Dietary composition and physiologic adaptations to energy restriction[1–3]

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ABSTRACT

Background: The concept of a body weight set point, determined predominantly by genetic mechanisms, has been proposed to explain the poor long-term results of conventional energy-restricted diets in the treatment of obesity.

Objective: The objective of this study was to examine whether dietary composition affects hormonal and metabolic adaptations to energy restriction.

Design: A randomized, crossover design was used to compare the effects of a high-glycemic-index (high-GI) and a low-glycemic-index (low-GI) energy-restricted diet. The macronutrient composition of the high-GI diet was (as percent of energy) 67% carbohydrate, 15% protein, and 18% fat and that of the low-GI diet was 43% carbohydrate, 27% protein, and 30% fat; the diets had similar total energy, energy density, and fiber contents. The subjects, 10 moderately overweight young men, were studied for 9 d on 2 separate occasions. On days –1 to 0, they consumed self-selected foods ad libitum. On days 1–6, they received an energy-restricted high- or low-GI diet. On days 7–8, the high- or low-GI diets were consumed ad libitum.

Results: Serum leptin decreased to a lesser extent from day 0 to day 6 with the high-GI diet than with the low-GI diet. Resting energy expenditure declined by 10.5% during the high-GI diet but by only 4.6% during the low-GI diet (7.38 ± 0.39 and 7.78 ± 0.36 MJ/d, respectively, on days 5–6; $P = 0.04$). Nitrogen balance tended to be more negative, and energy intake from snacks on days 7–8 was greater, with the high-GI than the low-GI diet.

Conclusion: Diets with identical energy contents can have different effects on leptin concentrations, energy expenditure, voluntary food intake, and nitrogen balance, suggesting that the physiologic adaptations to energy restriction can be modified by dietary composition.   *Am J Clin Nutr* 2000;71:901–7.

INTRODUCTION

Excessive body weight is among the most important medical conditions in the United States, with prevalence rates of $\approx 25\%$ in children (1) and $> 50\%$ in adults (2). Although the health consequences and economic costs of obesity are enormous (3), there is currently no effective dietary treatment for this problem (4).

One explanation for the poor long-term results of conventional diets involves the concept of a body weight set point (5).

The results of numerous studies suggest that body weight is regulated within a specific range. When lean or obese weight-stable subjects were underfed to achieve a 7.5–10% change in body weight, total energy expenditure (TEE) decreased by ≈ 12–15% (5–8). Other physiologic changes induced by energy restriction include increased hunger and down-regulation of neuroendocrine functions (9–12). These adaptations together may act to antagonize further weight loss. Genetic factors are known to influence the range in which body weight is regulated (13). However, the increasing prevalence of obesity among genetically stable populations (14) indicates that environment must also play an important role in the regulation of body weight.

One environmental factor that may affect the apparent body weight set point is the dietary glycemic index (GI). The GI is defined as the area under the glycemic response curve for 2 h after consumption of 50 g carbohydrate from a test food divided by the area under the curve for 2 h after consumption of 50 g carbohydrate from a control substance (either white bread or glucose) (15). Most starchy foods commonly eaten in North America, chiefly refined-grain products and potatoes, have high GIs, exceeding that of table sugar by up to 50% (16). By contrast, vegetables, legumes, and fruit generally have low GIs (16). The presence of fiber, protein, and fat in a meal lowers the GI of co-ingested carbohydrate through effects on gastric emptying, glucose absorption, or insulin secretion (17–20). Numerous studies showed an inverse relation between GI and satiety in lean and obese subjects (21–26). High-GI meals were shown to elicit a sequence of hormonal changes that limit availability of metabolic fuels and cause overeating (26).

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Moreover, diets designed to reduce insulin secretion (eg, low-GI diets) may produce greater weight loss than do standard diets (27). We conducted a study to compare the hormonal and metabolic effects of 2 moderately energy-restricted diets with different GIs to test the hypothesis that dietary composition may modify the physiologic adaptations to energy restriction in overweight persons.

SUBJECTS AND METHODS

Subjects were young men with a mean age of 27.9 y (range: 18–34 y) who were moderately overweight [$\overline{x} \pm$ SEM body mass index (in kg/m^2): 30.6 ± 1.5, range: 28.7–32.2]. The subjects were otherwise in good health as determined by physical examination and laboratory tests (blood count, glycosylated hemoglobin, thyroid function, and liver function). All subjects were weight stable (within 5% of current body weight during the previous 6 mo, by self-report). We recruited subjects by advertising through local newspapers, flyers, and radio. Ten subjects successfully completed the protocol; one subject dropped out of the study and his data were not included in the results. The research was conducted in the General Clinical Research Center (GCRC), Children's Hospital, Boston, with approval from the Institutional Review Board and written, informed consent from the subjects.

The experimental protocol followed a randomized, crossover design involving two 9-d admissions to the GCRC separated by a washout period of 2–6 wk. During the first 2 d of each admission (day −1 and day 0), subjects consumed a self-selected diet ad libitum and baseline measurements were obtained. During the next 6 d (days 1–6), subjects consumed either a high-GI or a low-GI energy-restricted test diet. On days 7 and 8, subjects continued to eat the high- or low-GI diets but were allowed to eat additional foods ad libitum from a private food bar. The study was concluded at dinnertime on day 8, allowing a total of 34 h for ad libitum food consumption. Subjects were required to exercise daily on a treadmill until 10% of TEE had been reached. TEE was determined for each subject by the Harris-Benedict equation multiplied by an activity factor of 1.4 (28). Before and between admissions to the GCRC, subjects were instructed to follow their usual diet and exercise patterns and to avoid caffeine, alcohol, and tobacco products.

Resting energy expenditure (REE) was measured by fasting indirect calorimetry (Vmax 29; SensorMedics Corporation, Yorba Linda, CA) for a total duration of 20–30 min while the subjects rested in bed. Blood samples were obtained after measurement of REE and before breakfast. In addition, blood samples were obtained on day 1 every 30 min by indwelling venous catheter for measurement of plasma glucose and serum insulin responses to breakfast, lunch, and dinner to verify predicted differences in GI (*see* below).

The macronutrient composition of the high-GI diet was (as percent of energy) 67% carbohydrate, 15% protein, and 18% fat and that of the low-GI diet was 43% carbohydrate, 27% protein, and 30% fat. The energy content of the 2 diets on days 1–6 was 50% of predicted TEE. The high-GI diet was predicted to have a GI approximately double that of the low-GI diet (15). For the average subject (aged 27.9 y, measuring 179.3 cm, and weighing 98.4 kg), the energy content of the diet was 6247 kJ, including breakfast, lunch, and dinner (each 1874 kJ) and a bedtime snack (625 kJ). Each meal was calculated to meet the high- or low-GI target macronutrient distribution. The high- and low-GI diets had similar fiber contents (25.6 and 29.0 g/d, respectively) and energy densities (2.95 and 2.96 kJ/g, respectively). Two rotating menus were used for each diet. Representative menus are shown in

Table 1. The foods eaten ad libitum on days 7 and 8 included cold meats (turkey and roast beef), cheese, vegetables (celery and carrots), and condiments (mayonnaise and mustard). To maintain differences in GI, there were also slight differences between the high- and low-GI diets in terms of bread (white and pumpernickel), cereal (granola and bran cereal), fruit (banana and apple), milk (lactase-treated skim milk and 2%-fat milk), fruit drinks (sweetened with glucose and saccharine and sweetened with fructose), and gelatin (sweetened with glucose and saccharine and sweetened with fructose). Palatability of the ad libitum foods was assessed by using a 10-cm visual analogue scale. All meals were prepared under the supervision of the GCRC research dietitians at Brigham and Women's Hospital, Boston. Nutrient compositions were measured by using FOOD PROCESSOR (version 7.0, 1996; ESHA Research, Salem, OR).

Blood samples were analyzed with the following instruments or kits: plasma glucose, Glucose Analyzer (APEC, Inc, Peabody, MA); serum insulin, Abbott IMx (Abbott Laboratories, Abbott Park, IL); and serum leptin, radioimmunoassay kit (Linco Research, Inc, St Charles, MO). Twenty-four–hour urine collections were analyzed for total nitrogen by using the Kjeldahl method (29) and were also analyzed for creatinine to assess adequacy of collection. Nitrogen balance, reported as the average of values obtained on days 3 and 6, was computed by using the following equation (30):

$$N_{balance} = N_{in}(\text{dietary N}) - [N_{urine}(\text{measured}) + N_{stool}(12 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{d}^{-1})] \quad (1)$$

Areas under the glucose and insulin curves were determined by using the trapezoidal rule (FIGP 2.98 software; BIOSOFT, Cambridge, United Kingdom) and the effects of the diets were compared by using a paired Student's *t* test. Changes in serum leptin during the 2 diets were compared by using GLM repeated-measures analysis (SPSS 9.0.0; SPSS Inc, Chicago). The effects of diet on REE at the end of treatment (mean of days 5 and 6) and the change in REE from baseline values were evaluated by using paired *t* tests. Results are reported as means (±SEMs).

RESULTS

Weight loss did not differ significantly between the 2 diets (3.62 ± 1.14 kg with the low-GI diet and 3.23 ± 0.92 kg with the high-GI diet), as shown in **Figure 1**. The mean area under the glycemic response curve was twice as large with the high-GI diet (2.69 ± 0.47 mmol·h/L) as with the low-GI diet (1.30 ± 0.19 mmol·h/L; *P* = 0.001). The mean area under the insulinemic response curve was nearly 50% larger with the high-GI diet (700 ± 98.4 pmol·h/L) than with the low-GI diet (478 ± 82.2 pmol·h/L; *P* = 0.01) (**Figure 2**).

Serum leptin (**Figure 3**) decreased more rapidly and to a greater extent during the low-GI diet than during the high-GI diet (*P* = 0.03). By day 6, leptin had decreased by 50.0 ± 5.5% from baseline with the low-GI diet, compared with 38.3 ± 3.5% with the high-GI diet.

REE (**Figure 4**) decreased from baseline to the end of the period of energy restriction (mean of days 5 and 6) by 4.6% with the low-GI diet (*P* = 0.03) and by 10.5% with the high-GI diet (*P* = 0.005). Mean REE was lower on days 5 and 6 of the high-GI diet (7.38 ± 0.39 MJ/d) than on days 5 and 6 of the low-GI diet (7.78 ± 0.36 MJ/d; *P* = 0.04).

Nitrogen balance was positive with the low-GI diet and negative with the high-GI diet (25.7 ± 14.1 and −9.7 ± 5.5 mg N·kg^{-1}·d^{-1}, respectively; *P* = 0.06).

TABLE 1
One of 2 alternating menus for the high-glycemic-index (high-GI) and low-glycemic-index (low-GI) diets

	High-GI diet	Low-GI diet
Carbohydrate (% of energy)	67	43
Protein (% of energy)	15	27
Fat (% of energy)	18	30
Breakfast	Oatmeal (instant oatmeal, 2%-fat milk with lactase added, half and half cream, dextrose, wheat bran) Banana	Omelet (1 whole egg, 1 egg white, spinach, tomato, low-fat cheddar cheese) Apple, with peel Pumpernickel bread Diet jelly
Lunch	Roast beef sandwich (roast beef, top round; wheat bread; mayonnaise; iceberg lettuce; tomato) Raisins Dried apricots Nonfat frozen yogurt	Turkey breast sandwich (whole-grain 3-kernel bread, skinless turkey breast, mayonnaise, iceberg lettuce) Salad (iceberg lettuce, celery, cucumber, Italian dressing) Stewed tomatoes Apple, with peel Sugar-free gelatin
Dinner	Chicken Jambalaya (long-grain white rice, cooked; chicken breast; butter; sweet green bell pepper; tomato sauce; chopped onion) Butternut squash, cooked Angel food cake Skim milk with lactase added	Salmon fillet String beans Sweet red bell pepper Butter Salad (iceberg lettuce, cucumber, tomato, fat-free French dressing) Pumpernickel bread Grapefruit
Snack	Half turkey sandwich (wheat bread, smoked turkey breast, mayonnaise, fat-free American cheese) Applesauce, sweetened	Canned peaches in light syrup Whole-milk cottage cheese Half and half cream

Ad libitum food intake during days 7 and 8 was 25% greater with the high-GI diet (17.0 ± 2.2 MJ) than with the low-GI diet (13.5 ± 1.9 MJ; $P = 0.009$). Subject ratings of ad libitum food palatability did not differ significantly between diets (7.2 ± 0.8 with the high-GI diet and 6.3 ± 0.9 with the low-GI diet).

DISCUSSION

Conventional energy-restricted diets have very poor long-term outcomes with regard to weight loss (4), possibly because these diets elicit changes in hunger and metabolism that promote weight regain (5). The results of the present study suggest that
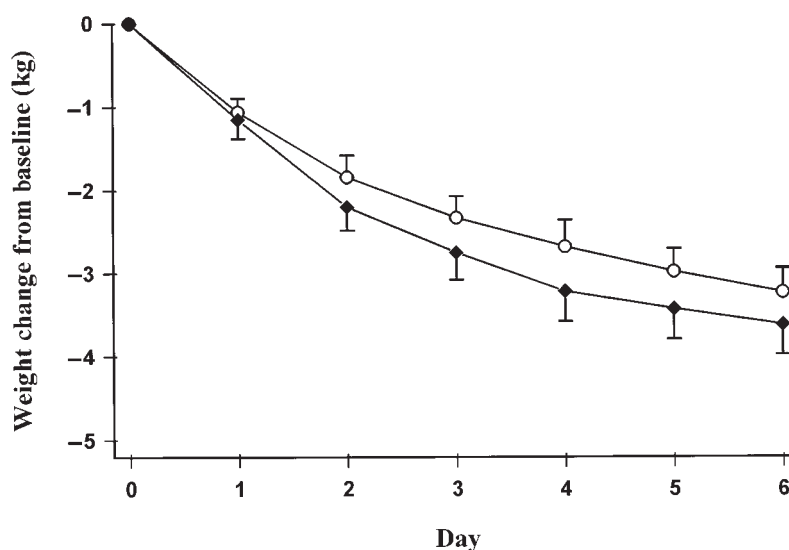

FIGURE 1. Mean (±SEM) weight loss from baseline during 6 d of energy restriction. Baseline weight for the high-glycemic-index diet (○) was 98.5 ± 2.7 kg and for the low-glycemic-index diet (◆) was 99.2 ± 2.9 kg (NS; $n = 10$).
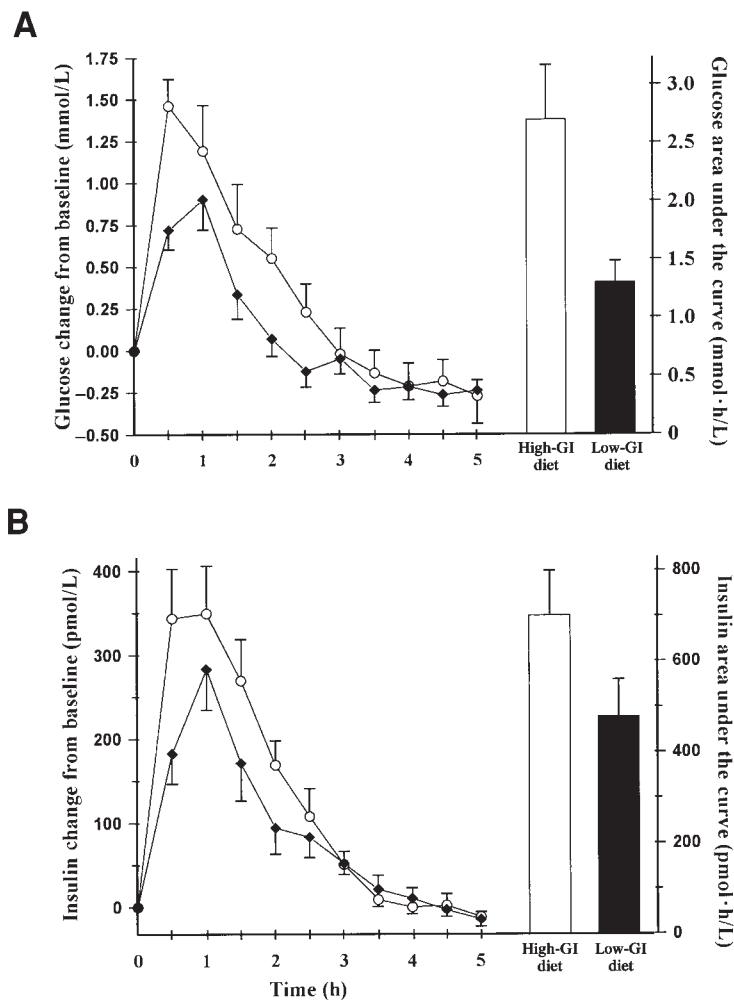
FIGURE 2. Glycemic (A) and insulinemic (B) responses measured at 0.5-h intervals. Curves are mean (±SEM) values after breakfast, lunch, and dinner on day 1. Columns represent area under the concentration-versus-time curve calculated by using the trapezoidal rule. Actual baseline blood glucose for the high-glycemic-index (high-GI) diet (○) was 5.5 ± 0.2 mmol/L and for the low-glycemic-index (low-GI) diet (◆) was 5.3 ± 0.2 mmol/L (NS; $n = 10$).

dietary composition can modify the physiologic adaptations to energy restriction, which might have relevance to the design of novel dietary treatments for obesity.

Weight loss did not differ significantly between the high-GI diet and the low-GI diet, as would be expected from the identical energy contents of the diets. However, serum leptin decreased to a greater extent with the low-GI diet. This difference may be explained by the lower insulin concentrations associated with this diet, because insulin is a leptin secretagogue (31, 32), or by decreased adipocyte glucose metabolism (33). This observation is consistent with that of Jenkins et al (34), who showed a positive association between carbohydrate consumption and leptin concentration during energy restriction. Interestingly, the lower leptin concentration with the low-GI diet occurred without evidence of increased hunger (ad libitum food intake was actually lower with this diet), suggesting a functional improvement in the leptin resistance associated with obesity (35, 36). Further investigation into the significance of this phenomenon is warranted.

REE decreased to a lesser extent with the low-GI than with the high-GI diet. Consistent with this finding, Whitehead et al (37) showed that sleeping metabolic rate fell less rapidly with a high-protein than a low-protein energy-restricted diet. In the present study, the low-GI diet did contain more protein than did the high-GI diet. We note, however, that the present results were not caused by the increased thermic effect of protein relative to that of the other macronutrients because metabolic rate was measured 10 h after the last meal. The preservation of REE during energy restriction with the low-GI diet, together with the differences in voluntary food intake and satiety shown by us and others (21–26), suggests that low-GI diets may be better tolerated than high-GI diets.

Although both diets were protein sufficient (the average subject received 56 or 100 g protein/d), analysis of nitrogen balance suggested that fat tissue was oxidized to a lesser degree, and muscle to a greater degree, with the high-GI than the low-GI diet. This finding is consistent with that of Pasquali et al (38), who observed a more negative nitrogen balance with an isoenergetic, very-low-energy diet with a high carbohydrate-to-protein ratio than with a diet with a low carbohydrate-to-protein ratio. The possible adverse effects of the high-GI diet on body composition can be explained
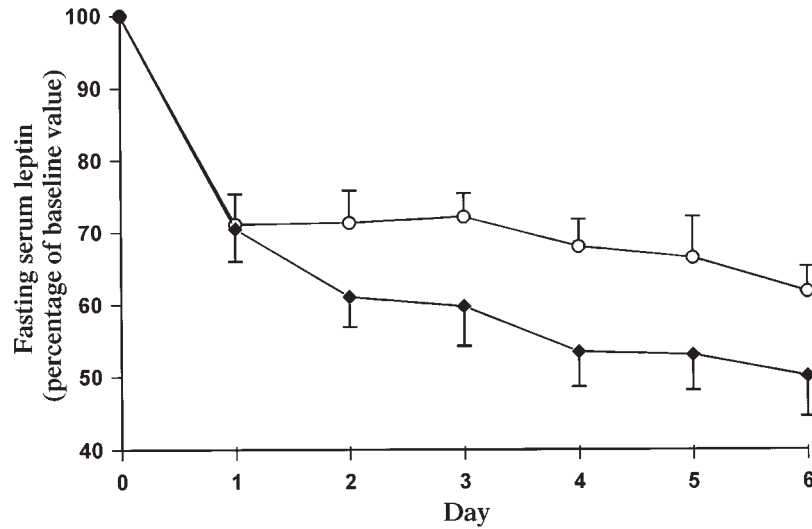
FIGURE 3. Mean (±SEM) daily fasting serum leptin as a percentage of baseline values. Baseline serum leptin for the high-glycemic-index diet (○) was 14.9 ± 1.7 µg/L and for the low-glycemic-index diet was 13.4 ± 1.2 µg/L (NS; $n = 10$).

by hormonal responses to meals with different GIs (26). Consumption of a high-GI meal results in relatively high insulin concentrations and low glucagon concentrations. This hormonal response tends to promote uptake of glucose and triacylglycerol in the liver and adipose tissue, limit glycogenolysis and lipolysis, and, therefore, suppress concentrations of glucose and fatty acids in the postabsorptive period. The low circulating concentrations of these major metabolic fuels elicit marked increases in the counterregulatory hormones, some of which have proteolytic actions (39). Thus, decreased mobilization of the primary metabolic fuels with high-GI, energy-restricted diets may induce a series of physiologic events that favor catabolism of lean body tissue.

Two methodologic issues should be discussed. First, although the formula used for calculating nitrogen balance was validated across a variety of dietary conditions (30), the possibility remains that greater delivery of nutrients to the lower digestive tract with the low-GI than with the high-GI diet led to increased nitrogen trapping by colonic bacteria. If this were the case, we may have overestimated nitrogen balance with the low-GI diet. This possibility should be addressed in future studies. Second, previous studies by us and others sought to examine the hormonal and metabolic effects of dietary GI while controlling for other potentially confounding variables, such as macronutrient composition (21–26). However, GI is a complex dietary component that is affected by
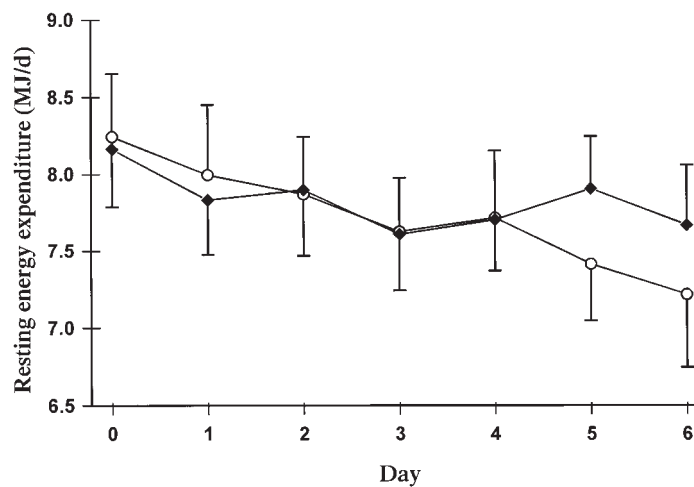

FIGURE 4. Mean (±SEM) daily resting energy expenditure with the high- (○) and low- (◆) glycemic-index diets ($n = 10$).

other factors, including protein and fat (15, 16, 20). Thus, one cannot simultaneously obtain maximum differences in GI and control for confounding variables. We chose to maximize differences between treatment groups because of the relative inaccuracy and imprecision of measuring metabolic rate compared with measuring hormone concentration. We believed that it would be difficult to show significant differences in resting metabolic rate in a relatively brief study using a small number of subjects without varying macronutrients. Therefore, our results cannot be definitively attributed solely to GI. Nevertheless, these results do suggest that the adaptations to energy restriction can be modified by dietary composition. Moreover, the findings are consistent with the possibility that the increased availability of metabolic fuels with a low-GI diet (26) improves tolerance to energy restriction.

In summary, this study showed beneficial effects of a low-GI, medium-fat diet compared with a high-GI, low-fat diet that accorded with current nutritional recommendations. This finding suggests that the hormonal and metabolic responses to energy restriction—involving leptin concentrations, energy expenditure, voluntary food intake, and nitrogen balance—can be affected by dietary composition. Additional research is needed to confirm these results in other populations and over a longer period, to determine which specific dietary factors mediate these physiologic events, and to examine the long-term effects of GI on the regulation of body weight.

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