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COMMENTS AND RESPONSES

Influence of Glycemic Index/Load on Glycemic Response, Appetite, and Food Intake in Healthy Humans

Response to Alfenas and Mattes

In their recent article, Alfenas and Mattes (1) conclude that the glycemic index values of individual foods do not predict glycemic response to mixed meals, nor influence measures of hunger. Because the observed glycemic response did not differ between diets, the lack of effect on appetite is not surprising. Thus, the potentially important aspect of the study pertains to the prediction of glycemic index in mixed meals.

The authors' approach was to validate published glycemic index values in a pretest, selecting 48 of 79 foods with consistent glycemic responses. However, their methods do not conform to standard procedures (2–4). Only 3 subjects were used for each food instead of the recommended minimum number of 10 (3). Blood glucose was measured by glucometer, a device that is not sufficiently accurate in the normal range for research purposes (4). With such a small subject number, CIs around the mean would likely overlap for most foods on both diets. From a statistical perspective, the selection of foods with an underpowered pretest using inaccurate methods would produce regression to the mean.

It is important to emphasize that published values for specific foods cannot be used for a study such as this without careful validation because published values may not have been determined correctly, the composition or manufacturing procedures of individual products may change over time, and shelf life and preparatory methods may also affect glycemic index. Such concerns are not unique to studies of glycemic index. One cannot assume, for example, that a published value for vitamin C content of Valencia orange will apply to every piece of fruit, at all times of year, from any location.

Major categories of food differ in glycemic index with reasonable consistency; most fruits, legumes, minimally processed grain products, and pasta prepared from hard wheat have low– to moderate–glycemic index, whereas highly processed grains products and pasta previously prepared and canned have a high–glycemic index. Most of the foods used by Alfenas and Mattes for the low–glycemic index diet included highly processed grain products (quick pizza, quiche, pita, bagel, etc.).

There are many studies demonstrating that the glycemic index of individual foods predicts a response to mixed meals when appropriate methodology is utilized (5–7). With regard to the authors' description of our study, two of the test meals did have identical macronutrient composition and solid food components, and the measured glycemic response corresponded closely with prediction (8).

Clearly, research into the relationship between glycemic index and glycemic response merits study. To advance the dialogue, adequately powered studies employing accepted methodology will be needed. A more fundamental question is whether diets comprised of low–glycemic index foods improve important clinical end points related to obesity, diabetes, heart disease, and cancer.

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Response to Alfenas and Mattes

Recently, Alfenas and Mattes (1) concluded that the differential glycemic responses of foods tested in isolation are not preserved under conditions of chronic ad libitum consumption of mixed meals (1). This conclusion is unwarranted because of serious methodological problems that undermine the validity of their results.

Foods were classified as low– or high–glycemic index by the investigators; the glycemic index of each food was determined in three subjects by measuring glucose four times with a glucose meter and discarding means with inconsistent values. Since white bread was used as the reference, all glycemic index values discussed here are adjusted accordingly. We commend the authors for wanting to mea-

sure glycemic index; however, nonstandard methods were used (2). Discarding means with inconsistent values is questionable; bootstrap analysis of our data (2) suggests, paradoxically, that the discarded means may be more reliable estimates of the true mean than the remaining ones.

Different blood sampling schedules influence the mean and variation of glycemic index values (3). Using our data (five foods tested by 47 subjects) (2), we found that the average SD of glycemic index values calculated from glucose results for the blood sampling times used by Alfenas and Mattes was 35, compared with 29 for the recommended seven blood samples. If a glucose meter is used to measure glycemic index the SD is increased by ~15% (4); thus, we estimate the SD of glycemic index values determined using Alfenas-Mattes methodology to be $35 \times 1.15 = 40$. With SD = 40 and $n = 3$, the 95% CI of a mean glycemic index value is ±99, and the chance of obtaining a mean within ±10 of the true mean is only ~33%. Thus, it is likely that the glycemic index category (high or low glycemic index) of many of the foods was misclassified. This is consistent with the failure to detect a difference in glucose response on day 1 of the period when subjects consumed only one food for breakfast.

Also, Alfenas and Mattes compared glycemic responses elicited by low– and high–glycemic index foods in different groups of subjects. Since large between-subject variation of glycemic responses exists, groups of normal subjects can have different means; e.g., the mean response after 50 g glucose in different groups of 10 subjects of similar ethnicity varied from 153 to 210 (2). Between-subject variation is a confounding variable the authors have not accounted for.

The combination of these several methodological problems seriously undermines the reliability of the results.

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Response to Ludwig and Roberts and to Wolever and Brand-Miller

We are pleased to respond to the comments of Ludwig and Roberts (1) as well as Wolever and Brand-Miller (2). We will address the points raised by the former first.

Ludwig and Roberts state that we "conclude that the glycemic index values of individual foods do not predict glycemic response to mixed meals." Actually, we go beyond that and demonstrate that the glycemic index value of individual foods do not even reliably predict the glycemic response to that food alone. Indeed, Jenkins et al. (3) showed 15 years ago that the glycemic response to the gold-standard stimulus, glucose in water, depends on the timing of ingestion.

Second, Ludwig and Roberts state that "[b]ecause the observed glycemic response did not differ between diets, the lack of effect on appetite is not surprising." This assumes glucose or insulin is a key determinant of appetite. While both are correlated with hunger after meals, this is not evidence for causality. Euglycemic clamp studies demonstrate that independent manipulation of plasma glucose or insulin does not alter reported hunger (4).

Third, a question is raised about the adequacy of the methods used to select study foods. This concern was surprising because we considered this a study strength. We selected potential foods from the 2002 International Table of Glycemic Index and Glycemic Load Values (5). This table includes values verified as being determined by methods proposed by the Food and Agriculture Organization of the United Nations and the World Health Organization, as Ludwig and Roberts recommend. However, we then conducted a second round of testing, albeit less vigorous, to verify the values. Thus, the foods were more vigorously tested than in nearly any other published study. In addition, each food, not the combined mean, was comprised of comparable macronutrient composition, energy density, and palatability. This reduced several additional common confounds to study interpretation.

Interestingly, Ludwig and Roberts note that "the composition or manufacturing procedures of individual products may change over time, and shelf life and preparatory methods may also affect glycemic index." This is the very reason we question the utility of expected glycemic index influences on outcome measures. Given this agreed-upon fact, the concern with our test foods leads to an untenable argument that this variability does not negate the predicted responses of glycemic index diets in free-living consumers but does in more controlled clinical trials.

Fourth, Ludwig and Roberts state, "There are many studies demonstrating that the glycemic index of individual foods predicts response to mixed meals when appropriate methodology is utilized." We recognize there are studies finding associations, but to be fair to the literature, it should be acknowledged that there are also those that do not (6), and the latter are likely under-represented due to publication bias. It is in part this reason that glycemic index diets have not been endorsed for weight management by most biomedical societies and governmental agencies.

Wolever and Brand-Miller raise three points. The first reflects the same misunderstanding expressed by Ludwig and Roberts regarding the criteria we used for food selection. Their power analysis assumes the foods were only tested by 3