Effects of Dietary Composition on Energy Expenditure During Weight-Loss Maintenance

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Context  Reduced energy expenditure following weight loss is thought to contribute to weight gain. However, the effect of dietary composition on energy expenditure during weight-loss maintenance has not been studied.

Objective  To examine the effects of 3 diets differing widely in macronutrient composition and glycemic load on energy expenditure following weight loss.

Design, Setting, and Participants  A controlled 3-way crossover design involving 21 overweight and obese young adults conducted at Children’s Hospital Boston and Brigham and Women’s Hospital, Boston, Massachusetts, between June 16, 2006, and June 21, 2010, with recruitment by newspaper advertisements and postings.

Intervention  After achieving 10% to 15% weight loss while consuming a run-in diet, participants consumed an isocaloric low-fat diet (60% of energy from carbohydrate, 20% from fat, 20% from protein; high glycemic load), low–glycemic index diet (40% from carbohydrate, 40% from fat, and 20% from protein; moderate glycemic load), and very low–carbohydrate diet (10% from carbohydrate, 60% from fat, and 30% from protein; low glycemic load) in random order, each for 4 weeks.

Main Outcome Measures  Primary outcome was resting energy expenditure (REE), with secondary outcomes of total energy expenditure (TEE), hormone levels, and metabolic syndrome components.

Results  Compared with the pre–weight-loss baseline, the decrease in REE was greatest with the low-fat diet (mean [95% CI], −205 [−265 to −144] kcal/d), intermediate with the low–glycemic index diet (−166 [−227 to −106] kcal/d), and least with the very low–carbohydrate diet (−138 [−198 to −77] kcal/d). The decrease in TEE showed a similar pattern (mean [95% CI], −423 [−606 to −239] kcal/d; −297 [−479 to −115] kcal/d; and −97 [−281 to 86] kcal/d, respectively; overall P = .03; P for trend by glycemic load = .009). The decrease in TEE showed a similar pattern (mean [95% CI], −423 [−606 to −239] kcal/d; −297 [−479 to −115] kcal/d; and −97 [−281 to 86] kcal/d, respectively; overall P = .03; P for trend by glycemic load < .001). Hormone levels and metabolic syndrome components also varied during weight maintenance by diet (leptin, P < .001; 24-hour urinary cortisol, P = .005; indexes of peripheral [P = .02] and hepatic [P = .03] insulin sensitivity; high-density lipoprotein [HDL] cholesterol, P < .001; non-HDL cholesterol, P < .001; triglycerides, P < .001; plasminogen activator inhibitor 1, P for trend = .04; and C-reactive protein, P for trend = .05), but no consistent favorable pattern emerged.

Conclusion  Among overweight and obese young adults compared with pre–weight-loss energy expenditure, isocaloric feeding following 10% to 15% weight loss resulted in decreases in REE and TEE that were greatest with the low-fat diet, intermediate with the low–glycemic index diet, and least with the very low–carbohydrate diet.

Trial Registration  clinicaltrials.gov Identifier: NCT00315354

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DIETARY COMPOSITION, ENERGY EXPENDITURE, AND WEIGHT LOSS

herence and weight loss, regardless of dietary treatment group assignment. However, 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.

Diets that aim to attenuate the increase in blood glucose levels after eating—specifically, low–glycemic index (emphasizing carbohydrate source) and very low–carbohydrate (focusing on carbohydrate restriction) diets—have been hypothesized to confer such a “metabolic advantage.” Acutely, reducing dietary 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. Chronically, a low–glycemic load diet may attenuate the decline in resting energy expenditure (REE) that occurs during weight loss.

We conducted a controlled feeding study to evaluate the effects of 3 weight-loss maintenance diets, which encompass prevailing ranges of macronutrient composition and glycemic load (a low-fat diet, a low–glycemic index diet, and a very low–carbohydrate diet) on energy expenditure, hormones, and components of the metabolic syndrome.

METHODS

The study comprised run-in and test phases (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 established energy requirements for stabilizing weight at the reduced level. We assessed body composition by dual-energy x-ray absorptiometry before and after weight loss. During the test phase, we used a 3-way crossover design to evaluate test diets (low-fat, low–glycemic index, and very low–carbohydrate) 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, Boston, Massachusetts, between June 16, 2006, and June 21, 2010. Stable isotope analysis for assessing total energy expenditure (TEE) was conducted at Baylor College of Medicine, 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 eMethods (http://www.jama.com).

Participants

Participants included men and women aged 18 to 40 years with a body mass index (calculated as weight in kilograms divided by height in meters

**Figure 1. Study Design of the Run-in and Test Phases**

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 before 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 participant could be randomly assigned (as described in the eMethods; http://www.jama.com).

**Table 1. Composition of the Run-in and Test Diets During Weight-Loss Maintenance (per 2000 kcal)**

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>Run-in Diet</th>
<th>Low Fat</th>
<th>Low Glycemic Index</th>
<th>Very Low Carbohydrate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Targeted macronutrient distribution, % energy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbohydrate</td>
<td>68.9 (13.1)</td>
<td>185.1 (8.6)</td>
<td>51.6 (6.3)</td>
<td>3.9 (2.2)</td>
</tr>
<tr>
<td>Fat</td>
<td>25.0 (5.3)</td>
<td>20.0 (5.3)</td>
<td>20.0 (5.3)</td>
<td>30.0 (5.3)</td>
</tr>
<tr>
<td>Saturated</td>
<td>15.0 (2.0)</td>
<td>12.8 (5.3)</td>
<td>22.4 (7.3)</td>
<td>47.8 (8.4)</td>
</tr>
<tr>
<td>Monounsaturated</td>
<td>27.4 (4.4)</td>
<td>15.3 (2.2)</td>
<td>40.5 (5.8)</td>
<td>47.7 (7.1)</td>
</tr>
<tr>
<td>Polyunsaturated</td>
<td>16.6 (3.8)</td>
<td>15.7 (2.4)</td>
<td>22.3 (6.3)</td>
<td>22.0 (7.4)</td>
</tr>
<tr>
<td>Protein, mg/d</td>
<td>126.9 (5.6)</td>
<td>104.8 (6.6)</td>
<td>105.5 (2.0)</td>
<td>151.5 (1.1)</td>
</tr>
<tr>
<td>Fiber, g/d</td>
<td>27.1 (3.4)</td>
<td>30.3 (2.8)</td>
<td>32.8 (1.8)</td>
<td>11.2 (2.0)</td>
</tr>
<tr>
<td>Cholesterol, mg/d</td>
<td>216.4 (47.5)</td>
<td>140.3 (12.2)</td>
<td>280.1 (173.1)</td>
<td>978.1 (329.7)</td>
</tr>
<tr>
<td>Sodium, mg/d</td>
<td>2363 (604)</td>
<td>2546 (379)</td>
<td>2647 (329)</td>
<td>2646 (718)</td>
</tr>
</tbody>
</table>

**a**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.

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

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Dietary Interventions

Our goal was 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. 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 I shows the composition of the run-in and test diets. The run-in diet was consistent with the Acceptable Macronutrient Distribution Range specified by the Institute of Medicine,13 with protein intake at the upper end of the range to enhance satiety during weight loss.16 The low-fat diet, which had a high glycemic load, was designed to reflect conventional dietary recommendations to reduce dietary fat, emphasize whole grain products, and include a variety of vegetables and fruits.17 The low–glycemic index diet aimed to achieve a moderate glycemic load by replacing some grain products and starchey vegetables with sources of healthful fat and low–glycemic index vegetables, legumes, and fruits. The low-fat and low–glycemic index diets had similar protein and fiber contents. The very low-carbohydrate diet was modeled on the Atkins Diet and had a low glycemic load due to more severe restriction of carbohydrate. We provided 3 g of fiber with each meal (Metamucil, Procter & Gamble) during the very low-carbohydrate diet as recommended.18 To ensure micronutrient adequacy and minimize the influence of micronutrient differences among test diets, we gave each participant a daily multivitamin and mineral supplement.

Statistical Analyses

The crossover trial was designed to provide more than 80% power to detect a difference of 80 kcal/d in REE between diets, as observed in our prior study.14 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 adherence.

Analytical procedures were based on methods for crossover trials described by Senn.19 For each outcome, we fitted a repeated-measures mixed-effects model with measurement period as independent variable (baseline, low-fat diet, low–glycemic index diet, very low-carbohydrate diet), adjusting for sex, age, weight after run-in phase, sequence of diets, mean weight during measurement period, order of measurement period (baseline always first; test-phase diets second, third, or fourth), within-participant covariance among measurement periods, and where applicable correlation among 3 daily measures within the measurement period. Variables with skewed distribution were log-transformed for analysis. One variable with extreme skew (CRP) was rank transformed for analysis.20

We tested the overall null hypothesis of equal mean in the 3 test-phase

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Figure 2. Flow Diagram of Participants

681 Participants screened by telephone
547 Excluded
177 Did not meet BMI body weight, or weight change criterion
99 Had exclusionary medical history or used medications that could affect outcomes
65 Unable to commit to inpatient hospital admissions
64 Smokers
142 Ineligible for a variety of other reasons

134 Screened in person and in communication with primary care physician
32 Began run-in phase
24 Randomly assigned
22 Began test diet phase
1 Dropped out during first test diet
2 Dropped out before starting a test diet, with no knowledge of diet order
1 Dropped out during first weight-monitoring period
8 Excluded
7 Dropped out during weight-loss period
53 Did not attend any study visit
19 Unable to commit to study schedule
7 Had an exclusionary medical history or used medications that could affect outcomes
7 Did not have a primary care physician from whom to obtain medical clearance
16 Ineligible for a variety of other reasons

BMI indicates body mass index, calculated as weight in kilograms divided by height in meters squared.
periods (H2: low fat = low glycemic index = very low carbohydrate) using a 2-sided criterion of \( P < .05 \). Whenever this hypothesis was rejected, we performed pairwise comparisons with a Bonferroni-adjusted criterion of \( P < .017 \) (= .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.21 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.22 We used SAS version 9.2 (SAS Institute Inc) for all computations. Data are shown as mean (95% CI) unless otherwise noted.

RESULTS

We enrolled 32 participants, including 17 men and 15 women. Of these, 11 participants did not complete the study (Figure 2). Baseline characteristics for the 21 participants who completed the study are shown in Table 2. Noncompleters did not differ from completers with respect to any of these characteristics. During the run-in phase, participants lost a mean (SD) of 14.3 (0.9) kg, corresponding to 13.6% of baseline body weight. Percentage body fat by dual-energy x-ray absorptiometry decreased from a mean of 33.6% (95% CI, 30.0%-37.2%) at baseline to 29.1% (95% CI, 25.1%-33.1%) after weight loss. Mean (SD) energy intake during the test diet phase was 2626 (868) kcal/d. Body weight did not differ significantly among the 3 diets (mean [95% CI], 91.5 [87.4-95.6] kg for low fat; 91.1 [87.0-95.2] kg for low glycemic index; and 91.2 [87.1-95.3] kg for very low carbohydrate; \( P = .80 \)).

Energy Expenditure

Energy expenditure during weight-loss maintenance differed significantly among the 3 diets (Table 3 and Figure 3). The decrease in TEE from pre–weight-loss levels, measured by indirect calorimetry in the fasting state, was greatest for the low-fat diet (mean relative to baseline [95% CI], –205 [–265 to –144] kcal/d), intermediate with the low–glycemic index diet (–156 [–227 to –106] kcal/d), and least for the very low–carbohydrate diet (mean [95% CI], –115 [–178 to –52] kcal/d; overall \( P = .03 \); \( P \) for trend by glycemic load = .009). The decrease in TEE, assessed using the doubly-labeled water method, also differed significantly by diet (mean [95% CI], –423 [–606 to –239] kcal/d for low fat; –297 [–479 to –115] kcal/d for low glycemic index; and –97 [–281 to 86] kcal/d for very low carbohydrate; overall \( P = .003 \); \( P \) for trend by glycemic load < .001). This result was not materially changed when substituting measured respiratory quotient (RQ) for calculated food quotient (FQ). Neither total physical activity nor time spent in moderate- to vigorous-intensity physical activity differed among the diets.

Hormones and Components of the Metabolic Syndrome

Serum leptin was highest with the low–glycemic index diet (12.7 [10.3-15.6] ng/mL), and lowest with the very low–carbohydrate diet (11.2 [9.1-13.8] ng/mL; overall \( P < .001 \)) (Table 3). For the 3 diets, cortisol excretion measured with a 24-hour urine collection (mean [95% CI], 50 [41-60] µg/d for low fat; 60 [49-73] µg/d for low glycemic index; and 71 [58-86] µg/d for very low carbohydrate; overall \( P = .005 \)) and serum thyrotrpin-stimulating hormone (mean [95% CI], 1.27 [1.01-1.60] µIU/mL for low fat; 1.22 [0.97-1.54] µIU/mL for low glycemic index; and 1.11 [0.88-1.40] µIU/mL for very low carbohydrate; overall \( P = .04 \)) also differed in a linear fashion by glycemic load. Serum triiodothyronine was lower with the very low–carbohydrate diet compared with the other 2 diets (mean [95% CI], 121 [108-135] ng/dL for low-fat diet and 123 [110-137] ng/dL for low–glycemic index diet vs 108 [96-120] ng/dL for very low–carbohydrate diet; overall \( P = .006 \)).

Regarding components of the metabolic syndrome, indexes of peripheral insulin sensitivity were lowest with the low-fat diet. Comparing the low-fat, low–glycemic index, and very low–carbohydrate diets, serum HDL cholesterol (mean [95% CI], 40 [35-45] mg/dL; 45 [41-50] mg/dL; and 48 [44-53] mg/dL, respectively; overall \( P < .001 \)), triglycerides (107 [87-131] mg/dL; 87 [71-106] mg/dL; and 66 [54-81] mg/dL, respectively; overall \( P < .001 \)), and plasminogen activator inhibitor 1 (mean [95% CI], 1.39 [0.94-2.05] mg/mL; 1.15 [0.78-1.71] mg/mL; and 1.01 [0.68-1.49] mg/mL, respectively; \( P \) for trend by glycemic load = .04) were most favorable with the very low–carbohydrate diet and least favorable with the low-fat diet. However, CRP tended to be higher with the very low–carbohydrate diet (median [95% CI], 0.78 [0.38-1.92] mg/L for low-fat diet; 0.76 [0.50-2.20] mg/L for low–glycemic index diet; and 0.87 [0.57-2.69] mg/L for very low–carbohydrate diet; \( P \) for trend by glycemic load = .05).

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**Table 2. Baseline Characteristics of the Study Participants**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Study Participants (N = 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Continuous variables, mean (SD)</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>30.3 (5.7)</td>
</tr>
<tr>
<td>Height, cm</td>
<td>174.3 (11.3)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>105.0 (20.1)</td>
</tr>
<tr>
<td>BMI</td>
<td>34.4 (4.9)</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>103.5 (12.9)</td>
</tr>
<tr>
<td>Categorical variables, No. (%)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>13 (62)</td>
</tr>
<tr>
<td>Female</td>
<td>8 (38)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>4 (19)</td>
</tr>
<tr>
<td>Black</td>
<td>8 (38)</td>
</tr>
<tr>
<td>Asian</td>
<td>4 (19)</td>
</tr>
<tr>
<td>Other</td>
<td>5 (24)</td>
</tr>
</tbody>
</table>

Abbreviation: BMI, body mass index, calculated as weight in kilograms divided by height in meters squared.

\(^{a}\)Age was calculated from date of birth and date of baseline hospital admission. Waist was measured at the midpoint between the lower rib and iliac crest. Participants were asked to self-report race and ethnicity.

\(^{b}\)Other race included no response (n = 2), Caribbean (n = 1), Latino (n = 1), and Persian (n = 1).
Blood pressure did not differ among the 3 diets.

**Hunger and Well-being**

Using a 10-cm visual analog scale, ratings of subjective hunger (mean [95% CI], 5.7 [4.6-6.8] cm; 5.4 [4.4-6.5] cm; and 5.8 [4.8-6.9] cm, respectively; \( P = .62 \)) and well-being (6.1 [5.2-7.0] cm; 6.9 [6.0-7.8] cm; and 6.3 [5.3-7.2] cm, respectively; \( P = .21 \)) obtained before breakfast did not differ significantly among the low-fat, low–glycemic index, and very low-carbohydrate diets.

**COMMENT**

The results of our study challenge the notion that a calorie is a calorie from a

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**Table 3. Study Outcomes**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pre-Weight-Loss Baseline</th>
<th>Low Fat</th>
<th>Low Glycemic Index</th>
<th>Very Low Carbohydrate</th>
<th>Overall</th>
<th>Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>REE, kcal/d</td>
<td>1781 (1737 to 1824)</td>
<td>1576 (1528 to 1624)</td>
<td>1614 (1566 to 1662)</td>
<td>1643 (1595 to 1691)</td>
<td>.03b,c</td>
<td>.009</td>
</tr>
<tr>
<td>REE, kcal/kg FFM/d</td>
<td>27.4 (26.6 to 28.5)</td>
<td>24.4 (23.6 to 25.2)</td>
<td>25.0 (24.2 to 25.8)</td>
<td>25.5 (24.7 to 26.4)</td>
<td>.04c</td>
<td>.01</td>
</tr>
<tr>
<td>Resting RQ</td>
<td>0.901 (0.884 to 0.918)</td>
<td>0.905 (0.894 to 0.924)</td>
<td>0.861 (0.845 to 0.875)</td>
<td>0.826 (0.817 to 0.848)</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>TEE, kcal/kg FFM/d</td>
<td>3234 (3081 to 3388)</td>
<td>2812 (2599 to 3024)</td>
<td>2937 (2730 to 3145)</td>
<td>3137 (2926 to 3348)</td>
<td>.003b</td>
<td>.001</td>
</tr>
<tr>
<td>Physical activity</td>
<td>299 (259 to 339)</td>
<td>301 (258 to 344)</td>
<td>314 (271 to 358)</td>
<td>287 (245 to 330)</td>
<td>.20</td>
<td>.33</td>
</tr>
<tr>
<td>MVPA, min/d</td>
<td>13.5 (10.2 to 18.0)</td>
<td>15.8 (10.9 to 22.8)</td>
<td>14.7 (10.3 to 20.9)</td>
<td>11.7 (8.2 to 16.6)</td>
<td>.18</td>
<td>.08</td>
</tr>
<tr>
<td>Insulin sensitivity index&lt;sup&gt;e&lt;/sup&gt;</td>
<td>Peripheral</td>
<td>0.24 (-0.11 to 0.59)</td>
<td>0.53 (0.24 to 0.83)</td>
<td>0.87 (0.56 to 1.18)</td>
<td>0.93 (0.63 to 1.22)</td>
<td>.02b,c</td>
</tr>
<tr>
<td>Cholesterol, mg/dL</td>
<td>HDL</td>
<td>46 (41 to 50)</td>
<td>40 (45 to 45)</td>
<td>45 (41 to 50)</td>
<td>45 (44 to 53)</td>
<td>.001</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>Non-HDL</td>
<td>131 (121 to 142)</td>
<td>109 (95 to 122)</td>
<td>111 (98 to 124)</td>
<td>127 (114 to 140)</td>
<td>&lt;.001b</td>
</tr>
<tr>
<td>Blood pressure, mm Hg</td>
<td>Systolic</td>
<td>114 (114 to 119)</td>
<td>110 (107 to 113)</td>
<td>109 (107 to 112)</td>
<td>111 (110 to 114)</td>
<td>.34</td>
</tr>
<tr>
<td>PAI-1, mg/mL</td>
<td>3.90 (2.54 to 5.98)</td>
<td>1.39 (0.94 to 2.05)</td>
<td>1.15 (0.78 to 1.71)</td>
<td>1.01 (0.68 to 1.49)</td>
<td>.11</td>
<td>.04</td>
</tr>
<tr>
<td>CRP, mg/L</td>
<td>1.75 (0.44 to 4.61)</td>
<td>0.78 (0.38 to 1.92)</td>
<td>0.76 (0.50 to 2.20)</td>
<td>0.87 (0.57 to 2.69)</td>
<td>13</td>
<td>.05</td>
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**Energy Metabolism**

**Hormone Levels**

**COMMENT**

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<td>0.87 (0.56 to 1.18)</td>
<td>0.93 (0.63 to 1.22)</td>
<td>.02b,c</td>
</tr>
<tr>
<td>Cholesterol, mg/dL</td>
<td>HDL</td>
<td>46 (41 to 50)</td>
<td>40 (45 to 45)</td>
<td>45 (41 to 50)</td>
<td>45 (44 to 53)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>Non-HDL</td>
<td>131 (121 to 142)</td>
<td>109 (95 to 122)</td>
<td>111 (98 to 124)</td>
<td>127 (114 to 140)</td>
<td>&lt;.001b</td>
</tr>
<tr>
<td>Blood pressure, mm Hg</td>
<td>Systolic</td>
<td>114 (114 to 119)</td>
<td>110 (107 to 113)</td>
<td>109 (107 to 112)</td>
<td>111 (110 to 114)</td>
<td>.34</td>
</tr>
<tr>
<td>PAI-1, mg/mL</td>
<td>3.90 (2.54 to 5.98)</td>
<td>1.39 (0.94 to 2.05)</td>
<td>1.15 (0.78 to 1.71)</td>
<td>1.01 (0.68 to 1.49)</td>
<td>.11</td>
<td>.04</td>
</tr>
<tr>
<td>CRP, mg/L</td>
<td>1.75 (0.44 to 4.61)</td>
<td>0.78 (0.38 to 1.92)</td>
<td>0.76 (0.50 to 2.20)</td>
<td>0.87 (0.57 to 2.69)</td>
<td>13</td>
<td>.05</td>
</tr>
</tbody>
</table>

**Energy Metabolism**

**Hormone Levels**

**COMMENT**

The results of our 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 higher with the very low-carbohydrate diet compared with the low-fat diet. TEE differed by approximately 300 kcal/d between these 2 diets, an effect corresponding with 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. Triiodothyronine was lowest with the very low-carbohydrate diet, consistent with previously reported effects of carbohydrate restriction; thus, changes in thyroid hormone concentration cannot account for the higher energy expenditure on this diet. The thermic effect of food (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 the thermic effect of food tends to be greater for carbohydrate than fat, it would also not explain the lower TEE on the low-fat diet. Although protein has a high thermic effect of food, the content of this macronutrient was the same for the low-fat and low–glycemic index diets and contributed only 10% more to total energy intake with the very low-carbohydrate diet compared with the other 2 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 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.

![Figure 3. Changes in Resting and Total Energy Expenditure During 3 Test Diets for Weight-Loss Maintenance](http://jama.jamanetwork.com/)

Each summary box (shown in cyan) with error bars indicates mean (95% CI) change from a common baseline period preceding weight loss obtained from analysis of crossover experiment and adjusted for sex, age, order of diets, baseline weight, and mean weight during the 4-week diet period. Connected lines indicate individual outcomes for each participant. Both resting and total energy expenditure showed a significant linear trend in mean change from low-fat to low–glycemic index to very low-carbohydrate diets (P < .01).

Although the very low-carbohydrate diet produced the greatest improvements in most metabolic syndrome components examined herein, we identified 2 potentially deleterious effects of this diet. Twenty-four hour urinary cortisol excretion, a hormonal measure of stress, was highest with the very low-carbohydrate diet. Consistent with this finding, Stimson et al 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 very low- vs moderate-carbohydrate diet. Higher cortisol levels may promote adiposity, insulin resistance, and cardiovascular disease, as observed in epidemiological studies. 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. C-reactive protein also tended to be higher with the very low-carbohydrate diet in our study, consist-
tent with the findings of Rankin and Turpyn.36 Other studies also have found reductions in measures of chronic inflammation, including CRP with a low–glycemic index diet.37-39

A main strength of our study was use of a controlled feeding protocol to establish weight stability following weight loss. Other strengths included a crossover design to allow for within-individual comparisons, examination of 3 physiologically sustainable diets spanning a wide range of prevailing macronutrient compositions, control for dietary protein between the low-fat and low–glycemic index 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 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. In particular, the very low-carbohydrate diet 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. Although we could not assess participant adherence 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 crossover feeding studies involves the possibility of carry-over 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 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. In addition, we did not assess physiological differences among participants (for example, involving insulin secretion) that might influence individual responses to the test diets.

In conclusion, our 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 low-fat diet produced changes in energy expenditure and serum leptin72-74 that would predict weight regain. In addition, this conventionally recommended diet had unfavorable effects on most of the metabolic syndrome components studied herein. In contrast, the very low-carbohydrate 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 low–glycemic index diet appears to have qualitatively similar, although smaller, metabolic benefits to the very low-carbohydrate 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.

Author Contributions: Dr Ludwig 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: Ebbeling, Swain, Feldman, Wong, Ludwig.

Acquisition of data: Ebbeling, Swain, Wong, Garcia-Lago.

Analysis and interpretation of data: Ebbeling, Feldman, Wong, Hachey, Ludwig.

Drafting of the manuscript: Ebbeling, Swain, Feldman, Wong, Ludwig.

Critical revision of the manuscript for important intellectual content: Ebbeling, Feldman, Wong, Hachey, Garcia-Lago, Ludwig.

Statistical analysis: Feldman.

Obtained funding: Ebbeling, Feldman, Ludwig.

Administrative, technical, or material support: Ebbeling, Swain, Wong, Garcia-Lago, Ludwig.

Study supervision: Ebbeling, Swain, Ludwig.

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