High Glycemic Index Foods, Overeating, and Obesity

David S. Ludwig, MD, PhD*; Joseph A. Majzoub, MD*; Ahmad Al-Zahrani, MD*; Gerard E. Dallal, PhD‡; Isaac Blanco‡; and Susan B. Roberts, PhD‡

ABSTRACT. Objective. The prevalence of obesity has increased dramatically in recent years. However, the role of dietary composition in body weight regulation remains unclear. The purpose of this work was to investigate the acute effects of dietary glycemic index (GI) on energy metabolism and voluntary food intake in obese subjects.

Methods. Twelve obese teenage boys were evaluated on three separate occasions using a crossover study protocol. During each evaluation, subjects consumed identical test meals at breakfast and lunch that had a low, medium, or high GI. The high- and medium-GI meals were designed to have similar macronutrient composition, fiber content, and palatability, and all meals for each subject had equal energy content. After breakfast, plasma and serum concentrations of metabolic fuels and hormones were measured. Ad libitum food intake was determined in the 5-hour period after lunch.

Results. Voluntary energy intake after the high-GI meal (5.8 megajoule [mJ]) was 53% greater than after the medium-GI meal (3.8 mJ), and 81% greater than after the low-GI meal (3.2 mJ). In addition, compared with the low-GI meal, the high-GI meal resulted in higher serum insulin levels, lower plasma glucagon levels, lower postabsorptive plasma glucose and serum fatty acids levels, and elevation in plasma epinephrine. The area under the glycemic response curve for each test meal accounted for 53% of the variance in food intake within subjects.

Conclusions. The rapid absorption of glucose after consumption of high-GI meals induces a sequence of hormonal and metabolic changes that promote excessive food intake in obese subjects. Additional studies are needed to examine the relationship between dietary GI and long-term body weight regulation. Pediatrics 1999; 103(3). URL: http://www.pediatrics.org/cgi/content/full/103/3/e26; glycemic index, obesity, dietary carbohydrate, diets, insulin.

ABBREVIATIONS. GI, glycemic index; GCRC, General Clinical Research Center; RMR, resting metabolic rate; mJ, megajoule.

The prevalence of obesity in the United States is now higher than at any time in recorded history.1 Approximately 20% of children and >33% of adults are considered to be significantly overweight.12 However, there remains considerable controversy over the roles of dietary and other modifiable factors in the treatment of this common disorder.

Excessive fat consumption is widely believed to be a major dietary cause of obesity.2–5 For this reason, the US Department of Health and Human Services,6 American Heart Association,7 and American Diabetes Association8 currently advocate consumption of a low-fat diet in the prevention and treatment of obesity. Recently, however, the relationship between dietary fat and obesity has been questioned on several grounds9–11 including that both cross-sectional and longitudinal analyses have failed to show a consistent association between dietary fat and body fat,10,12,13 and that weight loss on low-fat diets is usually modest and transient.9,14 In addition, and perhaps of particular significance, mean fat intake in the United States reportedly has decreased over the past 3 decades, from 42% to ~34% of dietary energy,11,12,15,16 whereas the rate of obesity has continued to rise.

Another dietary factor that may influence body weight is the glycemic index (GI). GI is a property of carbohydrate-containing food that describes the rise of blood glucose occurring after a meal.17 Foods that are rapidly digested and absorbed or transformed metabolically into glucose have a high GI.18–22 The GI of a meal is determined primarily by the amount of carbohydrate consumed and by other dietary factors affecting food digestibility, gastrointestinal motility, or insulin secretion (including carbohydrate type, food structure, fiber, protein, and fat).17–24 Most starchy foods commonly eaten in North America, chiefly refined grain products and potatoes, have a high GI, exceeding that of even table sugar by up to 50%.22 By contrast, vegetables, legumes, and fruits generally have a low GI.22

A potential adverse consequence of the decrease observed in mean fat intake in recent years is a concomitant increase in dietary GI. A reduction of dietary fat tends to cause a compensatory increase in sugar and starch intake.25–27 Indeed, a rise in total carbohydrate consumption since the 1970s has been documented.12,25,27 Furthermore, because fat slows gastric emptying,21 carbohydrate absorption from low-fat meals may be accelerated. In view of these observations, it seems likely that the GI of the Amer-
ican diet has risen in recent years. Previously, an inverse relationship between GI and satiety has been shown in several,28–32 but not all,33 single-meal studies. Although these reports suggest a potential influence of GI on short-term energy intake, the practical relevance of GI to energy regulation and obesity remains unclear.

The purpose of this investigation was to test the hypothesis that consumption of high-GI foods induces a sequence of hormonal changes that lead to decreased availability of metabolic fuels, excessive hunger, and overeating in obese subjects.

METHODS

Subjects

The subjects were pubertal boys (mean age, 15.7 ± 1.4 [standard deviation] years) >120% of ideal body weight (mean, 190 ± 30.8%) by comparison with national standards.34 Mean values for weight and height were 106.6 ± 22.3 kg and 1.68 ± 0.09 m, respectively. All subjects were healthy, as assessed by physical examination and laboratory analysis (complete blood count, electrolytes, liver function tests, glycosylated hemoglobin, thyroid stimulating hormone and urinalysis). Twelve subjects successfully completed the protocol; one additional individual agreed to participate but was removed from the study because of recurrent difficulties establishing and maintaining intravenous access. The research was conducted at the General Clinical Research Center (GCRC), Children’s Hospital, Boston, MA, with approval from the institutional review board and written informed consent from the subjects and parents of minors.

Protocol

A crossover study was conducted, consisting of three separate 24-hour admissions separated by a 1- to 2-week wash-out period. A different test meal (low-, medium-, or high- GI) was given at each admission; otherwise, the admissions were conducted in an identical manner. Subjects were randomly assigned to receive low-GI or high-GI test meals during the first two admissions, followed by medium-GI test meals during the third admission.

Subjects were admitted to the GCRC at 6:00 pm, consumed a low-GI dinner and bedtime snack, and then went to bed at 10:00 pm. The next morning, subjects were awakened at 6:45 am, and an intravenous line placed, baseline blood samples obtained, and a 11-cm analog hunger scale rating (anchored with statements “not at all hungry” and “extremely hungry”) completed. A low-, medium-, or high-GI test meal was given for breakfast and consumed completely in 20 minutes. Blood samples were obtained and hunger scale ratings performed every 30 minutes for 5 hours from the start of breakfast. After 5 hours, the intravenous line was removed. A second test meal (identical to the breakfast on that day) then was given for lunch and consumed completely in 20 minutes. After lunch, subjects were allowed out of bed to perform quiet activities and were encouraged to ask for an ad libitum meal platter if and when they were “very hungry” at any time during the subsequent 5-hour period. They were told to eat as much or as little as they wanted from this platter to feel satisfied and to request additional fresh platters if they became “very hungry” again later in the afternoon. Subjects were discharged 5 hours after lunch and instructed to follow their usual diet until the next admission.

Diet

All meals were prepared under supervision of the research dietitians at Brigham and Women’s Hospital, Boston, MA. Nutrient compositions were determined using the software Food Processor Plus, Version 6.0, 1994 (ESHA Research, Salem, OR).

The standard low-GI dinner given on the evening of each admission consisted of chicken, broccoli, salad with dressing, fruit and cookies (40% energy from carbohydrate, 30% from protein, 30% from fat; total energy content 18.5% of predicted resting metabolic rate (RMR) calculated from body weight at predmission physical examination35). The bedtime snack consisted of fruit and cheese (energy content 5% of predicted RMR35) and had the same macronutrient breakdown as the dinner.

Three different test meals with low, medium, and high GI were studied (Table 1). The high- and medium-GI meals contained identical foods and nutrients with the exception of the type of oatmeal (“instant oatmeal” was used for the high-GI meal and “steel cut” oats for the medium-GI meal, both cooked for 15 minutes) and the type of sweetener (glucose plus artificial sweetener for the high-GI meal and fructose for the medium-GI meal). Also, milk used in the high-GI meal was treated with 2 drops of lactase (Dairy Ease Lactaid Drops, Rite Aid Corp, Harrisburg, PA) to increase the GI of the milk sugar. The instant oatmeal was produced from whole-grain, dehulled oats according to standard methods35 (Vargarda Kvarn AB, Vargarda, Sweden). Steel-cut oats, a preparatory method that preserves the structure of the oat kernel, thereby lowering GI, also was produced from whole-grain, de-hulled oats (Heartland Mill Inc, Scott City, KS). The instant oats had a slightly lower water content than the steel-cut oats, as determined by bomb calorimetry (1.024 vs 4.971 kilojoule/g, respectively), and the amount of oats used for the two meals were adjusted accordingly to ensure equivalent energy. In addition to the two oatmeal test meals, a third, low-GI test meal was used. This meal (a vegetable omelet and fruit) contained more protein and fat and less carbohydrate than did the high-GI meal and was designed to increase the range of GI in the study beyond that which could be achieved by manipulating only food structure and carbohydrate type (as with the high- and medium-GI meals). The size of the test meals was determined individually for each subject as 18.5% of predicted RMR.33 Although values for predicted RMR were not expected to be accurate for each subject, they provided a means to standardize meal size among individuals of different body weight.

The ad libitum meal food platters used for measurement of voluntary energy intake after the lunch test meals contained ~22.6 mJ each and included bread, bagels, cold cuts, cream cheese, regular cheese, spreads, cookies, fruit, and water. Two platters containing preweighed items were prepared for each subject. The first platter was given to the subject after the first request for food during the afternoon of the test day, and the second platter was given if a second request was made. No subject requested food more than twice during any of the afternoon measurements. Leftovers were not taken into account. The purpose of giving two separate platters was to estimate ad libitum energy intake under conditions simulating ad libitum eating and to ensure that all subjects were truly hungry.

TABLE 1. Meal Composition Based on Sample Test Meals Containing 1.65 mJ

<table>
<thead>
<tr>
<th></th>
<th>Low GI</th>
<th>Medium GI</th>
<th>High GI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foods</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whole egg</td>
<td>55 g</td>
<td>63.9 g</td>
<td>60.9 g</td>
</tr>
<tr>
<td>Egg white</td>
<td>45 g</td>
<td>160 g 2% Milk</td>
<td>160 g 2% Milk*</td>
</tr>
<tr>
<td>Low-fat cheese</td>
<td>40 g</td>
<td>15 g Half &amp; Half cream</td>
<td>15 g Half &amp; Half cream</td>
</tr>
<tr>
<td>Spinach</td>
<td>200 g</td>
<td>16.0 g Fructose</td>
<td>19.0 g Dextrose</td>
</tr>
<tr>
<td>Tomato</td>
<td>30 g</td>
<td>0.0 g Saccharine</td>
<td>0.2 g Saccharine</td>
</tr>
<tr>
<td>Grapefruit</td>
<td>185 g</td>
<td>397 g Water</td>
<td>397 g Water</td>
</tr>
<tr>
<td>Apple slices</td>
<td>115 g</td>
<td>64</td>
<td>64</td>
</tr>
<tr>
<td>% Energy from carbohydrate</td>
<td>40</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>% Energy from protein</td>
<td>30</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Energy density (kJ/g)</td>
<td>2.46</td>
<td>2.52</td>
<td>2.52</td>
</tr>
</tbody>
</table>

Figures represent precooked weights. * Weight of oats used were adjusted to reflect differences in hydration, as described in “Methods.” ** Treated with lactase to increase the GI of milk sugar.
over foods on each platter were weighed to determine the amount of energy consumed at each meal request.

**Blood Analysis**

Blood samples were analyzed with the following instruments or kits: plasma glucose, APEC Glucose Analyzer (APEC, Inc, Peabody, MA); serum insulin, Abbott IMx (Abbott Laboratories, Abbott Park, IL); serum fatty acids, Hitachi 917 Analyzer (Wako Chemicals USA, Inc, Richmond, VA); and serum growth hormone, IRMA kit (Quest Diagnostics Incorporated, San Juan Capistrano, CA). Plasma glucagon and epinephrine were determined at Quest Diagnostics Incorporated by modifications of standard methods.

**Data Analysis**

Responses were evaluated by using repeated-measures analysis of variance with meal alone or meal and time as within-subjects factors, as appropriate. Tukey's honestly significant differences was used to adjust for multiple meal comparisons except in the cases of fatty acids, epinephrine, and growth hormone, for which only the high- and low-GI meals were compared. Within-subject correlation coefficients between afternoon energy intake and hormonal and metabolic parameters were calculated by using the method of Bland and Altman. The effect of the order in which meals were taken was investigated by fitting a set of models that included a term denoting the order in which a meal was eaten. No order effect reached statistical significance, and the order effects were not included in subsequent analyses. Areas under the glycemic and insulin response curves were calculated using the trapezoidal rule for values above baseline. All calculations were performed by using SYSTAT for Windows, version 7 (SPSS, Inc, Chicago, IL).

**RESULTS**

Hormonal and metabolic responses to the three test meals given at breakfasts are shown in Fig 1. The mean area under the glycemic response curve for the high-GI meal (284 mmoles-min/L) was twice that of the medium-GI meal (141 mmoles-min/L; \( P < .001 \)) and nearly fourfold that of the low-GI meal (76.6 mmoles-min/L; \( P < .001 \)). The mean plasma glucose concentration nadir was lower after the high-GI meal (1.1 mmole/L below baseline) than after the medium-GI meal (0.64 mmole/L below baseline; \( P = .02 \)) or the low-GI meal (0.64 mmole/L below baseline; \( P = .02 \)). Insulin level, as assessed by area under the insulin response curve, was greater after the high-GI meal (135 nmoles-min/L) than after the medium-GI meal (88.5 nmoles-min/L; \( P < .01 \)) or low-GI meal (62.7 nmoles-min/L; \( P < .01 \)). Plasma glucagon level rose after the low-GI meal but was suppressed after the medium- and high-GI meals, as measured by area under the curve from 0.5 hour to 4.5 hours (low GI vs medium or high GI; \( P < .01 \)). Serum fatty acids, averaged over the period from 2.5 to 4.5 hours, were suppressed to a greater degree after the high-GI meal compared with the low-GI meal (\( P < .05 \)). Higher concentrations of the counterregulatory hormones epinephrine (\( P < .05 \)) and growth hormone (\( P = .07 \))
occurred at 4.5 and 5.0 hours after the high-GI meal relative to the low-GI meal.

Furthermore, morning ratings of hunger were greater at all time points after the high-GI breakfast compared with the low-GI breakfast, with the medium-GI breakfast yielding intermediate scores (Fig 2).

After completion of the morning study measurements, a second test meal was given at lunch (identical in composition and amount to the breakfast meal for that day), and the amount and timing of voluntary food requests were recorded for a subsequent period of 5 hours. Subjects consumed significantly more energy after the high-GI meal (5.8 MJ) than after the medium-GI meal (3.8 MJ; \(P < .05\)) or the low-GI meal (3.2 MJ; \(P = .01\)), as shown in Fig 3. In addition, mean time to the first meal request after lunch (2.6, 3.2, and 3.9 hours for the high-, medium-, and low-GI meals, respectively) differed between test meal groups (high GI vs low GI; \(P = .01\); high GI vs medium GI, not significant).

Multiple regression analysis (Table 2) showed that the area under the glycemic response curve was the strongest predictor of voluntary food intake, accounting for 53% of the intrasubject variance (\(P < .001\)). In models using pairs of hormonal and metabolic parameters for all three dietary treatments combined, the area under the glycemic response curve was consistently the only statistically significant independent predictor of within-subject variability in voluntary energy intake.

**DISCUSSION**

On average, our obese subjects ate 81% more total energy after consuming two meals of instant oatmeal than they did after consuming two meals with the same amount of energy in the form of a vegetable omelet and fruit. In addition, they ate 53% more energy after the high-GI instant oatmeal than they did after the medium-GI steel-cut oatmeal. These results demonstrate that commonly consumed meals containing identical amounts of energy may have markedly different effects on metabolism, perceived hunger, and subsequent food intake. Indeed, relatively unfavorable responses were observed after the high-GI meal, a low-fat, whole-grain meal consistent with current nutritional recommendations.6–8

To maximize differences in GI, the low-GI vegetable omelet with fruit contained more protein, more fat, and less carbohydrate than did the high-GI instant oatmeal. However, the observed differences in subsequent voluntary energy intake can be primarily attributed to differences in the GI itself, because similar differences, although of slightly lesser magnitude, were obtained when comparing the energy intake after the high-GI instant oatmeal versus the medium-GI steel-cut oatmeal. For these two oatmeal preparations, macronutrient compositions were identical and alterations in GI were obtained through differences in food structures and sugar type.

The importance of GI was demonstrated further in multiple regression analyses of relationships between voluntary energy intake after the test meals and hormonal and metabolic responses to the meals. Fully 53% of within-subject variability in voluntary energy intake after the three different test meals was accounted for by differences in area under the glycemic response curve. Moreover, in models using pairs of hormonal and metabolic parameters, area under the glycemic response curve emerged as the only significant independent predictor of energy intake.

Concerning the underlying reason for why high-GI meals may influence hunger and voluntary energy intake, the hormonal and metabolic responses to the high-, medium-, and low-GI meals were markedly different. Serum insulin concentrations were high after the high-GI meal because of the rapid absorption of glucose. By contrast, plasma glucagon levels were suppressed, most likely because of the low protein content of the meal and the inhibitory effects of high plasma glucose and insulin concentrations.39 This combination of relative hyperinsulinemia and hypoglucagonemia would tend to promote glucose uptake in muscle and liver, restrain hepatic glucose production, and suppress lipolysis. As a consequence, circulating concentrations of glucose and fatty acids were decreased after the absorption of the high-GI meal, compared with the low-GI...
meal. Elevations in counterregulatory hormones provide evidence that the reduction observed in availability of these two major metabolic fuels is of physiologic importance. The increased hunger and food intake after a high-GI meal thus can be viewed as an attempt to restore energy homeostasis, as demonstrated, for example, after glucoprivation and related experiments. These results suggest a reason why conventional diets have such poor long-term outcomes; high-GI hypocaloric diets would tend to exacerbate hunger, leading eventually to overeating; by contrast, low-GI diets may lessen hunger and improve long-term compliance.

These physiologic changes may be understood further by a consideration of glucose pharmacodynamics. The body has a constant minimum requirement for glucose, in contrast to that of other macronutrients, determined largely by the metabolic demands of the brain. However, nutrient intake is episodic. During the absorptive phase after a meal, the rate of glucose delivery tends to exceed oxidation, and excess glucose is stored as glycogen. The situation is reversed in the postabsorptive phase, when glucose is released from the liver. Meals resulting in rapid glucose influx (ie, high GI) challenge the body’s ability to shift smoothly from absorptive to postabsorptive physiology, in part because of altered insulin and glucagon secretion. Several studies have suggested metabolic advantages, including possibly decreased adiposity, associated with consumption of frequent small meals compared with infrequent large ones. Low-GI meals, by slowing the rates of nutrient absorption, may provide similar benefits.

Two methodologic issues should be addressed. First, for logistic reasons, this study was not performed in a “double-blind” manner and, therefore, the presence of uncontrolled bias cannot be ruled out. Although this concern cannot be negated completely, it should be noted that standardized procedures were used for each different test and, in addition, the results reported are consistent with those from previous studies describing an inverse relationship between GI and short-term satiety. Second, we chose obese subjects, believing that this group (perhaps for genetic reasons as presented below) would demonstrate the greatest sensitivity to GI. However, other studies have reported a direct association between GI and appetite in lean subjects.

Regarding a central issue of interpretation, we recognize that this study evaluated only the acute effects of low-GI meals; the effectiveness of a low-GI diet in promoting long-term weight loss is unknown. Indeed, several lines of investigation suggest that body weight is regulated within a specific range, raising the concern that compensatory, genetically determined mechanisms may tend to antagonize weight loss on a low-GI diet over the long term. However, environmental factors also must play an important role in body weight regulation, as demonstrated simply by the dramatic increase in mean body mass index in recent years among genetically stable populations. The present study suggests that dietary GI may be one of those environmental factors. Long-term dietary intervention studies are necessary to resolve this question.

Additional insight into the relationship between genetics and environment can be found in a report by Sigal and colleagues. When the results of intravenous glucose tolerance tests were compared prospectively with body weight changes in glucose-tolerant offspring of parents with diabetes mellitus, high acute insulin secretion and insulin sensitivity were found to correlate with weight gain. Thus, various factors that augment insulin secretion or action (intrinsic to islet cells, at peripheral sites of action, or dietary) might promote obesity. Individuals who, perhaps for genetic reasons, have an exuberant insulin response to glucose may be especially sensitive to dietary GI.

In summary, this study demonstrates that consumption of high-GI foods induces hormonal and metabolic changes that limit availability of metabolic fuels and lead to overeating in obese subjects. Additional research is required to determine the long-term significance of GI to human health and the optimal composition of a low-GI diet. Nevertheless, this study suggests possible advantages for treatment of obesity of a diet with abundant quantities of vegetables, legumes, and fruits; decreased amounts of high-GI carbohydrates; and moderate intake of protein and fats. Moreover, reductions in dietary GI also may have beneficial effects on serum lipids, risk of diabetes mellitus, and other diseases associated with hyperinsulinemia.

<table>
<thead>
<tr>
<th>High-, Medium-, and Low-GI Meals Combined</th>
<th>R</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Area under glycemic response curve</td>
<td>+0.731</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Plasma glucose nadir</td>
<td>−0.563</td>
<td>.004</td>
</tr>
<tr>
<td>Serum fatty acids (2.5–4.5 h)</td>
<td>−0.600</td>
<td>.01</td>
</tr>
<tr>
<td>Area under insulin response curve</td>
<td>+0.645</td>
<td>.001</td>
</tr>
<tr>
<td>Peak insulin concentration</td>
<td>+0.515</td>
<td>.01</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>High- and Medium-GI Meals Only (Containing Identical Foods)</th>
<th>R</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Area under glycemic response curve</td>
<td>+0.748</td>
<td>.003</td>
</tr>
<tr>
<td>Blood glucose nadir</td>
<td>−0.692</td>
<td>.009</td>
</tr>
<tr>
<td>Serum fatty acids (2.5–4.5 h)</td>
<td>−0.682</td>
<td>.02</td>
</tr>
<tr>
<td>Area under insulin response curve</td>
<td>+0.656</td>
<td>.02</td>
</tr>
<tr>
<td>Peak insulin concentration</td>
<td>+0.460</td>
<td>.11</td>
</tr>
</tbody>
</table>

Table 2. Within-subject Correlation Coefficients for Associations Between Afternoon Energy Intake and Hormonal and Metabolic Parameters
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