Review

Is Glycemic Index of Food a Feasible Predictor of Appetite, Hunger, and Satiety?

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Summary This review assesses the feasibility of using glycemic index (GI) as a predictor of appetite, hunger and satiety by surveying published human intervention studies. We also discuss the relationship between GI and two appetite/satiety control hormones, leptin and ghrelin. Ingestion of high-GI food increased hunger and lowered satiety in short-term human intervention studies. This effect may be attributed to the rapid decline in blood glucose level following a hyperinsulinemic response caused by a sharp and transient increase in blood glucose level that occurs after the ingestion of high-GI food, which is defined as the glucostatic theory. However, appetite, hunger and satiety after the ingestion of foods with varying GI were inconsistent among long-term human intervention studies. From the few relevant long-term studies available, we selected two recent well-designed examples for analysis, but they failed to elicit clear differences in glycemic and insulinemic responses between high- and low-GI meals (consisting of a combination of different foods or key carbohydrate-rich foods incorporated into habitual diets). One of the reasons that these studies could not predict glycemic response to mixed meals is presumably that the GI of each particular food was not reflected in that of the mixed meals as a whole. Thus, it is difficult to conclude that the GI values of foods or mixed meals are a valid long-term predictor for appetite, hunger and satiety. Both insulin and insulin-mediated glucose uptake and metabolism in adipose tissue affect blood leptin concentration and its diurnal pattern. Circulating ghrelin level is suppressed by carbohydrate-rich meals, presumably via glycemia and insulinemia. Accordingly, low-GI foods may not necessarily increase satiety or suppress appetite and/or hunger because of the lack of insulin-mediated leptin stimulation and ghrelin suppression. However, insulin-mediated leptin stimulation and ghrelin suppression per se is not consistent among studies; thus we were not able to identify a clear relationship among GI, satietogenic leptin, and appetitic ghrelin.

Key Words glycemic index, appetite, hunger, satiety, insulin

Glycemic index (GI) was first defined by Jenkins et al. as an indicator of the potential of glycemic carbohydrates in different types of food to raise blood glucose levels within 2 h of ingestion. It was originally expressed as the percentage of the area under a 2 h blood glucose curve attributable to the food of interest divided by that for the same amount of standard carbohydrates such as glucose (1). As described by Brouns et al. (2), low-GI foods are classified as being digested and absorbed slowly and high-GI foods as being digested and absorbed rapidly. Thus, a food with a higher GI is assumed to result in a higher glycemic response, which should induce various hormonal and metabolic changes that negatively affect health conditions; foods eliciting low glycemic responses should generally induce clinically important benefits (3–5).

The prevalence of obesity has increased over recent decades. Because the GI of food may affect body composition and body weight, interest in low-GI foods or diets has gradually increased owing to their potential benefit as a part of strategies to treat obesity by reducing food (energy) intake, and their impact on satiety. However, the evidence to support the beneficial effects of low-GI food on satiety, appetite or hunger from human intervention studies is inconclusive. The purpose of this review is to evaluate the effects of GI on appetite, hunger, and satiety in relation to body composition based on the scientific evidence obtained from human intervention studies. In addition, both insulin and insulin-mediated glucose uptake and metabolism in adipose tissue have been reported to affect the levels of circulating satietogenic-hormone leptin and appetitic-hormone ghrelin (6–14). Therefore, we also assess the relationship between GI and leptin/ghrelin.

1. Glycemic Index, Appetite, Hunger, and Satiety

1–1. Short-term intervention studies

In this review, we use the terms “short-term” and
"long-term" to refer to a study of 1–3 d, and one of several days or more, respectively.

Four short-term human intervention studies showed that ingestion of test meals with high GI increased the level of food intake during subsequent meals, which in turn suggests that meals with low GI presumably prolong satiety (15–19). Preadolescent boys and girls (9–12 y of age) ate less lunch and had a lower hunger rating after a low-GI breakfast than those who ate a high-GI breakfast (15). The sex of a child, and whether or not they were of normal weight or overweight/obese did not alter the effect of the GI of the breakfast on the subsequent lunch intake (15). Rapid absorption of glucose after the consumption of high-GI meals induced a sequence of hormonal and metabolic changes that promote excessive food intake in obese teenage boys (16). Ingestion of a low-GI meal resulted in a lower insulin response than that following a moderately high-GI meal in both male and female obese adolescents, and the low-GI meal resulted in prolonged satiety, i.e. a longer time passed before additional food was requested (17). Arumugam et al. examined the effects of variation in the severity of postprandial glycemia and insulinemia on subjective satiety in overweight and obese women (18). They altered the rate of ingestion of a glucose beverage to simulate the postprandial effects of high- and low-glycemic meals: rapid (bolus) ingestion of a large dose of glucose beverage consumed with breakfast and lunch versus slow (intermittent) ingestion of the same amount of the same glucose beverage consumed in eight portions (one with each meal, and the remaining seven at 20 min intervals after the meal). Sharp declines in glucose and insulin levels followed their transient peaks in subjects with bolus consumption, which was a marked difference from the relatively stable levels of glucose and insulin in subjects with intermittent consumption (Fig. 1). Note that the glucose level fell below the baseline in the subjects with bolus consumption. As shown in Fig. 2, subjects with bolus consumption reported higher ratings of hunger, appe-
tate and prospective consumption than those with intermittent consumption at 4 h after breakfast and several hours after lunch, and sharp peaks in glucose and insulin levels were observed in the former group (Fig. 1). Serum glucose level was more strongly correlated with appetite in the bolus consumption group than in the intermittent consumption group.

Flint et al. (19) found that after the intake of a typical European breakfast, including bread, cookies, cereals, and porridge by healthy male subjects the insulinemic response, but not the glycemic response was positively associated with postprandial satiety. In contrast, the glycemic response, but not the insulinemic response after the breakfast positively associated with the subsequent energy intake at lunch, although no significant relations were found between glycemic response and appetite sensations.

The glucostatic theory (20) was supported by human intervention studies showing that transient decline in blood glucose gave rise to meal initiation (21, 22). Arumugam et al. (18) further supported the glucostatic theory by showing the link between the postprandial changes in blood glucose and appetite sensation. Although the above results of Flint et al. (19) do not support the glucostatic theory’s (20–22) assertion that is “hunger and the initiation of eating is the result of a decline in blood glucose,” their study did identify a possible reduction in energy intake in a subsequent meal following the intake of a low-GI meal.

Thus, these short-term studies indicate that both glycemic response and insulimetic response are associated with appetite, hunger, and/or satiety irrespective of age, sex, or weight. The relatively early and sharp decline to below the baseline in blood glucose seems to be a key to the earlier disappearance of satiety and the earlier return of appetite and hunger.

1–2. Long-term intervention studies

In contrast to the short-term studies, there is no clear evidence that meals with a low GI prolong satiety or reduce appetite and/or hunger over a long period of time.

Among the few relevant long-term studies available, we selected two recent well-designed examples to be assessed. In a study conducted by Alfenas and Mattes (23), 39 healthy adults consumed either only low- or only high-GI foods ad libitum in a laboratory for 8 d. The mean GI value for each of 79 types of food was determined, and the 48 that resulted in consistent glycemic responses were selected for use. In a controlled trial study, participants from both the high- and the low-GI-food groups first participated in a variety session where a combination of three different foods was served for each of the three daily meals (breakfast, lunch, and dinner). Unlimited ingestion of any of the foods was allowed. After completion of the first session, the participants selected their favorite food, which was to be the
only food eaten, one per meal, during the entire 8 days of the monotony session. The authors found no significant difference in plasma glucose, plasma insulin, appetite, or food intake among the treatments, indicating that the differential glycemic response of foods tested in isolation under a fixed duration are not preserved under conditions of chronic ad libitum consumption of mixed meals (Fig. 3). This study raised questions about the predictive power of the GI of a specific food or diet for either appetite or dietary responses.

Aston et al. (24) investigated the effect of a diet consisting of whole meals of reduced-GI food on appetite, energy intake, body weight and body composition in overweight and obese female subjects, and found no evidence to support the effect of a reduced-GI diet on satiety, energy intake or body weight. More precisely, in their randomized crossover intervention study that included two consecutive 12-wk periods, key carbohydrate-rich foods were provided. These comprised low- or high-GI bread, breakfast cereals and rice, plus pasta for the low-GI diet and potatoes for the high-GI diet. Nineteen subjects (overweight and obese women with moderate hyperinsulinemia at 34–65 y of age) were provided with either low- or high-GI versions of the key carbohydrate-rich foods in ad libitum quantities to be incorporated into their habitual diets. Dietary data were collected from 4 d diet diaries before intervention and during the final week of each intervention period. Based on the dietary data, all subjects reduced their dietary GI on the low GI diet compared with the high GI diet with a mean difference of 8.4 units (55.5 for low GI versus 63.9 for high GI). However, energy intake, body weight, body composition and subjective ratings of hunger or satiety did not differ between periods. In addition, plasma glucose and insulin responses did not differ between periods in this study, in agreement with the findings of Alfenas and Mattes (23).

The results of these two studies suggest that long-term ingestion of a diet either partially consisting of low-GI food, or only consisting of reduced-GI food hardly achieves prolonged satiety and suppressed appetite and/or hunger unless a marked difference in blood glucose levels is attained.

1–3. Comparison between short-term and long-term studies

As discussed above, acute or short-term studies, but not long-term studies, support the hypothesis that meals with low GI increase satiety, delay the return of hunger, and reduce energy intake during the subsequent meal. In long-term studies glycemic and insulminemic responses were not affected by the ingestion of high- or low-GI foods. At present, we have little explanation for this lack of glycemic and insulminemic response. Some studies demonstrate that the appropriate summation of the GI of individual foods is valid to predict the glycemic response of a mixed meal (24–26). Accordingly, an objective assessment of the additivity of GI values in mixed meals is required, especially in long-term studies. It is also important to review the long-term stability of glycemic and insulminemic responses to a specific carbohydrate-containing food. A long-term analysis of glycemic and insulminemic responses after the ingestion of such a food should be systematically conducted. Considering the large coefficient of variance in measured GI values, often reaching 30%, it is considered appropriate to employ the concept of “least significant difference” for GI values. For example, a difference in GI of less than 10 units (27) might simply be caused by random fluctuation. In other words, we should critically and quantitatively plan experiments by considering the degree of difference in GI between planned experimental groups that is appropriate. Furthermore, we should bear in mind that GI is an indicator of the quality of glycemic carbohydrates but is not an indicator of a whole meal. Thus, another indicator that reflects the postprandial glycemic response might be required instead of the GI.

2. Is Glycemic Index a Valid Predictor of Leptin and Ghrelin Levels?

2–1. Background

As shown in Fig. 4, insulin and glucose stimulate the release of the satiogenic hormone leptin and suppress that of the appetitic hormone ghrelin (6–14). Thus, increases in blood glucose and insulin seem to have contradictory effects in terms of appetite, hunger, and satiety, which is a possible explanation for the above-mentioned discrepancy between short-term and long-term results. Therefore, we conducted a survey of literature describing the relationship among GI, leptin, and ghrelin.

2–2. Leptin and ghrelin

Leptin was discovered by Zhang et al. in 1994 (28). Leptin, which is produced by adipocytes in proportion to fat stores, communicates the state of energy reserves to the brain to decrease food intake by enhancing satiety and increasing energy expenditure (29, 30). A novel gastrointestinal peptide hormone was characterized and named ghrelin in 1999 by Kojima et al. (31), based on its ability to act as a ligand for the growth hormone secretagogue receptor and to cause growth hormone release. Ghrelin is able to stimulate appetite that is mediated via the hypothalamus (32–34).
The relationship among glycemic response, leptin, and ghrelin has been intensively examined in terms of the control of appetite and satiety. Barkoukis et al. reported that low-glycemic meals promote a postprandial metabolic milieu favorable for reduced food consumption in young healthy volunteers \(^{(35)}\). The purpose of their study was to evaluate the metabolic effects of meals with varying GI. Their results showed that the area under the insulin response curve (insulin AUC) following a low-glycemic meal was significantly smaller than that after a high-glycemic meal, and that the leptin AUC was smaller after a high-glycemic meal than after a low-glycemic meal. In contrast, Herrmann et al. \(^{(36)}\) reported contradictory results of a two-way factorial experiment examining the effects of dietary high- or low-GI carbohydrates and fat energy content (20% vs 30% energy from fat) on 24 h serum profiles of leptin, insulin, and glucose in healthy slim adults for 8 d. Although no significant differences in serum glucose and insulin concentrations among the four dietary groups (A, high GI carbohydrate and 30% fat; B, low GI carbohydrate and 30% fat; C, high GI carbohydrate and 20% fat; and D, low GI carbohydrate and 20% fat) were observed, diets that contained high-GI carbohydrates increased the 24-h leptin AUC, but not the 24 h insulin AUC, independently of fat energy content on day 8 (Fig. 5). The results indicate that neither the amount of carbohydrate in the diet nor the serum insulin response was responsible for the increased 24 h leptin AUC, because the carbohydrate content did not vary between diets A and B (55%), or between diets C and D (65%).

Furthermore, although high-GI carbohydrates increased the 24-h leptin AUC, satiety levels after the test lunch did not differ significantly among the four dietary groups.

In a long-term study with moderately overweight men by Bouché et al. \(^{(37)}\), 5 wk of a low-GI diet ameliorated some plasma lipid parameters, decreased total fat mass and tended to increase lean body mass without changing body weight. In this study, the decrease in fat mass accompanied the decrease in leptin; however, decreased food intake was not confirmed. The authors proposed possible mechanisms to explain why the low-GI diet induced a selective decrease in fat and an increase in lean body mass. One is the difference in nitrogen balance and protein metabolism. Because of the greater negative nitrogen balance with the high-GI diet than the low-GI diet, fat tissue was oxidized to a lesser degree and muscle to a greater degree with the high-GI diet. Another mechanism is the relative shift in substrate utilization for a low-GI diet that lowers carbohydrate oxidation and increases fat oxidation. Changes in lipoprotein lipase (LPL) activity in adipose tissue might be an alternative possibility. Consistent with the reduction in postprandial blood insulin and triacylglycerol, the authors found that there was a significant reduction in LPL expression in adipose tissue after a low-GI diet, which could have attenuated plasma triacylglycerol hydrolysis and the uptake of fatty acids in adipose tissue. Figure 6 illustrates how reduced LPL results in decreased fatty-acid uptake by adipose tissue. LP, lipoprotein; $\downarrow$, reduced activity.

As for ghrelin, the effect of the physiological level of blood insulin on plasma ghrelin concentrations in healthy humans is unclear. Caixás et al. compared effects of combined pulse administration of intravenous glucose and subcutaneous insulin and of one meal on plasma ghrelin, and further studied the effect of oral glucose load on plasma ghrelin level in humans \(^{(38)}\). Unlike food intake or oral glucose load, the combined administration of insulin plus glucose did not suppress the ghrelin level. Thus, the authors suggested that it is unlikely that the suppressive effect of food intake or oral glucose on serum ghrelin is mediated via changes in
plasma insulin or postprandial blood glucose. Schaller et al. also reported that meal-related suppression of ghrelin was not directly regulated by glucose or insulin (39). In their study, plasma ghrelin concentration was examined during exogenous hyperinsulinemia, exogenous hyperglycemia, and inhibition of endogenous insulin production by somatostatin infusion in healthy male volunteers. The results showed that hyperglycemia did not result in decreased ghrelin and that the reduction in ghrelin was only seen at supraphysiological insulin concentrations (Fig. 7), whereas systemic ghrelin concentration was decreased by somatostatin.

On the other hand, Saad et al. suggested that insulin was a physiological and dynamic modulator of plasma ghrelin and that insulinemia directly or indirectly mediates the effect of nutritional status on plasma ghrelin concentration (40). They infused insulin for 2 h to maintain euglycemia and observed plasma ghrelin levels in healthy volunteers. They found a negative correlation between insulin and ghrelin in all subjects with the maximum insulin-induced suppression of ghrelin ranging from 19 to 64%. Lucidi et al. also reported that plasma ghrelin concentrations decreased after insulin infusion in healthy volunteers, raising the possibility that postprandial hyperinsulinemia is responsible for the reduction in plasma ghrelin after a meal (41).

2–3. Overview

As reviewed above, the concept of insulin-mediated leptin stimulation and ghrelin suppression per se is unclear. Since leptin level is likely to be affected by body fat mass, long-term studies presumably failed to detect the stimulatory effect of insulin and/or glucose on leptin due to possible changes in body fat mass. As for ghrelin, the effect of exogenous insulin on blood ghrelin levels was inconsistent even among short-term studies. Thus, the present situation does not allow clear characterization of the relationship among GI, satietogenic leptin, and appetitic ghrelin.

3. Conclusion

At present, it is difficult to simply conclude that the GI value of food or mixed meals is a valid predictor of appetite, hunger and satiety over a long period of time.

The concept of insulin-mediated leptin stimulation and ghrelin suppression per se seems unclear, and we could not identify a clear relationship among GI, satietogenic leptin, and appetitic ghrelin.

Thus, it seems too early to rely too much on GI values to control appetite, hunger, and/or satiety in the long term. One of the major causes for the above-mentioned lack of clarity might be the large variance in GI values, mainly due to inter- and intra-individual variance in glycemic response. In this regard, we suggest the establishment of a reliable in vivo, ex vivo or even in vitro method to predict the rate of glucose entry from food into the body.

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