Weighing in on glycemic index and body weight$^{1,2}$

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This issue of the Journal includes a provocative observational study by Hare-Bruun et al (1) on a topic vigorously debated among scientists (2–9)—the role of the dietary glycemic index (GI) in the development of obesity. The concept of GI was developed by Jenkins et al (10, 11) at the University of Toronto more than a quarter-century ago as a physiologic, rather than a structural, approach to classifying carbohydrate. The GI is defined as the area under the 2-h postprandial blood glucose concentration curve per 50 g available carbohydrate consumed from a test food, relative to a reference food (either white bread or pure glucose) (11, 12). A related concept included in the study by Hare-Bruun et al (1) is the glycemic load (GL), or the product of the food GI and the amount of available carbohydrate (ie, that without fiber) in that food (or beverage) portion, which purportedly is a better indicator of the glycemic response to habitual mixed meals than is either the GI or the carbohydrate amount alone (12–15). The GI approach to ranking carbohydrate was initially developed in the context of research aimed at identifying foods and eating patterns that may help to manage diabetes through the control of postprandial glycemia and perhaps also hyperinsulinemia (10, 16–18). Indeed, experimental and observational studies in animals and humans have provided good evidence to support the direct effect or association of low-GI or -GL diets in both the management of diabetes and the prevention of diabetes and cardiovascular disease (19–24). However, as with all lines of nutrition research, the literature is not entirely consistent in supporting this hypothesis (15, 16, 25, 26). Longer, high-quality, randomized controlled trials are needed.

In the late 1990s, Ludwig (27) and Ludwig et al (28) extended the GI theory from risk of cardiovascular disease and diabetes to risk of obesity. The central feature of this theory is that hyperinsulinemic compensation to early postprandial hyperglycemia may have mid- to late-postprandial consequences for fuel partitioning (favoring storage over oxidation), a mechanism of central import to obesity etiologists (16, 28, 29). Additional hypothesized mechanisms, downstream of hyperinsulinemia, include re-active hypoglycemia that coincides with up-regulation of the stress axis and perceived hunger (16, 27–31). Certainly, if diet-modulated glycemia and insulinemia—ie, GI or GL—do have an important effect on body weight, one would expect several mechanisms to be at work, because the complex metabolic control of body weight would be expected to prevent any single mechanism in isolation from having a measurable effect. Animal experiments provided some compelling results in support of these mechanisms (20, 21). The few small or short-term (or both) intervention studies in humans that have focused on GI or GL and body weight change have had mixed results (32–34). Definitive longer-term trials are needed. In the meantime, it is worthwhile to look to prospective observational studies with valid measures of diet and endpoints.

Hare-Bruun et al (1) point out that few prior cohort studies on GI and obesity risk have been published, and most of those studies were cross-sectional studies with mixed findings. Hare-Bruun et al took advantage of an existing data set to examine the relation of dietary GI and GL with changes in body habits and composition over a 6-y follow-up period in 376 middle-aged Danish men and women. The dietary GL was not associated with changes in body weight or body fat in men or women, whereas the dietary GI was directly associated with changes in weight, waist circumference, and body fat in women but not in men. Furthermore, the association of GI with weight change (and with fat change) was modified by self-reported physical activity: the association was particularly strong in the 44 sedentary women but absent in the 147 active women. Strengths of this study include the method of dietary assessment and GI calculations, the random and stratified (birth year) sampling frame for the original cohort data set, and the careful handling of the statistical models and their interpretation. An exception to this latter point may be the adjustment for energy intake and dietary fiber, in which the former may reside on the causal pathway (GI → energy intake → obesity) and the latter, especially the soluble form (35–38), is an important contributor to the GI of certain high-carbohydrate foods (eg, oats and barley). Even though GI is based on 50 g available carbohydrate, the fiber is of course consumed along with the available carbohydrate, and soluble fiber is known to delay gastric emptying and glucose absorption—ie, to reduce the GI (35–38).

Assuming that the inverse association between GI and body weight in sedentary women is real, a difficult issue is the null association between GL and body weight change in the men and women in the study by Hare-Bruun et al. As indicated earlier, GI is thought to be superior to either GI or total carbohydrate intake alone in predicting the glycemic response to mixed meals. One could argue that the GI is a better measure of carbohydrate quality than is the GL, because any given overall dietary GL value is driven by some combination of GI and carbohydrate quantity.

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That is, a high-GL diet could be a high-carbohydrate diet featuring a large proportion of refined grain and sugar-sweetened beverages. On the other hand, a high-GL diet could include a variety of whole-grain products that are high in nutrients, phytochemicals, and insoluble fiber but still high in carbohydrate and moderately high in GI. Elegant epidemiologic analyses have supported this concept by showing independent and additive associations between GL and cereal fiber on risk of diabetes in women and men (23, 24). However, diets that are high in GI, whether they are high in GL (ie, carbohydrate amount) or not, are almost invariably abundant in nutrient-poor carbohydrates of a fiber-depleted, highly processed nature. Thus, in observational studies of habitual diets, low-GI diets may be more likely to reflect a prudent nutrient-rich, fiber-rich diet than are low-GL diets. Indeed, Table 2 in the study of Hare-Bruun et al (1) shows a strong direct association between GL and both fiber and added sugar.

An important limitation of the study by Hare-Bruun et al that should be considered in some detail is the number of extensive exclusions that reduced the sample size from the original population-based sample of 4851 to only 376. The most detrimental factor in these exclusions was the limited number of persons who completed the diet history interview. In addition to the severely restricted statistical power of the study, one should not underestimate the possibility of systematic biases that limit generalizability and may further reduce the likelihood of finding associations between diet and obesity risk. Indeed, the age-adjusted percentage body fat was significantly lower in the study sample than in the overall cohort. Although the authors built a logical case for the sex × GI and activity × GI interactions to be biologically meaningful, with such a small sample and low power, it would be premature to conclude that the interactions are real and that no association exists in physically active women or in men of any activity level. To balance the known high level of dietary classification from self-reported diet, it is unfortunately necessary to have sample sizes in the thousands, and logical case for the sex

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