calculating the percentage of pills taken over the course of the study excluding pill bottles never handed out (eg, participant did not attend a visit or discontinued the study) (15%) or never returned to be counted (15%). After analyzing those pill bottles returned, we found that a mean (SD) of 89% (15%) of pills were taken over the 48 weeks.

BODY MEASUREMENTS

Over 48 weeks, weight loss was statistically significant and similar in the 2 groups: the expected mean change from baseline in the LCKD participants was –9.5% (95% CI [confidence interval], –12.1 to –6.9) or –11.4 kg (95% CI, –14.8 to –7.9) compared with –8.5% (95% CI, –11.0 to –6.1) or –9.6 kg (95% CI, –11.9 to –7.3) in the O + LFD participants (mean difference, –1.0%; 95% CI, –4.5 to 2.6) (**Table 3**, **Figure 2**, and **Figure 3**). Waist circumference also decreased similarly in the 2 groups. The pro-

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Table 1. Baseline Participant Characteristics[a]

Characteristic	LCKD			O + LFD			*P* Value for Between-Group Comparison of Enrollees[b]
	Enrollees (n=72)	Completers (n=57)	Noncompleters (n=15)	Enrollees (n=74)	Completers (n=65)	Noncompleters (n=9)	
Demographics							
Age, y	52.9 (10.2)	54.5 (9.7)	47.1 (10.2)	52.0 (9.2)	53.2 (8.9)	43.5 (5.7)	.57
Women, No. (%)	20 (28)	14 (25)	6 (40)	21 (28)	17 (26)	4 (44)	.94
Race or ethnicity, No. (%)							>.99
White	31 (43)	26 (46)	5 (33)	31 (42)	28 (43)	3 (33)	
African American	40 (56)	31 (54)	9 (60)	41 (55)	35 (54)	6 (67)	
College degree, No. (%)	33 (46)	28 (49)	5 (33)	33 (45)	29 (45)	4 (44)	.88
Risk factors, No. (%)							
Smokers	4 (6)	3 (5)	1 (7)	12 (16)	10 (15)	2 (22)	.04
Hypertension	44 (61)	38 (67)	6 (40)	54 (73)	50 (77)	4 (44)	.13
Hyperlipidemia	33 (46)	30 (53)	3 (20)	31 (42)	28 (43)	3 (33)	.63
Diabetes	22 (31)	17 (30)	5 (33)	24 (32)	23 (35)	1 (11)	.81
Framingham physical activity index,[16] score[c]	29.6 (4.0)	29.4 (3.7)	30.5 (5.0)	29.6 (4.3)	29.5 (4.3)	29.9 (4.7)	.96
Clinical measures							
Body weight, kg	123.1 (25.4)	124.0 (25.7)	119.9 (24.5)	117.4 (26.0)	119.0 (26.8)	105.4 (16.3)	.18
BMI	39.9 (6.9)	39.5 (6.9)	41.1 (7.0)	38.8 (7.0)	39.3 (7.2)	34.9 (3.5)	.36
Waist circumference, cm	127.4 (16.9)	127.6 (17.2)	126.5 (16.5)	124.8 (17.4)	126.1 (17.5)	115.4 (14.6)	.37
Systolic blood pressure, mm Hg	135.0 (17.0)	135.1 (16.4)	134.5 (19.5)	128.2 (15.5)	128.8 (15.9)	124.4 (11.9)	.01
Diastolic blood pressure, mm Hg	89.6 (9.7)	89.4 (9.3)	90.3 (11.2)	85.0 (10.4)	84.6 (10.8)	87.9 (5.7)	.01
Blood tests							
Total cholesterol, mg/dL	181.5 (32.1)	182.5 (33.7)	177.8 (25.6)	185.0 (34.4)	184.0 (35.2)	191.6 (28.9)	.54
Triglycerides, mg/dL	142.2 (73.8)	151.9 (74.3)	105.2 (60.8)	139.1 (74.3)	136.4 (74.1)	158.4 (76.9)	.80
LDL-C, mg/dL[c]	115.6 (29.8)	115.5 (31.4)	116.0 (23.8)	118.1 (31.4)	117.5 (32.4)	123.0 (23.6)	.62
HDL-C, mg/dL	37.6 (8.1)	36.7 (8.1)	40.7 (7.9)	39.1 (12.1)	39.4 (12.5)	36.9 (8.3)	.40
Triglyceride/HDL-C ratio	4.1 (2.7)	4.5 (2.7)	2.9 (2.1)	4.0 (2.6)	3.9 (2.6)	4.7 (2.8)	.73
C-reactive protein, mg/L	0.6 (0.5)	0.6 (0.4)	0.8 (0.7)	0.8 (0.7)	0.8 (0.8)	0.6 (0.4)	.17
Hemoglobin A_{1c}, %	6.3 (1.1)	6.2 (1.0)	6.7 (1.4)	6.4 (1.3)	6.4 (1.4)	5.9 (0.9)	.78

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); HDL-C, high-density lipoprotein cholesterol; LCKD, low-carbohydrate, ketogenic diet; LDL-C, low-density lipoprotein cholesterol; O + LFD, orlistat plus a low-fat, reduced-calorie diet.

SI conversion factors: To convert cholesterol and triglycerides to millimoles per liter, multiply by 0.0259 and 0.0113, respectively; C-reactive protein to nanomoles per liter, multiply by 9.524; and hemoglobin A_{1c} to a proportion of total hemoglobin, multiply by 0.01.

[a] Data are given as mean (SD) unless otherwise specified.

[b] Baseline variables of the enrollees in the 2 interventions were compared using *t* tests for continuous variables and χ^2 tests for categorical variables.

[c] One patient in the LCKD completer group was missing a measurement for LDL-C; 1 patient in the LCKD noncompleter group was missing a Framingham physical activity score.

portions of participants in each intervention who achieved the following levels of weight change over 48 weeks were similar: less than 5% weight loss (LCKD, 36%; O + LFD, 41%), 5% to less than 10% weight loss (LCKD, 19%; O + LFD, 18%), 10% to less than 20% weight loss (LCKD, 31%; O + LFD, 31%), and 20% or greater weight loss (LCKD, 14%; O + LFD, 11%) (χ^2=0.54; *P*=.91). Participants who attended 80% or more of the group counseling sessions lost considerably more weight, regardless of treatment assignment (observed means: LCKD [n=26], –14.9%; O + LFD [n=27], –13.9%).

BLOOD PRESSURE AND SERUM LIPID AND LIPOPROTEIN LEVELS

The LCKD participants had greater improvements than O + LFD participants in systolic and diastolic blood pressures (Table 3). For the LCKD participants, change in systolic blood pressure was –5.9 mm Hg (95% CI, –8.8 to –3.1) and diastolic blood pressure was –4.5 mm Hg (95% CI, –6.6 to –2.5), whereas the corresponding changes for the O + LFD participants were 1.5 mm Hg (95% CI, –0.9 to 3.9) and 0.4 mm Hg (95% CI, –1.3 to 2.2), respectively (Table 3).

The 2 interventions appeared to have differential effects on fasting serum lipid and lipoprotein levels over the first 36 weeks, but these differences converged by 48 weeks (Table 3). The LCKD participants appeared to have greater improvements initially in serum high-density lipoprotein cholesterol and triglyceride levels, whereas the O + LFD participants appeared to have greater improvements initially in serum total and LDL-C levels. However, there were no statistically significant differences between the groups in changes of these measures from baseline to 48 weeks.

OTHER METABOLIC EFFECTS

From baseline to 48 weeks, serum urea nitrogen level increased more in the LCKD group than in the O + LFD group (mean difference, 2.0 mg/dL; 95% CI, 0.4 to 3.5) (Table 3). Within the LCKD group, the following para-

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Table 2. Mean (SD) Dietary Energy and Nutrient Intake by Intervention Group and Time Point[a]

Nutrient	LCKD	O + LFD
Energy, kcal/d		
Baseline	2385 (1050)	2184 (941)
2 wk	1597 (708)	1494 (610)
12 wk	1633 (687)	1577 (749)
24 wk	1723 (697)	1471 (692)
36 wk	1679 (794)	1596 (689)
48 wk	1698 (633)	1566 (777)
Carbohydrates, g/d		
Baseline	262.0 (125.1)	223.0 (112.8)
2 wk	40.1 (47.2)	170.1 (76.4)
12 wk	49.9 (63.3)	188.5 (100.7)
24 wk	54.8 (60.5)	183.4 (95.3)
36 wk	59.0 (55.0)	192.6 (100.9)
48 wk	62.0 (56.3)	186.4 (109.1)
Total fat, g/d		
Baseline	104.9 (60.8)	99.9 (55.3)
2 wk	103.9 (54.0)	54.5 (37.6)
12 wk	103.1 (50.9)	56.5 (40.6)
24 wk	109.2 (49.9)	50.2 (37.1)
36 wk	103.7 (58.3)	57.9 (35.2)
48 wk	106.7 (50.1)	56.9 (40.8)
Saturated fat, g/d		
Baseline	34.2 (21.9)	31.8 (18.8)
2 wk	37.6 (22.3)	16.5 (13.6)
12 wk	36.5 (19.8)	16.4 (11.4)
24 wk	39.2 (22.3)	15.0 (12.7)
36 wk	34.9 (23.2)	17.4 (11.8)
48 wk	37.9 (20.8)	16.6 (12.7)
Monounsaturated fat, g/d		
Baseline	24.5 (19.4)	24.4 (19.3)
2 wk	27.4 (17.8)	13.6 (13.0)
12 wk	25.2 (15.6)	13.9 (14.5)
24 wk	29.6 (16.2)	13.0 (13.2)
36 wk	25.7 (17.8)	13.8 (12.3)
48 wk	27.4 (18.6)	14.7 (16.0)
Polyunsaturated fat, g/d		
Baseline	10.6 (9.8)	10.5 (9.3)
2 wk	8.9 (7.5)	6.3 (6.1)
12 wk	8.8 (7.5)	6.0 (5.7)
24 wk	9.4 (5.9)	6.2 (5.3)
36 wk	8.8 (6.4)	5.6 (4.5)
48 wk	9.2 (6.9)	6.6 (7.1)
trans Fat, g/d		
Baseline	2.7 (4.0)	2.2 (3.6)
2 wk	1.1 (1.2)	0.9 (1.8)
12 wk	1.4 (2.5)	1.1 (3.9)
24 wk	1.3 (1.5)	0.6 (1.3)
36 wk	0.9 (1.1)	0.9 (2.6)
48 wk	1.2 (1.4)	0.9 (2.4)
Protein, g/d		
Baseline	95.5 (41.4)	97.1 (45.6)
2 wk	118.2 (54.6)	80.5 (35.3)
12 wk	116.9 (52.2)	78.0 (33.7)
24 wk	119.1 (50.8)	73.8 (35.4)
36 wk	115.3 (56.4)	79.5 (34.6)
48 wk	112.2 (46.8)	78.0 (35.5)
Cholesterol, mg/d		
Baseline	449.8 (315.4)	444.2 (321.4)
2 wk	804.4 (356.6)	288.5 (225.0)
12 wk	740.1 (337.2)	274.7 (208.5)
24 wk	795.8 (385.8)	259.1 (230.3)
36 wk	735.5 (423.9)	251.4 (204.5)
48 wk	721.2 (351.2)	296.2 (284.1)
Fiber, g/d		
Baseline	17.3 (9.5)	15.7 (9.6)
2 wk	5.7 (4.8)	15.6 (10.3)
12 wk	6.2 (5.9)	16.2 (11.0)
24 wk	6.8 (6.1)	16.3 (10.1)
36 wk	7.2 (5.3)	19.0 (11.1)
48 wk	7.6 (5.0)	17.5 (11.6)

Abbreviations: LCKD, low-carbohydrate, ketogenic diet; O + LFD, orlistat plus a low-fat, reduced-calorie diet.

[a] Data presented are unadjusted raw data with no imputations for missing data. Sample sizes for baseline, 2, 12, 24, 36, and 48 weeks are n=71, n=58, n=48, n=48, n=23, and n=31, respectively, for the LCKD and n=73, n=63, n=49, n=50, n=36, and n=34, respectively, for the O + LFD.

meters decreased significantly from baseline to week 48: fasting glucose level (–9.7 mg/dL; 95% CI, –16.9 to –2.6), fasting insulin level (–7.3 μIU/mL; 95% CI, –13.5 to –1.2 [participants without diabetes only]), and hemoglobin A_{1c} (–0.3%; 95% CI, –0.5 to –0.1).

MEDICATION CHANGES

We examined medication changes from baseline to 48 weeks in those individuals who took medication for hypertension or diabetes during the study. For antihypertension medication, 4 of 43 LCKD participants (9%) had an increase (new medication added or dosage of existing medication raised) and 20 (47%) had a decrease (medication discontinued or dosage lowered). In the O + LFD group, 9 of 53 participants (17%) had an increase and 11 (21%) had a decrease in antihypertension medication. For diabetes medication, 1 of 16 LCKD participants (6%) had an increase and 13 (81%) had a decrease, while 1 of 22 O + LFD participants (5%) had an increase and 15 (68%) had a decrease.

ADVERSE EFFECTS

The following symptomatic adverse effects were reported at least once by more LCKD participants than O + LFD participants: constipation (69% vs 41%; $P < .001$), increased urinary frequency (79% vs 55%; $P = .003$), halitosis (44% vs 19%; $P = .001$), or leg muscle cramps (61% vs 39%; $P = .01$). More O + LFD than LCKD participants reported increased flatus (78% vs 59%; $P = .01$), bowel incontinence (35% vs 17%; $P = .01$), or diarrhea (73% vs 55%; $P = .02$), resulting in discontinuation of orlistat by 1 participant. One participant with diabetes in the LCKD group developed worse proteinuria during the study. Similar proportions from each group reported a hospitalization or emergency department visit for any reason (LCKD, 38%, vs O + LFD, 35%; $P = .72$). There were few serious adverse events that may have been related to the intervention: 1 LCKD participant was hospitalized for syncope attributed to excessive antihypertension medication and 2 O + LFD participants were hospitalized for unstable angina.

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Table 3. Expected Mean Changes in Clinic and Serum Measurements Relative to Baseline for All Participants[a]

Measurement	LCKD (n=72)[b]	O + LFD (n=74)[b]	LCKD – O + LFD at 48 Weeks	*P* Value at 48 Weeks
Clinic measures				
Body weight, %				
12 wk	–8.40	–6.80		
24 wk	–10.73	–9.21		
36 wk	–10.06	–9.14		
48 wk	–9.48 (–12.05 to –6.91)	–8.53 (–10.99 to 6.07)	–0.95 (–4.50 to 2.61)	.60
Body weight, kg				
12 wk	–9.68	–7.51		
24 wk	–12.81	–10.42		
36 wk	–12.38	–10.51		
48 wk	–11.37 (–14.84 to –7.89)	–9.62 (–11.94 to –7.29)	–1.75 (–5.90 to 2.40)	.41
Waist circumference, cm				
12 wk	–8.49	–6.36		
24 wk	–11.46	–9.29		
36 wk	–11.47	–9.85		
48 wk	–11.07 (–13.85 to –8.29)	–9.08 (–10.98 to –7.18)	–1.99 (–5.33 to 1.35)	.24
Systolic blood pressure, mm Hg				
12 wk	–1.49	0.37		
24 wk	–2.97	0.75		
36 wk	–4.45	1.12		
48 wk	–5.94 (–8.80 to –3.08)	1.50 (–0.88 to 3.87)	–7.44 (–11.12 to –3.75)	<.001
Diastolic blood pressure, mm Hg				
12 wk	–2.85	–1.70		
24 wk	–4.55	–2.19		
36 wk	–5.11	–1.48		
48 wk	–4.53 (–6.57 to –2.49)	0.43 (–1.34 to 2.21)	–4.97 (–7.64 to –2.29)	<.001
Framingham physical activity index,[16] score				
12 wk	0.6	–0.4		
24 wk	0.1	0.3		
36 wk	–0.4	0.3		
48 wk	–0.2 (–1.4 to 1.0)	0.3 (–0.9 to 1.5)	–0.5 (–2.2 to 1.2)	.58
Blood tests				
Total cholesterol, mg/dL				
12 wk	–4.54	–28.60		
24 wk	2.91	–17.18		
36 wk	–0.21	–19.08		
48 wk	–3.80 (–10.68 to 3.07)	–8.86 (–15.31 to –2.41)	5.05 (–4.37 to 14.48)	.29
Triglycerides, mg/dL[c]				
12 wk	–41.82	–28.82		
24 wk	–42.21	–21.13		
36 wk	–44.95	–27.83		
48 wk	–28.83 (–48.08 to –9.58)	–21.40 (–39.63 to –3.17)	–7.43 (–33.94 to 19.08)	.58
LDL-C, mg/dL				
12 wk	3.12	–20.75		
24 wk	8.09	–13.90		
36 wk	3.19	–15.43		
48 wk	–1.91 (–8.14 to 4.33)	–8.29 (–14.06 to –2.52)	6.39 (–2.11 to 14.88)	.14
HDL-C, mg/dL				
12 wk	1.23	–2.39		
24 wk	4.03	0.29		
36 wk	5.87	1.86		
48 wk	3.77 (1.84 to 5.70)	3.43 (1.61 to 5.25)	0.34 (–2.31 to 3.00)	.80

(continued)

COMMENT

In this randomized trial comparing LCKD with O + LFD, we found that the 2 interventions resulted in substantial yet similar weight loss over 48 weeks in an outpatient population. The interventions also had comparable beneficial effects on most measures of cardiovascular disease risk, including waist circumference, fasting serum lipid profiles, and C-reactive protein. The LCKD had a more favorable effect on blood pressure than the O + LFD in these outpatients, most of whom had hypertension. The improvement in blood pressure in the LCKD group (–5.9/–4.5 mm Hg) was near to that seen in a large cohort of patients who underwent bariatric surgery (approximately –8/–6 mm Hg).[25]

The majority of weight loss for both interventions occurred in the first 12 to 24 weeks with maximum weight loss achieved at 24 to 36 weeks, after which slight weight

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Table 3. Expected Mean Changes in Clinic and Serum Measurements Relative to Baseline for All Participants[a] (continued)

Measurement	LCKD (n=72)[b]	O + LFD (n=74)[b]	LCKD – O + LFD at 48 Weeks	*P* Value at 48 Weeks
Blood tests (continued)				
Total cholesterol–HDL-C ratio				
12 wk	–0.27	–0.54		
24 wk	–0.36	–0.49		
36 wk	–0.63	–0.67		
48 wk	–0.44 (–0.68 to –0.20)	–0.51 (–0.73 to –0.28)	0.07 (–0.26 to 0.40)	.68
Triglyceride–HDL-C ratio[c]				
12 wk	–1.30	–0.73		
24 wk	–1.42	–0.67		
36 wk	–1.69	–0.94		
48 wk	–1.00 (–1.65 to –0.35)	–0.77 (–1.38 to –0.15)	–0.23 (–1.12 to 0.66)	.61
C-reactive protein, mg/L				
24 wk	–0.07	–0.05		
48 wk	–0.18 (–0.30 to –0.06)	–0.15 (–0.26 to –0.04)	–0.03 (–0.20 to 0.13)	.69
Hemoglobin A_{1c}, %				
24 wk	–0.37	–0.21		
48 wk	–0.30 (–0.52 to –0.09)	–0.06 (–0.26 to 0.14)	–0.24 (–0.54 to 0.05)	.10
Fasting glucose, mg/dL				
12 wk	–8.46	–14.36		
24 wk	–7.88	–6.01		
36 wk	–7.46	–5.33		
48 wk	–9.74 (–16.93 to –2.55)	–3.26 (–10.05 to –3.54)	–6.48 (–16.38 to 3.42)	.20
Fasting insulin, μIU/mL[d]				
12 wk	–8.31	–5.31		
24 wk	–8.54	–6.82		
36 wk	–7.46	–4.01		
48 wk	–7.32 (–13.49 to –1.16)	–2.42 (–8.35 to 3.50)	–4.90 (–13.45 to 3.65)	.26
SUN				
12 wk	2.13	0.72		
24 wk	2.90	–0.52		
36 wk	1.99	0.50		
48 wk	3.19 (2.07 to 4.30)	1.23 (0.17 to 2.29)	1.96 (0.42 to 3.50)	.01
Creatinine				
12 wk	–0.02	0.02		
24 wk	–0.01	–0.01		
36 wk	0.00	–0.01		
48 wk	0.01 (–0.02 to 0.05)	0.00 (–0.03 to 0.04)	0.01 (–0.04 to 0.05)	.72
Urine albumin–creatinine ratio, mg/g of Cr[e]				
24 wk	12.34	–0.31		
48 wk	6.40 (–5.47 to 18.26)	1.18 (–9.86 to 12.22)	5.22 (–10.99 to 21.42)	.52

Abbreviations: Cr, creatinine; HDL-C, high-density lipoprotein cholesterol; LCKD, low-carbohydrate, ketogenic diet; LDL-C, low-density lipoprotein cholesterol; O + LFD, orlistat plus a low-fat, reduced-calorie diet; SUN, serum urea nitrogen.

SI conversion factors: To convert cholesterol and triglycerides to millimoles per liter, multiply by 0.0259 and 0.0113, respectively; C-reactive protein to nanomoles per liter, multiply by 9.524, hemoglobin A_{1c} to a proportion of total hemoglobin, multiply by 0.01; glucose to millimoles per liter, multiply by 0.0555; insulin to picomoles per liter, multiply by 6.945; and creatinine to micromoles per liter, multiply by 88.4.

[a] Values are expected means by linear mixed-effects models analysis.

[b] Ninety-five percent confidence intervals are give in parentheses at 48 weeks.

[c] One outlier was removed from the LCKD group where triglyceride level was 687 mg/dL and readings at 3 other time points were below 200 mg/dL.

[d] Fasting serum insulin level is reported for patients who did not have diabetes and were not taking diabetes medication.

[e] One outlier was removed from the LCKD group where urine albumin-creatinine ratio increased from 164 to 1144 mg/g of Cr.

regain occurred. These patterns of weight loss and regain are similar to previous trials that compared the LCKD with an LFD without adjunctive weight loss medication over 1 year.[6,26-28] In the only randomized trial to extend follow-up beyond 1 year, the weight regain in the LCKD arm leveled off early in the second year, and weight loss remained greater than the LFD arm at the end of 2 years.[3]

While the LCKD has lowered blood pressure in other studies, the greater effect compared with the O + LFD was unexpected because the 2 interventions resulted in similar weight loss and because the O + LFD also typically lowers blood pressure, albeit slightly.[2,29,30] More surprisingly, this effect occurred while antihypertension medication use was decreased more frequently in the LCKD than O + LFD participants. One potential mechanism for blood pressure improvement is that the LCKD may have a diuretic effect. In a previous study, we found that total body water decreased more sharply over the first 2 weeks with the LCKD than the LFD, but the levels remained parallel thereafter.[18] Another mechanism may be related to lower serum insulin levels seen with the LCKD; hyperinsulinemia has been associated with sodium reten-

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tion, proliferation of vascular smooth muscle, increased sympathetic nervous system activity, and diminished release of nitric oxide from the endothelium.[31,32]

In a meta-analysis of studies comparing the LCKD with an LFD, changes in systolic and diastolic blood pressure favored the LCKD but reached statistical significance for systolic blood pressure only.[2] In the OmniHeart Study, both the high-protein and high–monounsaturated fat diets (the LCKD is high in these macronutrients) lowered systolic and diastolic blood pressures more than the high-carbohydrate, low-fat diet.[33] In view of these data and studies showing that other weight loss medications (eg, sibutramine) typically attenuate the improvement in blood pressure expected from weight loss,[4] the LCKD should be considered in hypertensive patients who desire weight loss.

According to the food records, the 2 interventions resulted in noticeably different macronutrient intakes. During the intervention, the LCKD participants obtained more than 55% of their daily calorie intake from fat. Yet, because they also restricted energy intake, the amount of total fat they consumed was actually identical to their baseline diet. However, because the low-fat diet was combined with orlistat, which blocks the absorption of approximately 30% of ingested fat, the O + LFD group decreased their effective fat intake considerably, from approximately 100 g (41% of calories) per day to 35 to 40 g (21%-23% of calories) per day. The study results demonstrate how beneficial health effects can be achieved with either a proportionally very high-fat or very low-fat diet, so long as calorie intake is not high.

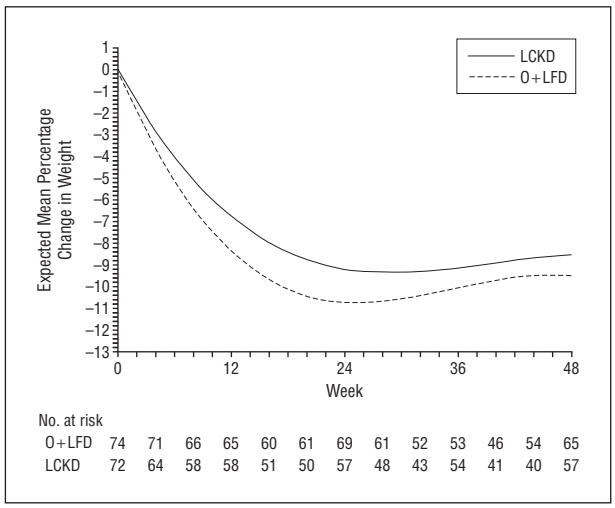

Figure 2. Expected mean percentage body weight changes over time by treatment group. Expected mean percentage body weight change estimates determined by linear mixed-effects analysis. LCKD indicates low-carbohydrate, ketogenic diet; O + LFD, orlistat plus a low-fat, reduced-calorie diet.

Compared with other trials, adherence was high over the 48 weeks. For example, the mean carbohydrate intake was 62 g/d (15% of calorie intake) at week 48 in the LCKD group. In most other trials reporting out to a year, the range was 120 to 190 g/d (33%-45% energy intake).[3,6,26,27,34] Although our data and recent data from Brinkworth et al[35] show that adherence to a low-carbohydrate diet can persist at 1 year, this duration is relatively short compared with the lifetime that many individuals must struggle with weight management. Adherence to either intervention over periods longer than a year has been examined in a few randomized trials, with some recidivism evident.[3,29,30,36,37] To truly have an impact on the obesity problem that our world faces, methods for improving long-term adherence to these and other weight loss strategies must be available.

Although adverse effects occurred with both interventions, participants learned to tolerate or alleviate them in most circumstances. The O + LFD participants reported gastrointestinal adverse effects more frequently than the LCKD participants, but only 1 participant discontinued orlistat treatment due to intolerance. Participants communicated that these adverse effects occurred predominantly after dietary indiscretions. Similarly, the LCKD had its own gastrointestinal adverse effect, constipation. In most cases, constipation resolved by in-

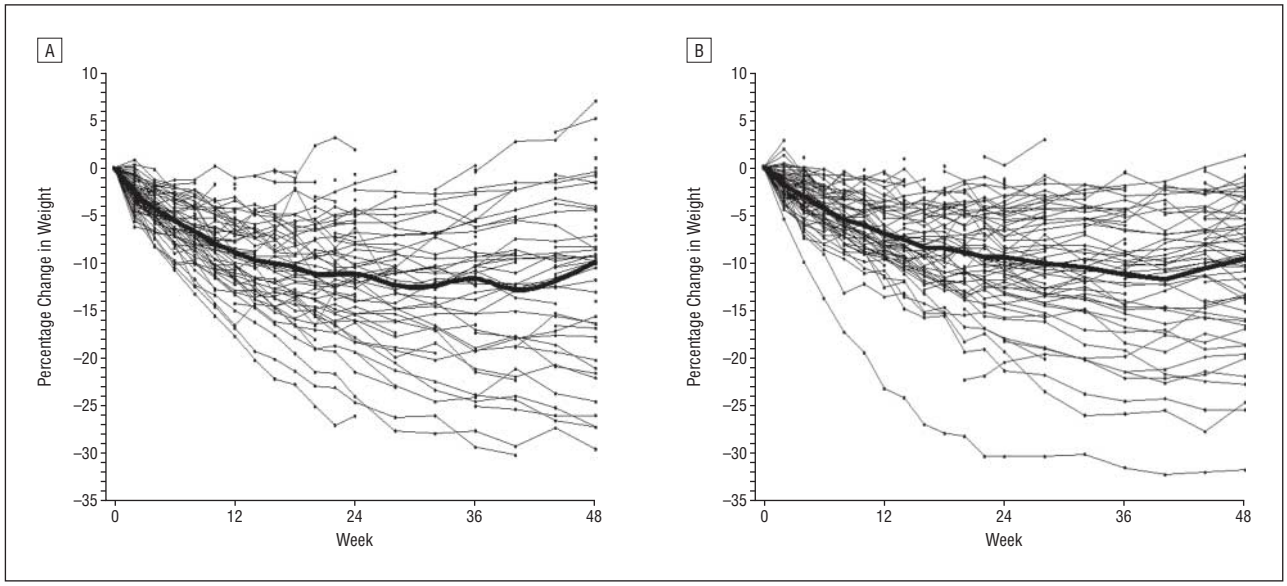

Figure 3. Individual percentage body weight change trajectories by diet group. The bold line represents a smoothed spline of the observed trajectory for the mean percentage body weight change in the low-carbohydrate, ketogenic diet group (A) or the orlistat plus low-fat, reduced-calorie diet group (B).

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creasing fluid and dietary fiber intake and/or adding a fiber supplement or stool softener. Our results highlight the importance of combining intensive dietary counseling and medical management with these interventions to maximize weight loss and minimize adverse effects and attrition.

There are limitations to our study. Our goal was to design the interventions so that they closely mimicked a weight loss program that could be instituted in an outpatient clinic. Therefore, we did not provide food, access to exercise facilities, or compensation to participants. We provided orlistat at no cost to participants, and this could have increased dietary adherence, group session attendance, and/or participant retention compared with the LCKD. In addition, providing orlistat at no cost may lead to different results than what might be seen in patients who must pay for orlistat. Because of feasibility issues, we did not blind participants or staff with the resultant potential for bias. The interventions, however, were comparable in all ways possible and measurements were performed as objectively as possible (eg, digital scale with printout, automatic sphygmomanometer). A small number of enrollees discontinued the study before attending their first intervention visit and learning their intervention assignment. By not including them in analyses, our results may slightly overestimate adherence to the interventions. Medication changes could have contributed to some of the observed beneficial effects, but this is unlikely because in order to prevent adverse effects such as dehydration, hypotension, or hypoglycemia, medication use for hypertension and diabetes was more frequently decreased than increased.

In conclusion, the LCKD and the O + LFD were equally effective for weight loss and several cardiovascular disease risk factors, although the low-carbohydrate diet was more effective for lowering blood pressure. Weight loss was substantially greater in participants who attended group sessions regularly, which may indicate the usefulness of these sessions, signify motivated participants, or both. How to identify these select individuals a priori and how to move more individuals into this category is vital to reversing the obesity epidemic. Efforts should be made to incorporate similarly intensive weight loss programs into medical practice.

Accepted for Publication: October 2, 2009.
Correspondence: William S. Yancy Jr, MD, MHS, Health Services Research and Development Service (Mail Stop 152), Durham VA Medical Center, 508 Fulton St, Durham, NC 27705 (yancy006@mc.duke.edu).
Author Contributions: Dr Yancy, together with those responsible for analysis and interpretation of the data, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Yancy, Westman, McDuffie, Grambow, and Oddone. *Acquisition of data:* Yancy, McDuffie, Bolton, and Chalecki. *Analysis and interpretation of data:* Yancy, McDuffie, Grambow, Jeffreys, Bolton, Chalecki, and Oddone. *Drafting of the manuscript:* Yancy, McDuffie, Grambow, and Bolton. *Critical revision of the manuscript for important intellectual content:* Yancy, Westman, McDuffie, Grambow, Jeffreys, Chalecki, and Oddone. *Statistical analysis:* Grambow and Jeffreys. *Obtained funding:* Yancy and Oddone. *Administrative, technical, and material support:* McDuffie, Bolton, Chalecki, and Oddone. *Study supervision:* Yancy, Westman, Grambow, and Chalecki.
Financial Disclosure: Drs Yancy and Westman have received grants from the Robert C. Atkins Foundation to perform clinical research.
Funding/Support: Funding for this study was provided by the Department of Veterans Affairs (CLIN-5-03F). Dr Yancy is supported by a VA Health Services Research Career Development Award (RCD 02-183-1).
Role of the Sponsor: The sponsor had no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the article for publication.
Additional Contributions: Marjorie Foy, MA, Dawn Penn, PhD, Shoshana Ungerleider, Beatrice Hong, MD, and Alex Cho, MD, MBA, assisted with the interventions and data collection; Maren Olsen provided statistical expertise during study design and data analysis; and a data and safety monitoring board (David Edelman, MD, Morris Weinberger, PhD, and Kevin Anstrom, PhD) reviewed the study protocol.

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Correction

Omission of Affiliation Information. In the Editorial titled "Can the Food and Drug Administration Ensure That Our Pharmaceuticals Are Safely Manufactured?" by Hubbard, published in the October 12 issue of the *Archives* (2009;169[18]:1655-1656), it should have been noted that Mr Hubbard is a former FDA Associate Commissioner and a former member of the group Alliance for a Stronger FDA. This omission was due to editorial oversight, and the journal apologizes for the error.

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