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Effects of Dietary Composition During Weight Loss Maintenance: A Controlled Feeding Study

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Abstract

Context—Many diets can produce weight loss over the short term, but the biological effects of dietary composition during weight loss maintenance have not been well studied.

Objective—To examine three diets differing widely in macronutrient composition and glycemic load following weight loss.

Design and Setting—Controlled feeding study with a three-way cross-over design conducted in major metropolitan area (June 2006 to June 2010), with recruitment by newspaper advertisements and postings.

Participants—Overweight and obese young adults (n=21).

Interventions—After achieving 10 to 15% weight loss on a run-in diet, participants consumed low-fat (LF; 60% of energy from carbohydrate, 20% fat, 20% protein; high glycemic load), low-glycemic index (LGI; 40%-40%-20%; moderate glycemic load), and very-low-carbohydrate (VLC; 10%-60%-30%; low glycemic load) diets in random order, each for 4 weeks.

Main Outcome Measures—Resting energy expenditure (REE, primary outcome), total energy expenditure (TEE), hormones, and metabolic syndrome components.

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Results—The decline in REE (mean [95% CI]) with weight loss was greatest with the LF diet (−205 [−265 to −144] kcal/d), intermediate with the LGI diet (−166 [−227 to −106] kcal/d), and least with the VLC diet (−138 [−198 to −77] kcal/d; P=0.03, P for trend by glycemic load=0.009). The decline in TEE showed a similar pattern (LF: −423 [−606 to −239] kcal/d; LGI:−297 [−479 to −115] kcal/d); VLC: −97 [−281 to +86] kcal/d; P=0.003, P for trend=0.0009). Hormones and metabolic syndrome components also varied during weight maintenance by diet: leptin (P=0.0006); 24-hour urinary cortisol (P=0.005); indexes of peripheral (P=0.02) and hepatic (P=0.03) insulin sensitivity; HDL cholesterol (P<0.0001); non-HDL cholesterol (P=0.0005); triglycerides (P<0.0001); PAI-1 (P for trend=0.04); and CRP (P for trend=0.05).

Conclusions—During isocaloric feeding following weight loss, declines in resting and total energy expenditure varied by dietary glycemic load and were least with the VLC diet, intermediate with the LGI diet, and greatest with the LF diet.

Trial Registration—ClinicalTrials.gov Identifier NCT00315354

Many people can lose weight for a few months, but most have difficulty maintaining clinically significant weight loss over the long term. According to data from the National Health and Nutrition Examination Survey (1999–2006), only 1 in 6 overweight and obese adults report ever having maintained weight loss of at least 10% for 1 year.[1] Among dietary weight loss trials, in which reporting bias can be eliminated, the long-term success rates may be even lower.[2] One explanation for the poor long-term outcome of weight loss diets relates to behavior, in that the motivation to adhere to restrictive regimens typically diminishes with time. An alternative explanation is that weight loss elicits biological adaptations – specifically a decline in energy expenditure (adaptive thermogenesis) and an increase in hunger – that promote weight regain.[3, 4] These two possibilities can be examined within the conceptual framework of thermodynamic theory.

According to the first law of thermodynamics, energy cannot be created nor destroyed. From this perspective, a calorie is a calorie,[5] and no weight reducing diet has inherent superiority to any other. Rather, obesity treatment should emphasize behavioral methods to foster and maintain decreased energy intake. In support of this possibility, several recent clinical trials indicate a direct relationship between dietary adherence and weight loss, regardless of dietary treatment group assignment.[6–8] However, the second law of thermodynamics recognizes that irreversible chemical processes tend to be inefficient and increase entropy. Because metabolic pathways vary in energetic efficiency, dietary composition could affect energy expenditure directly, by virtue of macronutrient differences, or indirectly, through hormonal responses to diet that regulate metabolic pathways.[9, 10]

Diets that aim to attenuate the rise in blood glucose after eating – specifically, low-glycemic index (LGI, emphasizing carbohydrate source)[11] and very-low-carbohydrate (VLC, focusing on carbohydrate restriction)[12] – have been hypothesized to confer such a “metabolic advantage.” Both of these diets have a low glycemic load (the mathematical product of GI and total carbohydrate), which comprises the single best predictor of how typical foods or meals affect postprandial glycemia.[13, 14] Acutely, a low glycemic load diet may elicit hormonal changes that improve the availability of metabolic fuels in the late postprandial period, and thereby decrease hunger and voluntary food intake.[10, 15] Chronically, a low glycemic load diet may attenuate the fall in resting energy expenditure that occurs during weight loss.[16, 17]

In light of debate regarding dietary composition, we conducted a controlled feeding study to evaluate the biological effects of three weight loss maintenance diets, encompassing prevailing ranges of macronutrient composition and glycemic load. The *low-fat (LF) diet*, consistent with conventional recommendations, had a high glycemic load due to high

carbohydrate content; the *LGI diet* had a moderate glycemic load, obtained by emphasizing sources of carbohydrate with a low GI; and the *VLC diet* had a low glycemic load achieved through carbohydrate restriction, consistent with the Atkins Diet.[12]

METHODS

The study comprised run-in and test phases, as shown in Figure 1. During the run-in phase, we obtained baseline data for study outcomes, restricted energy intake of participants to achieve a 12.5% decrease in body weight, and then established energy requirements for stabilizing weight at the reduced level. We assessed body composition by dual-energy x-ray absorptiometry (DXA) before and after weight loss. During the test phase, we used a three-way crossover design to evaluate test diets (LF, LGI, and VLC) in random order, under conditions of weight maintenance. We measured study outcomes during an inpatient hospital admission and under free-living conditions at baseline and the end of each test diet period. Data were collected at Children's Hospital Boston and Brigham and Women's Hospital in Boston, Massachusetts between June 2006 and June 2010. Stable isotope analysis for assessing total energy expenditure (TEE) was conducted at Baylor College of Medicine in Houston, Texas. The institutional review boards at all participating institutions approved the study protocol, and participants provided written informed consent. Methodological detail can be found in the eSupplement.

Participants

Participants included men and women aged 18 to 40 years, with a BMI of 27 kg/m^2 or above. To compensate participants for their effort, we provided $500 at the end of the run-in phase, following at least 10% weight loss, and an additional $2,000 upon completion of the final inpatient hospital admission.

Dietary Interventions

We aimed to design test diets that: 1) would encompass a broad range of macronutrient composition and glycemic load, 2) have been commonly recommended for obesity treatment, and 3) could be physiologically sustainable for long periods of time. To avoid bias, we formulated menus with healthful components inherent to typical prescriptions for respective diets. In view of the mechanistic nature of this study, relying on a feeding protocol, we did not design the diets for long-term practicality.

Table 1 summarizes the composition of the run-in and test diets. The run-in diet was consistent with the Acceptable Macronutrient Distribution Range (AMDR) specified by the Institute of Medicine,[18] with protein intake at the upper end of the range to enhance satiety during weight loss.[19] The LF diet, which had a high glycemic load, was designed to reflect conventional recommendations to reduce dietary fat, emphasize whole grain products, and include a variety of vegetables and fruits.[20] The LGI diet aimed to achieve a moderate glycemic load by replacing some grain products and starchy vegetables with sources of healthful fat and low-GI vegetables, legumes, and fruits. The LF and LGI diets had similar protein and fiber contents. The VLC diet was modeled on the Atkins Diet, and had a low glycemic load due to more severe restriction of carbohydrate. We provided 3 grams of fiber with each meal (Metamucil, Procter & Gamble, Cincinnati, OH) during the VLC diet, as recommended.[12] To ensure micronutrient adequacy and minimize the influence of micronutrient differences among test diets, we gave each participant a daily multi-vitamin and mineral supplement.

Study Outcomes

Assessments conducted during inpatient hospital admissions included resting energy expenditure (REE, the primary outcome) by indirect calorimetry, hormones (leptin, thyroid stimulating hormone [TSH], triiodothyronine [T3], free urinary cortisol), insulin sensitivity (indexes derived from an oral glucose tolerance test[21]), other metabolic syndrome components (high-density lipoprotein [HDL] cholesterol, total cholesterol, triglycerides, plasminogen activator inhibitor-1 activity [PAI-1], high sensitivity C-reactive protein [CRP], blood pressure), and participant ratings of hunger and well-being. Assessments conducted under free-living conditions included TEE by doubly-labeled water (DLW) and physical activity by accelerometry.

Statistical Analyses

This crossover trial was designed to provide over 80% power to detect a difference of 80 kcal/d in REE between diets, as observed in our prior study.[17] The order of diets in the test phase was randomly assigned for each participant. We followed the intention-to-treat principle, ascribing the assigned diet to each measure regardless of compliance.

Analytic procedures were based on methods for crossover trials described by Senn.[22] For each outcome, we fitted a repeated-measures mixed-effects model with measurement period as independent variable (baseline, LF, LGI, VLC), adjusting for sex; age; weight after run-in; sequence of diets; mean weight during measurement period; order of measurement period (baseline always first; test-phase diets second, third, or fourth); within-subject covariance among measurement periods; and, where applicable, correlation among three daily measures within period. Variables with skewed distribution were log-transformed for analysis. One variable with extreme skew (CRP) was rank-transformed for analysis.[23]

We tested the 'overall' null hypothesis of equal mean in the three test-phase periods (H_0: LF=LGI=VLC) using a two-sided criterion of $P<0.05$. Whenever this hypothesis was rejected, we performed pairwise comparisons with a Bonferroni-adjusted criterion of $P<0.05/3$. We also constructed a test for linear trend across diets, proceeding from highest to lowest glycemic load. We applied an outlier-deletion algorithm with optimal properties, equivalent to 'robust' regression.[24] As missing values were uncommon (typically 1 per outcome), we did not perform any imputation, relying on the unbiasedness of mixed-effects regression when data are missing at random.[25] We used SAS software (version 9.2, Cary, NC) for all computations. Data are presented as mean [95% CI] unless otherwise noted.

RESULTS

We enrolled 32 participants, including 17 males and 15 females. Of these, 11 participants did not complete the study, as summarized in Figure 2. Baseline characteristics for the 21 participants who completed the study are presented in Table 2. Non-completers did not differ from completers with respect to any of these characteristics. During the run-in phase, participants lost 14.3 ± 0.9 kg (mean ± SD), corresponding to 13.6% of baseline body weight. Percent body fat by DXA decreased from mean 33.6 [30.0 to 37.2]% at baseline to 29.1 [25.1 to 33.1]% after weight loss. Energy intake during the test diet phase was 2626 ± 686 kcal/d (mean ± SD). Body weight did not differ significantly among the three diets (LF: 91.5 [87.4 to 95.6] kg; LGI: 91.1 [87.0 to 95.2] kg; VLC: 91.2 [87.1 to 95.3] kg; P=0.80).

Energy Expenditure (Table 3, Figure 3)

Energy expenditure during weight loss maintenance differed significantly among the diets. The decline in REE from pre-weight loss levels, measured by indirect calorimetry in the fasting state, was greatest for the LF diet (mean relative to baseline, −205 [−265 to −144]

kcal/d), intermediate with the LGI diet (−166 [−227 to −106] kcal/d), and least for the VLC diet (−138 [−198 to −77] kcal/d; P=0.03, P for trend by glycemic load=0.009). The decline in TEE, as assessed using DLW methodology, also differed significantly by diet (LF: −423 [−606 to −239] kcal/d; LGI:−297 [−479 to −115] kcal/d; VLC: −97 [−281 to +86] kcal/d; P=0.003, P for trend=0.0009). This result was not materially changed when substituting measured RQ for calculated FQ. Neither total physical activity nor time spent in moderate-to-vigorous physical activity differed among the diets.

Hormones and Components of the Metabolic Syndrome (Table 3)

Serum leptin was highest with the LF diet (14.9 [12.1 to 18.4] ng/mL), intermediate with the LGI diet (12.7 [10.3 to 15.6] ng/mL) and lowest with the VLC diet (11.2 [9.1 to 13.8] ng/mL; P=0.0006). Cortisol excretion measured with a 24-hour urine collection (LF: 50 [41 to 60] μg/d; LGI: 60 [49 to 73] μg/d; VLC: 71 [58 to 86] μg/d; P=0.005) and serum TSH (LF: 1.27 [1.01 to 1.60] μIU/mL; LGI: 1.22 [0.97 to 1.54] μIU/mL; VLC: 1.11 [0.88 to 1.40] μIU/mL; P=0.04) also differed in a linear fashion by glycemic load. Serum T3 was lower with the VLC diet compared to the other two diets (LF: 121 [108 to 135] ng/dL; LGI: 123 [110 to 137] ng/dL; VLC: 108 [96 to 120] ng/dL; P=0.006).

Regarding components of the metabolic syndrome, indexes of peripheral (P=0.02) and hepatic (P=0.03) insulin sensitivity were lowest with the LF diet. Serum HDL-cholesterol (LF: 40 [35 to 45] mg/dL; LGI: 45 [41 to 50] mg/dL; VLC: 48 [44 to 53] mg/dL; P<0.0001), triglycerides (LF: 107 [87 to 131] mg/dL; LGI: 87 [71 to 106] mg/dL; VLC: 66 [54 to 81] mg/dL; P<0.0001), and PAI-1 (LF: 1.39 [0.94 to 2.05] ng/mL; LGI: 1.15 [0.78 to 1.71] ng/mL; VLC: 1.01 [0.68 to 1.49] ng/mL; P for trend=0.04) were most favorable with the VLC diet and least favorable with the LF diet. However, CRP (median [95% CI]) tended to be higher with the VLC diet (LF: 0.78 [0.38 to 1.92] mg/L; LGI: 0.76 [0.50 to 2.20] mg/L; VLC: 0.87 [0.57 to 2.69] mg/L; P for trend=0.05). Blood pressure did not differ among the diets.

Hunger and Well-being

Using a 10-cm scale visual analog scale, ratings of subjective hunger (LF: 5.7 [4.6 to 6.8] cm; LGI: 5.4 [4.4 to 6.5] cm; VLC: 5.8 [4.8 to 6.9] cm; P=0.62) and well-being (LF: 6.1 [5.2 to 7.0] cm; LGI: 6.9 [6.0 to 7.8] cm; VLC: 6.3 [5.3 to 7.2] cm; P=0.21) obtained prior to breakfast did not differ significantly among the diets.

COMMENT

The results of this study challenge the notion that a calorie is a calorie from a metabolic perspective. During isocaloric feeding following weight loss, REE was 67 kcal/d greater with the VLC diet compared to the LF diet. TEE differed by about 300 kcal/d between these two diets, an effect corresponding to the amount of energy typically expended in 1 hour of moderate-intensity physical activity.

The physiological basis for the differences in REE and TEE remains subject to speculation. T3 was lowest with the VLC diet, consistent with previously reported effects of carbohydrate restriction;[26] thus, changes in thyroid hormone concentration cannot account for the higher energy expenditure on this diet. The thermic effect of food (TEF, the increase in energy expenditure arising from digestive and metabolic processes) dissipates in the late postprandial period and would not affect REE measured in the fasting state. Because TEF tends to be greater for carbohydrate than fat[27, 28] it would also not explain the lower TEE on the LF diet. Although protein has a high TEF,[19] the content of this macronutrient was the same for the LF and LGI diets and contributed only 10% more to total energy intake with the VLC diet compared to the other two diets. Furthermore, physical activity as assessed by

accelerometry did not change throughout the study. Alternative explanations for the observed differences in REE and TEE may involve intrinsic effects of dietary composition on the availability of metabolic fuels[16, 17] or metabolic efficiency; changes in hormones (other than thyroid) or autonomic tone affecting catabolic or anabolic pathways; and (for TEE) skeletal muscle efficiency, as regulated by leptin.[29–32] Regarding the last possibility, the ratio of energy expenditure to leptin concentration has been proposed as a measure of leptin sensitivity,[33] and this ratio varied as expected in our study (VLC > LGI > LF).

Although the VLC diet produced the greatest improvements in most metabolic syndrome components examined here, we identified two potentially deleterious effects of this diet. Twenty-four hour urinary cortisol excretion, a hormonal measure of stress, was highest with the VLC diet. Consistent with this finding, Stimson et al[34] reported increased whole-body regeneration of cortisol by 11β-HSD1 and reduced inactivation of cortisol by 5α-and 5β-reductases over 4 weeks on a VLC vs. a moderate-carbohydrate diet. Higher cortisol levels may promote adiposity, insulin resistance, and cardiovascular disease, as observed in epidemiological studies.[35–37] In a 6-year prospective population-based study of older adults in Italy, individuals in the highest vs. lowest tertile of 24-hour cortisol excretion, with or without preexisting cardiovascular disease, had a 5-fold increased risk of cardiovascular mortality.[38] CRP also tended to be higher on the VLC diet in our study, consistent with the findings of Rankin and Turpyn.[39] Other studies also have found reductions in measures of chronic inflammation, including CRP with a low-GI diet.[40–42]

A main strength of this study was use of a controlled feeding protocol to establish weight stability following weight loss. Other strengths include a cross-over design to allow for within-individual comparisons, examination of three physiologically sustainable diets spanning a wide range of prevailing macronutrient compositions, control for dietary protein between the LF and LGI diets, state-of-the-art methods to assess TEE under free-living conditions, collection of other study outcomes under direct observation during inpatient hospital admissions to a metabolic ward, and use of observed respiratory quotient (RQ) by indirect calorimetry to verify macronutrient differences among the diets.

Main study limitations are the relatively short duration of the test diets and the difficulty extrapolating findings from a feeding study to a more natural setting, in which individuals consume self-selected diets. The VLC diet, in particular, involved more severe carbohydrate restriction than would be feasible for many individuals over the long term. Therefore, the study may overestimate the magnitude of effects that could be obtained by carbohydrate restriction in the context of a behavioral intervention. In addition, participants in the study were selected for ability to comply with the rigors of a 7-month feeding protocol and may not represent overweight and obese individuals in the general population. While we could not assess compliance during the outpatient phases of the study, good maintenance of weight loss throughout the test phase provides some reassurance on this point.

A methodological issue in cross-over feeding studies involves the possibility of carryover effects between test diets. However, random assignment of participants to a diet sequence and statistical control for order effects would diminish this possibility. In addition, we used compartmental modeling for analysis of TEE, to correct for residual tracer and possible variations in dilution spaces and water kinetics among study periods. Another limitation relating to TEE measurement involves reliance on several assumptions, including the food quotient (FQ) of the test diets. However, sensitivity analysis demonstrated that our results would withstand plausible inaccuracies in estimates of FQ, and qualitatively similar results were obtained when substituting measured RQ for calculated FQ. Finally, we did not assess physiological differences among participants, for example involving insulin secretion,[43, 44] that might influence individual responses to the test diets.

In summary, this study demonstrates that commonly consumed diets can affect metabolism and components of the metabolic syndrome in markedly different ways during weight loss maintenance, independent of energy content. The LF diet produced changes in energy expenditure and serum leptin[45–47] that would predict weight regain. In addition, this conventionally-recommended diet had unfavorable effects on most of the metabolic syndrome components studied here. In contrast, the VLC diet had the most beneficial effects on energy expenditure and several metabolic syndrome components, but this restrictive regimen may increase cortisol excretion and CRP. The LGI diet appears to have qualitatively similar, though smaller, metabolic benefits to the VLC diet, possibly without the deleterious effects on physiological stress and chronic inflammation. These findings suggest that a strategy to reduce glycemic load, rather than dietary fat, may be advantageous for weight loss maintenance and cardiovascular disease prevention. Ultimately, successful weight loss maintenance will require behavioral and environmental interventions to facilitate long-term dietary adherence. But such interventions will be most effective if they promote a dietary pattern that ameliorates the adverse biological changes accompanying weight loss.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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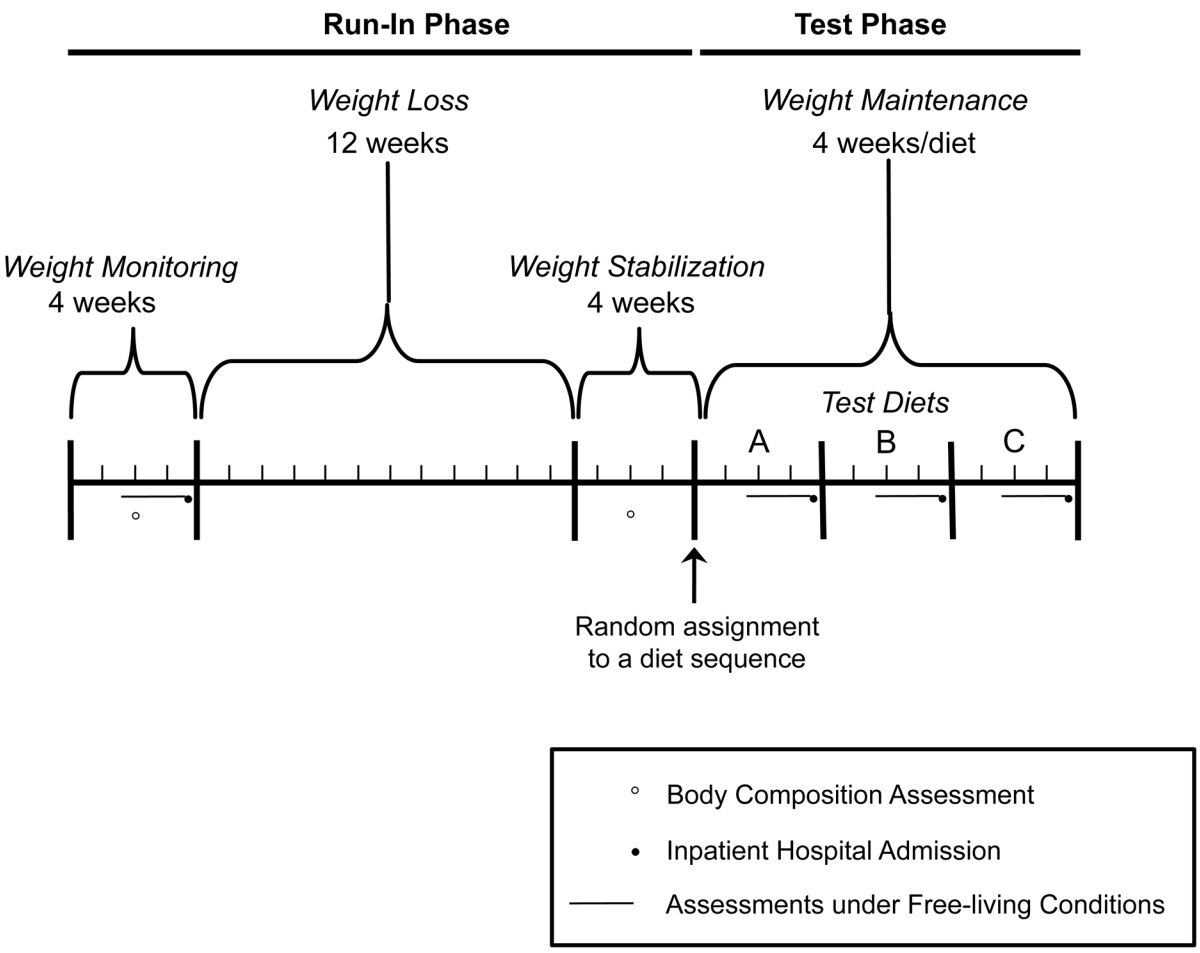

Figure 1. Study Design

Body composition was assessed during the weight monitoring period of the run-in phase and following weight loss. Assessments during inpatient hospital admissions and under free living conditions occurred during the weight monitoring period and at the end of each test diet period. Immediately prior to the 3-day inpatient hospital admission, the assessments under free living conditions were conducted over 14 (total energy expenditure) or 7 (physical activity) days. There were 6 possible diet sequences to which each subject could be randomly assigned, as described in the eSupplement.

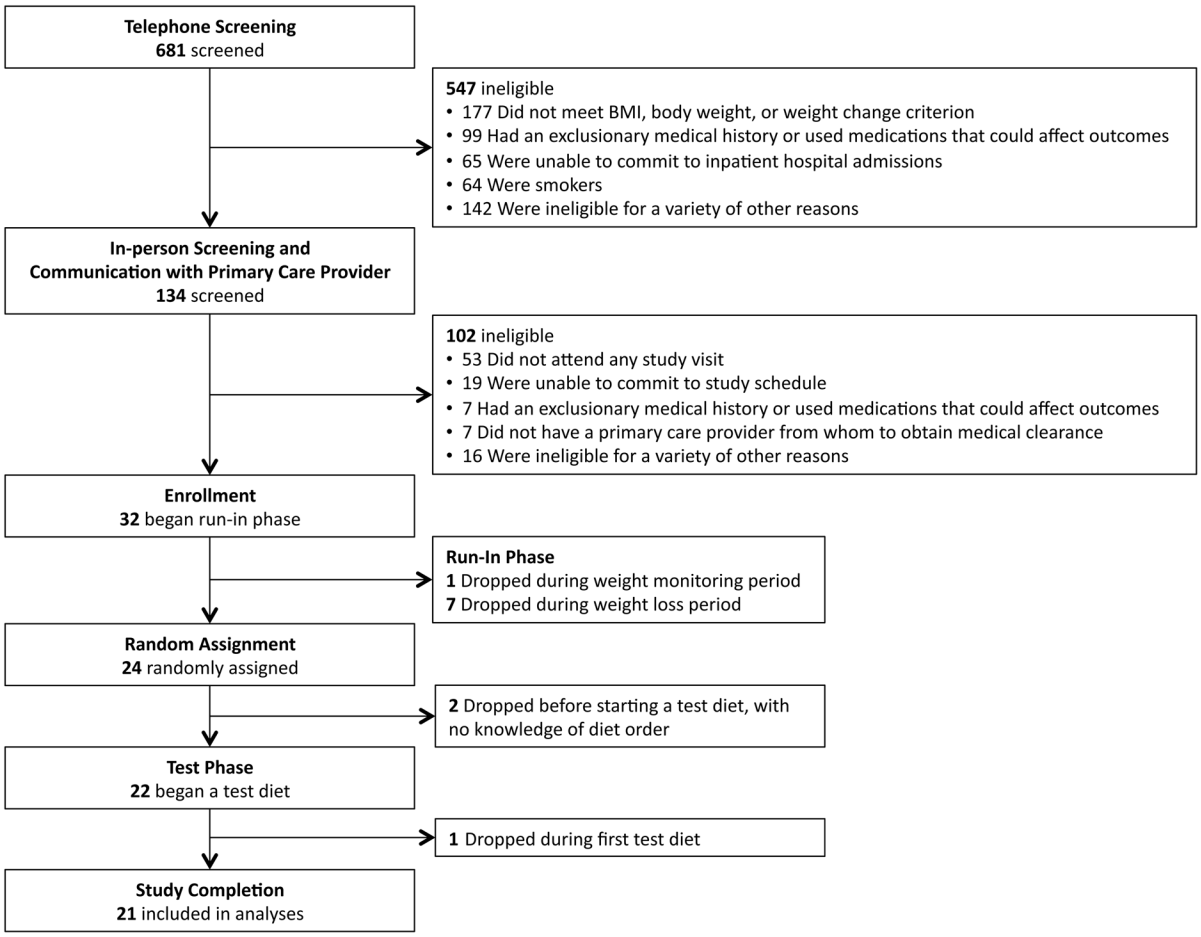

Figure 2. Participant Flow Chart

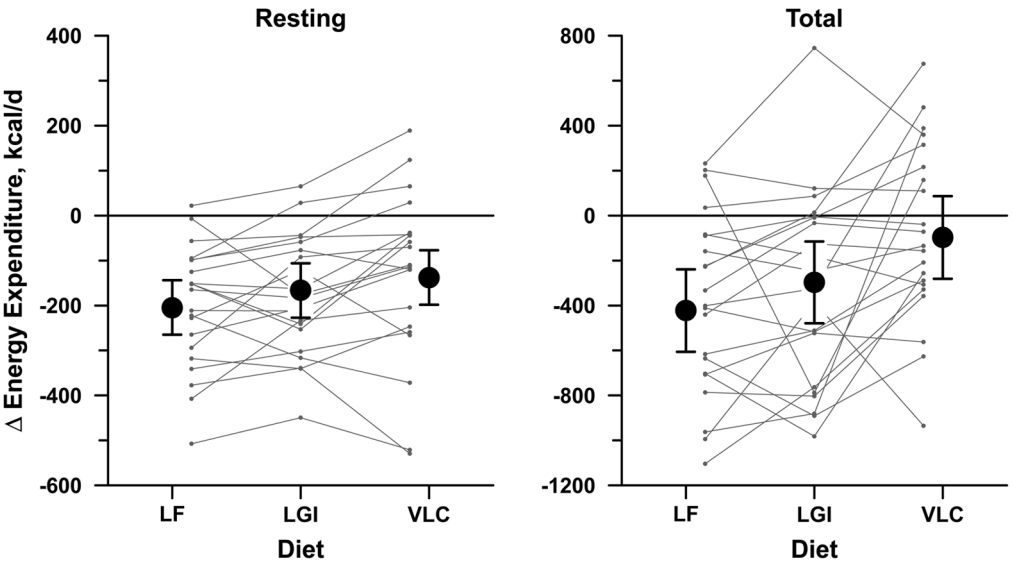

Figure 3. Changes in Energy Expenditure

Resting energy expenditure (left) and total energy expenditure (right) during three test diets for weight-loss maintenance: low-fat (LF), low-glycemic index (LGI), and very low carbohydrate (VLC). Each symbol with error bars indicates mean change from a common baseline period preceding weight loss, with 95% confidence interval, obtained from analysis of cross-over experiment and adjusted for sex, age, order of diets, baseline weight, and mean weight during the 4-wk diet period. Connected lines indicate individual outcomes for the 21 subjects. Both resting and total energy expenditure showed a significant linear trend in mean change from LF to LGI to VLC, $P < 0.01$.

Table 1

Composition of the Run-in and Test Diets (per 2,000 kcal).

Nutrient	Run-in Diet *	Test Diets During Weight Maintenance **		
		LF	LGI	VLC
Targeted Macronutrient Distribution – % energy				
Carbohydrate	45	60	40	10
Fat	30	20	40	60
Protein	25	20	20	30
Dietary Intake – Mean ± SD				
Carbohydrate – g/day	229.5 ± 9.1	310.4 ± 1.7	205.1 ± 3.3	50.1 ± 1.2
Glycemic Index	52.6 ± 5.9	67.7 ± 2.5	32.9 ± 3.2	28.4 ± 9.0
Glycemic Load – g/day	68.9 ± 13.1	185.1 ± 8.6	51.1 ± 6.3	3.9 ± 2.2
Fat – g/day	68.6 ± 2.7	46.5 ± 0.3	90.2 ± 4.3	133.4 ± 2.7
Saturated	15.0 ± 2.0	12.8 ± 0.5	22.4 ± 3.7	47.8 ± 8.4
Monounsaturated	27.1 ± 4.4	15.3 ± 2.2	40.0 ± 5.8	47.7 ± 7.1
Polyunsaturated	16.6 ±3.8	15.7 ± 2.4	22.3 ± 6.3	22.0 ± 7.4
Protein – g/day	126.9 ± 5.6	104.8 ± 0.6	105.5 ± 2.0	151.5 ± 1.1
Fiber – g/day	27.1 ± 3.4	30.3 ± 2.8	32.8 ± 1.8	11.2 ± 2.0
Cholesterol – mg/day	216.4 ± 47.5	140.3 ± 12.2	280.1 ± 173.1	978.1 ± 329.7
Sodium – mg/day	2363 ± 604	2546 ± 379	2647 ± 329	2646 ± 718

Abbreviations: LF, low-fat; LGI, low-glycemic index; VLC, very-low-carbohydrate

* The diet for the weight loss and weight stabilization periods of the run-in phase provided 60% and 100% of estimated energy requirements, respectively.

** The energy content of diets throughout the test phase remained constant, at the level required for weight stabilization at the end of the run-in phase.

Table 2

Baseline Characteristics of the Study Participants (n=21).

Continuous Variable	**Mean ± SD**
Age – yr *	30.3 ± 5.7
Height – m	174.3 ± 11.3
Weight – kg	105.0 ± 20.1
BMI – kg/m^2 **	34.4 ± 4.9
Waist Circumference – cm †	103.5 ± 12.9
Categorical Variable	**N (%)**
Sex – no. (%)	
Male	13 (62)
Female	8 (38)
Race – no. (%) ‡	
White	4 (19)
Black	8 (38)
Asian	4 (19)
Other	5 (24)
Ethnicity – no. (%) ‡	
Hispanic	4 (19)

*Age was calculated from date of birth and date of baseline hospital admission.

**Body mass index was calculated as weight in kg divided by height in m^2.

†Waist was measured at the midpoint between the lower rib and iliac crest.

‡We asked participants to self-report race and ethnicity.

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Table 3

Study Outcomes.

Variable	Mean (95% Confidence Interval)				P *	
	Baseline	Test Diets During Weight Maintenance			Overall (LF=LGI =VLC)	Trend (LF–LGI –VLC)
		LF	LGI	VLC		
Energy Metabolism						
REE – kcal/day	1781 (1737 to 1824)	1576 (1528 to 1624)[a]	1614 (1566 to 1662)[a,b]	1643 (1595 to 1691)[b]	0.03	0.009
REE – kcal/kg FFM/day	27.4 (26.6 to 28.5)	24.4 (23.6 to 25.2)[a]	25.0 (24.2 to 25.8)[a,b]	25.5 (24.7 to 26.4)[b]	0.04	0.01
Resting RQ	0.901 (0.884 to 0.918)	0.905 (0.894 to 0.924)	0.861 (0.845 to 0.875)	0.826 (0.817 to 0.848)	<0.0001	<0.0001
TEE – kcal/day						
Using calculated FQ	3234 (3081 to 3388)	2812 (2599 to 3024)[a]	2937 (2730 to 3145)[a]	3137 (2926 to 3348)	0.003	0.0009
Using measured RQ	3235 (3082 to 3389)	2767 (2564 to 2970)[a]	2926 (2729 to 3124)[a,b]	3013 (2811 to 3216)[b]	0.02	0.007
TEE – kcal/kg FFM/day						
Using calculated FQ	49.8 (46.6 to 52.9)	43.7 (40.3 to 47.1)[a]	45.8 (42.4 to 49.1)[a,b]	47.6 (44.2 to 51.0)[b]	0.008	0.003
Using measured RQ	49.7 (46.5 to 52.8)	42.9 (39.4 to 46.4)[a]	45.2 (41.8 to 48.7)[a,b]	46.6 (43.0 to 50.1)[b]	0.02	0.005
Physical Activity						
Total counts – thousands	299 (259 to 339)	301 (258 to 344)	314 (271 to 358)	287 (245 to 330)	0.20	0.33
MVPA – min/day **	13.5 (10.2 to 18.0)	15.8 (10.9 to 22.8)	14.7 (10.3 to 20.9)	11.7 (8.2 to 16.6)	0.18	0.08
Hormones						
Leptin – ng/mL **	29.2 (24.3 to 35.1)	14.9 (12.1 to 18.4)	12.7 (10.3 to 15.6)[b]	11.2 (9.1 to 13.8)[b]	0.0006	0.0002
Urinary Cortisol – μg/day **	58 (47 to 73)	50 (41 to 60)[a]	60 (49 to 73)[a,b]	71 (58 to 86)[b]	0.005	0.001
Thyroid Function						
TSH – μIU/mL **	1.15 (0.97 to 1.37)	1.27 (1.01 to 1.60)[a]	1.22 (0.97 to 1.54)[a,b]	1.11 (0.88 to 1.40)[b]	0.04	0.01
T3 – ng/dL **	137 (127 to 149)	121 (108 to 135)[a]	123 (110 to 137)[a]	108 (96 to 120)	0.006	0.007
Components of the Metabolic Syndrome						

Variable	Mean (95% Confidence Interval)				P *	
	Baseline	Test Diets During Weight Maintenance			Overall (LF=LGI =VLC)	Trend (LF–LGI –VLC)
		LF	LGI	VLC		
Insulin Sensitivity Indexes †						
Peripheral	0.24 (0.11 to 0.59)	0.53 (0.24 to 0.83)[a]	0.87 (0.56 to 1.18)[a,b]	0.93 (0.63 to 1.22)[b]	0.02	0.008
Hepatic **	0.56 (0.41 to 0.78)	0.93 (0.71 to 1.23)[a]	1.04 (0.78 to 1.37)[a,b]	1.24 (0.94 to 1.63)[b]	0.03	0.01
Cholesterol – mg/dL						
HDL	46 (41 to 50)	40 (35 to 45)	45 41 to 50)	48 (44 to 53)	<0.0001	<0.0001
Non-HDL	131 (121 to 142)	109 (95 to 122)[a]	111 (98 to 124)[a]	127 (114 to 140)	0.0005	0.0003
Triglycerides – mg/dL **	116 (93 to 144)	107 (87 to 131)	87 (71 to 106)	66 (54 to 81)	<0.0001	<0.0001
Blood Pressure – mm Hg						
Systolic	116 (114 to 119)	110 (107 to 113)	109 (107 to 112)	111 (109 to 114)	0.34	0.32
Diastolic	67 (64 to 70)	61 (59 to 64)	62 (59 to 65)	63 (61 to 66)	0.35	0.16
PAI-1 – ng/mL **	3.90 (2.54 to 5.98)	1.39 (0.94 to 2.05)	1.15 (0.78 to 1.71)	1.01 (0.68 to 1.49)	0.11	0.04
CRP – mg/L ‡	1.75 (0.44 to 4.61)	0.78 (0.38 to 1.92)	0.76 (0.50 to 2.20)	0.87 (0.57 to 2.69)	0.13	0.05

Abbreviations: LF, low-fat; LGI, low-glycemic index; VLC, very-low-carbohydrate; RQ, respiratory quotient; REE, resting energy expenditure; TEE, total energy expenditure; FFM, fat-free mass; FQ, food quotient; MVPA, moderate-to vigorous-intensity physical activity; TSH, thyroid stimulating hormone; T3, triiodothyronine; HDL-C, high-density lipoprotein cholesterol; PAI-1, plasminogen activator inhibitor-1; CRP, C-reactive protein.

* From repeated-measures analysis of variance modeling variation among the four measurement periods, adjusted for sex, age, order of diets, baseline weight, and mean weight during each period as well as covariance among periods within subject and covariance among three measurement days within period. P overall tests the hypothesis that mean outcome was equal in the three test diet periods (LF, LGI, VLC). P for trend tests the hypothesis of linear increase in mean outcome from LF to LGI to VLC, assuming equal spacing.

[a,b] A common superscript *a* or *b* indicates that two diet-phase means for a particular outcome were not significantly different as judged by Bonferroni-adjusted comparison (P>0.017) following significant overall test of H_0: LF=LGI=VLC (P<0.05).

** Log-transformed for analysis; adjusted mean and 95% confidence interval retransformed to natural units.

† Parameters calculated from oral glucose tolerance test according to Abdul-Ghani et al.[21] Peripheral insulin sensitivity is defined as rate of decline of glucose between 60 and 120 min, divided by time-weighted mean insulin between baseline and 120 min:

$$-[\mathrm{Glu}_{120}-\mathrm{Glu}_{60}]\div[(5\times\mathrm{Ins}_{\mathrm{Fast}}+10\times\mathrm{Ins}_{10}+10\times\mathrm{Ins}_{20}+20\times\mathrm{Ins}_{30}+30\times\mathrm{Ins}_{60}+30\times\mathrm{Ins}_{90}+15\times\mathrm{Ins}_{120})/120].$$

Hepatic insulin sensitivity is defined as the reciprocal product of area under the glucose curve and area under the insulin curve between baseline and 30 min:

$$[(5 \times \mathrm{Glu}_{\mathrm{Fast}} + 10 \times \mathrm{Glu}_{10} + 10 \times \mathrm{Glu}_{20} + 5 \times \mathrm{Glu}_{30})/60]^{-1} \times [(5 \times \mathrm{Ins}_{\mathrm{Fast}} + 10 \times \mathrm{Ins}_{10} + 10 \times \mathrm{Ins}_{20} + 5 \times \mathrm{Ins}_{30})/60]^{-1}$$

In these formulas, glucose is expressed in mg/dL and insulin in μIU/mL. In the table, hepatic insulin sensitivity is scaled up by 10^3 for readability.

≠Rank-transformed for analysis; entries are median and 95% confidence limits in natural units.