Glycemic index and disease1–4

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ABSTRACT  It has been suggested that foods with a high glycemic index are detrimental to health and that healthy people should be told to avoid these foods. This paper takes the position that not enough valid scientific data are available to launch a public health campaign to disseminate such a recommendation. This paper explores the glycemic index and its validity and discusses the effect of postprandial glucose and insulin responses on food intake, obesity, type 1 diabetes, and cardiovascular disease. Presented herein are the reasons why it is premature to recommend that the general population avoid foods with a high glycemic index. Am J Clin Nutr 2002;76:290S–8S.

KEY WORDS  Glycemic index, glucose, insulin, obesity, diabetes, cardiovascular disease

INTRODUCTION

Although Otto et al (1, 2) first brought attention to the different glycemic effects of various foods, the glycemic index (GI) was initially conceived by Jenkins et al (3) as a tool for the dietary management of type 1 diabetes and, later, dyslipidemia (4). Jenkins’ initial studies compared 50-g portions of various carbohydrates (calculated from food tables) with 50 g glucose. Venous blood samples were taken fasting and at 30-min intervals for 2 h after the ingestion of carbohydrate. The area above (or below, as sometimes occurs) the fasting glucose concentration was calculated and was expressed as a percentage of the area obtained after the ingestion of 50 g glucose; the higher the area under the curve (AUC), the higher the GI of a food.

Subsequently, the standard against which foods are compared was changed to white bread (5, 6). This is unfortunate for 2 reasons: first, published GI values conflict; second, 50 g carbohydrate in white bread is more difficult to determine accurately than is 50 g glucose. A comparative standard should be simple, accurate, and reproducible, and the one used to calculate GI is not.

It is important to remember in this debate that the GI was originally conceived as an inherent property of the food, and not as a metabolic response of an individual to the food. As such, any food would have a consistent and theoretically reproducible response from person to person, independent of other food with which it is ingested. The question debated at the symposium Is the Glycemic Index Important in Human Nutrition was whether a diet that includes high-GI foods is detrimental to health. This report begins with the calculation of GI and then discusses the factors that influence the GI of a food and the “carbohydrate/insulin/disease” hypothesis. The discussion includes a critical review of some of the reports dealing with this concept, particularly as they relate to food intake, obesity, and diabetes.

CALCULATION OF THE AREA UNDER THE CURVE FOR GLUCOSE

Several technical limitations to the calculation of the GI must be considered when determining its worth as a nutritive marker for dietary recommendations. Glucose molecules are all the same and circulate in the bloodstream similarly. Is a glucose molecule that is considered to be below the fasting glucose concentration different from one above it? If not, why should the AUC for all of the available glucose not be used for the calculation? Several experts favor the use of the whole AUC as the real measure of glucose availability (7, 8). If the AUC is calculated in this manner, the differences in GIs between foods are greatly attenuated. For example, a person with a fasting glucose of 75 mg/dL ingests 2 foods, one with a GI of 100 and the other a GI of 72. If the GI is calculated by using the whole glucose AUC instead of the area above the fasting glucose, the values would be 100 and 92, respectively. The difference changes from an impressive 28 units to an unimpressive 8 units.

The postprandial disposal of glucose can take much longer than 2 h, especially in persons with diabetes (7). The choice to codify the glucose response using the 2-h standard made little sense because this standard was established only as a diagnostic tool for identifying type 2 diabetes and impaired glucose tolerance, not to mark the total period of postprandial glucose elevation. Patients with type 2 diabetes require much longer than 2 h for their blood glucose to return to normal concentrations, if at all. Gannon and Nuttall (7) showed that differences in GIs between foods greatly narrow as longer postprandial time frames are used to measure GI. Thus, the difference between 100 and 72 would be considerably less if the AUC were calculated for a more reasonable postprandial period of 4 h.

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The GI has been defined as the testing of a person in the morning, after an overnight fast. However, AUCs differ if the test is given in the morning or as the second or third meal of the day (9–12). Had the standard been set to test for lunch rather than for breakfast, the differences in GIs between foods would be considerably less. A study by Brand-Miller (13) showed no difference between the glucose response to the second meal of the day whether it was a high-GI or a low-GI repast. This was also true of a study by Gannon et al (14). So, should we worry about GI primarily for breakfast?

FACTORS AFFECTING THE REPRODUCIBILITY OF THE GI

In tables compiled by Foster-Powell and Miller (15), the variability in the GI of glucose, the carbohydrate that can most accurately be measured, was 85–111 (ie, 25%). Even for foods that require no preparation (eg, cutting or cooking) before ingesting, such as whole milk and ice cream, the GI varied from 11 to 40 and from 36 to 68, respectively. In fact, the variability of GIs for many individual foods exceeds the calculated mixed-meal GI of the 5 population quintiles reported in the Nurses’ Health Study, which ranged from 72 to 80 in one report (16) and from 64 to 77 in another (17). So, can we really tell people that the GI of a food is predictable?

Ripeness of fruit

The ripeness of fruit affects the GI. As a fruit ripens, starch is changed to sugar. The starch generally has a higher GI than does the sugar, so as ripeness progresses, the GI decreases, such as was reported for bananas (18). So, are we going to tell the public that they can eat fruit at some points in their maturation and not in others?

Physical form of foods

Changing the particle size of some foods changes their GIs (19, 20). For example, the GI of a 1-inch cube of potato can increase by 25% just by mashing the cube (21). Consumption of whole apples, apple purée, and apple juice results in significantly different glucose and insulin excursions (22). So, are we going to tell the public that they can eat one physical form of a food but not another?

Variability within food classes

The GI value of an individual food can vary widely depending on its type, the way it is processed, and the way it is prepared.

Type

Different types of a particular food can have different GIs. For example, different types of rice can have different GIs. The GI of rice is affected by the proportion of amylase to amyllopectin in the grains. Amylose is a linear molecule with D-glucose units linked in an (α1–4) fashion. Amyllopectin has both (α1–4) and (α1–6) linkages (23), and is thereby a branched structure. The higher the proportion of amyllopectin, the higher the GI, because amyllopectin, which is made up of branched-starch molecules, is more easily hydrolyzed in the gut than is the single-strand amyllose (24). Thus, 50-g equivalents of different rices produce GIs ranging from 68 to 103 (15). So, are we going to specify for the public which kind of rice is eatable and which is not?

Pasta also produces different GIs depending on its type. The GIs of macaroni, star pastina, and spaghetti are 68, 54, and 45, respectively (25). Because different types of pasta can produce different glycemic responses, should we ban macaroni and allow spaghetti to be eaten? Even within a class of pasta, such as linguini, a different thickness will result in a different GI. Thin linguini has a GI of 87, and thick linguini has a GI of 68 (26). How would we advise the public about this major difference?

Processing

The method of processing of a single food can greatly change its GI. Starch exists in carbohydrate foods in the form of large granules. These granules must be disrupted so that the amyllose or amylopectin starch macromolecules become available for hydrolysis. Grinding, rolling, pressing, or even thoroughly chewing a kernel or other starch food can disrupt the granules. Rolling or pressing foods, such as is done in the processing of many grains, disrupts the outer germ layer and granules and increases GI (27).

Chemically modifying a food also affects its GI. For instance, 1–2% acetylated potato starch decreases the GI (28), as does the addition of β-cyclodextrin to stabilize the carbohydrate (28).

The application of heat and moisture affects starch granules. Disorganization of the crystalline structure occurs as it encounters greater heat and moisture for a longer period of time. Gelatinization occurs first, with disruption of the crystalline structure, followed by a disruption of the granules. If the starch is then let stand, or stored for a time, so that cooling occurs, the starch becomes a gel, which will vary in structure depending on the amount of moisture, the amyllose to amylopectin ratio and the time and temperature of storage (23). A crystallinity to the gel can occur that is called retrogradation of the starch. These starch complexes are insoluble and not amenable to hydrolysis in the small intestine. Repeated cycles of heating and cooling can further the retrogradation (29). Starch can also form insoluble complexes with proteins, such as occurs in the browning (Maillard) reaction, making it unavailable for digestion and absorption.

Preparation

The cooking method affects the GI beyond the effects of mashing or puréeing food, as mentioned above. For example, uncooked potato is resistant to hydrolysis, but when it is cooked the starch granules gelatinize and become readily digestible. When the potatoes are then cooled, the gelatinization reverses and some 12% of the potato starch is resistant to hydrolysis and cannot be absorbed (30).

The heat utilized, the amount of water, and the time of cooking, all have a significant effect on the GI (31, 32). Thus, the more a starch-containing food is heated, moistened, ground, or pressed, the more it will be amenable to hydrolysis and digestion, except for the portion that forms insoluble complexes. This then, belies the concept that a food has a definitive GI, because the GI is dependent on the history of the processing, storing, ripening, cutting, and cooking of the food. So, shall we allow a grain to be eaten if processed or cooked in one manner but not if processed or cooked in another manner? Does a consumer need to know about retrogradation?

EFFECTS OF A COMBINATION OF MACRONUTRIENTS ON THE GI

People do not generally eat single foods, they eat meals or snacks made up of ≥2 macronutrients. Several studies have investigated the effects of combinations of macronutrients on the GI and have shown 2 things: 1) the higher the proportion of
carbohydrate in a specific food, as opposed to protein and fat, the higher the GI; and 2) a mixed meal of carbohydrate, protein, and fat will have a different and variable glucose response depending on the proportions of each nutrient. Thus, the glucose responses of a food eaten alone or in combination with other foods differ (33–35). Proponents of the GI have denied this (13, 36), but I have provided some examples below.

Protein, fat, and carbohydrate

Protein-rich foods are known to increase insulin secretion without augmenting glucose concentrations (37–39). Thus, whereas the glucose response does not change much or actually decreases, the insulin response increases. Therefore, as more protein is taken in conjunction with carbohydrate, the insulin response will increase, whereas postprandial glucose will not change much. Similarly, adding fat to a carbohydrate meal also enhances insulin secretion even though the plasma glucose response actually decreases (12, 40, 41). Also, all 3 macronutrients stimulate the release of several gut peptides, but to different degrees. Protein and fat are particularly efficacious in stimulating gut peptide release despite a small glucose effect (42). Thus, the insulin response to a carbohydrate food varies with the amount of fat, protein, or both, with which it is ingested.

There are many foods that do not contain carbohydrates only, but are mixed with other macronutrients. Thus, there may be foods that have a lower GI but would not be recommended for other reasons. For example, chocolate and cashews have low GIs but contain large amounts of fat. Other foods may have high GIs but be nutritionally more attractive because they are less energy dense and more nutritionally rich with micronutrients. An example is carrots.

Fiber

The extent to which the fiber in a particular food is responsible for its GI is a subject of much debate. Wolever (43) studied this relation in 25 foods and found that total dietary fiber was related to the GI \((r = 0.461, P < 0.05)\), although weakly. Breaking it down, he found no significant relation between soluble fiber and GI, but found the strongest relation between insoluble fiber and GI \((r = 0.584, P < 0.001)\); he attributed the effect to the uronic acids in insoluble fiber. However, he could only explain 50% of the variability by fiber differences. In contrast with the above findings, other studies in which fiber was added to a carbohydrate meal suggested that only soluble fiber has an effect on postprandial glucose concentrations and not the insoluble component (44). However, does the presence of naturally occurring fiber in foods affect the glucose response? It seems to have very little relation (3, 45). Comparisons between brown and white rice, brown and white spaghetti, and whole-wheat and white bread showed small differences in the GI, although the fiber contents were quite different. Jenkins et al (3), in testing several foods, found no relation at all between the GI and the fiber content of the food. Holt et al (46) found no relation between the postprandial insulin response to and the fiber content of a food. In persons with type 2 diabetes, no effect of fiber on glucose concentrations was found (44, 47). Long-term studies have not been done in nondiabetic subjects.

Sugar

In the past, diabetic patients were prohibited from eating dietary sucrose because it was thought to raise blood glucose concentrations inordinately. We now know that the GI of sucrose (using white bread as a standard) is relatively low at 65. The GI of glucose is 97, whereas those of fructose and lactose are 23 and 46, respectively (15). One would expect that adding sugar to a meal would lower the GI; however, Jenkins et al (3) found no relation between the sugar content in foods and the GI in 62 commonly eaten foods, nor did Brand-Miller (13). These findings remain unexplained, but they certainly complicate the entire GI issue.

Acidity

An increase in the acidity of a meal can greatly lower its GI. Increasing the amount of vinegar in a meal, for instance, will affect the glucose response. The addition of sourdough bread to a meal can result in different GIs, depending on its content of organic acids (48). These foods apparently affect the glucose response, at least partially, by slowing gastric emptying. So, should we alert consumers to check how much vinegar they put on their food and how much acid is in their bread?

Predictability of the insulin response

It has been widely assumed that the insulin response is proportional to the glucose response, and therefore that the glycemic response is an accurate predictor of the insulin response. This is not the case. For instance, as one increases the amount of a carbohydrate food ingested, the amount of insulin does not increase proportionately. Plasma insulin responses increase at a much faster rate than do plasma glucose responses (49). One cannot therefore predict that the insulin effect expected from a 50-g portion of a particular food would be doubled by ingesting a 100-g portion. Therefore, if the culprit we are trying to guard against is a high insulin response, it is a moving target that will depend considerably more on the portion size than on the GI of a food.

What is the best way to compare foods if one is looking for the insulin response? One could argue that it is better to compare normal serving sizes of a particular food or isoenergetic servings rather than to compare 50-g portions. Holt et al (46) compared the effect of isoenergetic amounts of foods on the insulin secretary response and found that the postprandial insulin responses were not closely related to the carbohydrate content or to the glycemic effects of the foods. Whereas the glycemic response was a significant predictor of the insulin response, it accounted for only 23% of the variability in the insulinemina. This implies that many factors other than an increase in glucose influence the secretary response of insulin. This is certainly not a surprise to anyone familiar with β-cell physiology.

Another way of looking at the insulin response is to compare the insulin response with the response to 1 g carbohydrate. The result of this comparison does not fit well with the GI hypothesis that high-GI foods, such as potatoes, are “bad.” In fact, potatoes, baked beans, and lentils release insulin at rates of 284, 504, and 325 (pmol/L) ·g⁻¹ ·min⁻¹, respectively. Thus, of these foods, potatoes produce the least effect per gram carbohydrate (46).

Because the glycemic response can only predict 23% of the variability in the insulin response to an ingested food, other factors may be important. These factors include osmolality, gastric emptying, gut hormone release, and viscosity of gut contents (46); antecedent diet and degree of obesity (50); age (51); and even sex (12).
GI as the cause of disease

In recent years, the GI has been transformed by its popularizers from a potentially useful tool in planning diets for diabetic patients to a key player for the prevention of diabetes, dyslipidemia, cardiovascular disease, and even certain cancers in the general population. The debate concerns whether such a transformation is justified. That is, whether it is wise and reasonable to set as a public health policy for the entire population the avoidance of certain foods because of their high GI. To explore this question, one needs to examine the supporting data, their quantity and quality, their relation to causation, and the possible presence of confounders.

There are 2 theories about how high-GI foods increase food intake. The first is that it is a result of the elevation in glucose and the second, more commonly expressed recently, is that it is the result of a high insulin response. This high insulin response has been related to several phenomena: increased food intake leading to obesity (52), hyperinsulinemia leading to insulin resistance (53), β-cell exhaustion leading to type 2 diabetes (17, 54), dyslipidemia leading to coronary heart disease (CHD) (55), and unknown factors leading to certain kinds of cancers. What is the evidence for these suggested effects and how convincing is it?

Obesity

Single-meal studies

Several studies have examined whether a high postprandial glucose concentration is associated with satiety. In studies unrelated to the GI, results have generally shown that a high postprandial blood glucose concentration is associated with greater satiety (56–59). Also, several studies have tried to separate the effects of glucose and insulin on satiety (56–62) and most reported that glucose, rather than insulin, is the satiety signal.

Most of the data relating a high GI to increased food intake were collected in single-meal, experimental designs. The general pattern of investigation has been to give subjects a preload of a given carbohydrate food and observe the free food intake at a subsequent meal. Alternatively (and less satisfactorily), a preload was given but no measurement of meals followed; only a measure of hunger or satiety was ascertained by questionnaire.

Many of these studies used liquid preloads and sugars rather than starchy and some of the test meals that followed were liquid. At least 20 reports have measured hunger and satiety, but only 6 actually measured food intake.

Of the 20 studies that only measured subjective hunger or satiety rather than actual food intake, only 10 appear to be valid because they controlled for energy intake, energy density, and the palatability of the test meal (22, 24, 61, 63–69). In these studies, no consistent effect of a high-GI food compared with a low-GI food on hunger or satiety was shown. Four studies found a positive association between the high-GI food and greater hunger, reduced satiety, or both; 2 studies found a positive association between the high-GI food and greater hunger, reduced satiety, or both; and 4 studies found no difference. In 6 studies that actually measured intake at a subsequent meal, 3 found a significant effect of high-GI foods in increasing intake and 3 did not (64, 65, 68–71). Of the 3 that found significant effects, 2 compared only glucose and fructose, which is not a fair comparison of high- and low-GI foods because of other differential metabolic effects of these sugars that are unrelated to their GI effects.

Long-term studies

Long-term interventional studies are few, but worth reviewing, because the effect of a high- compared with a low-GI diet must surely be judged on the basis of its long-term effects on health and disease and not on the basis of a single-meal paradigm. The longest careful study was that by Kiens and Richter (72), who provided all food to lean volunteers who could eat as much as they wished for 30 d. After 30 d of consuming high- or low-GI diets in a crossover design, there was no difference in weight between the groups. This finding suggests that there was no significant difference in food intake between the groups. A shorter, 2-wk study, in which 6 healthy lean volunteers consumed high- or low-GI diets, also had no significant effect on body weight (9).

Insulin as a hyperphagic hormone

The experimental data that relates insulin to food intake suggest that insulin at physiologic concentrations reduces food intake (73). It is well known that insulin crosses the blood-brain barrier (74); that there are insulin receptors in the brain, and particularly in brain areas involved in energy homeostasis (75); that insulin suppresses food intake when injected directly into the brain (76); and that transgenic mice with a neuron-specific lack of insulin receptors become obese (77). Studies in rodents (78, 79) and primates (76) have shown that food intake and body weight decline when insulin is infused into the third ventricle.

Thus, there is no extant evidence that insulin at postprandial concentrations enhances food intake and body weight above normal. The belief that insulin increases body weight has grown out of the clinical experience of using large doses of insulin in type 2 diabetic patients. However, in these instances, insulin was given in amounts well above normal and systemically, not in the portal vein, which induces higher than usual circulating concentrations of the hormone. Also, investigators studying food intake regulation have given rodents large doses of insulin, enough to cause hypoglycemia, and have induced instances of overfeeding. However, nonphysiological amounts of the hormone were used. The theory that insulin, at physiologic concentrations, triggers weight gain has no evidence to support it (79). In fact, increased insulin secretion actually protects against subsequent weight gain in obese humans (80).

Postprandial hyperglycemia and hyperinsulinemia leading to insulin resistance

The argument has been made that the hyperglycemia and hyperinsulinemia produced by a high-GI diet lead to insulin resistance, and that insulin resistance then leads to the development of diabetes, coronary artery disease, and other features of Syndrome X (81). This is a puzzling charge, given the available experimental data.

Two relatively long metabolic studies compared the association between high- and low-GI diets and increasing insulin resistance, one of which was the previously mentioned study by Kiens and Richter (72). In that study, healthy young men were fed isoenergetic high- or low-GI diets for 30 d. The mean GI for the low-GI diet was 24 units lower than that of the high-GI diet. The carbohydrate contents of the 2 diets was kept the same. Euglycemic hyperinsulinemic clamp procedures were performed before and at the end of the dietary study. Fasting glucose, fasting insulin, and fasting triacylglycerol concentrations were no
A HIGH GI AND DISEASE: EVIDENCE FROM EPIDEMIOLOGIC STUDIES

Epidemiologic studies have been the primary impetus for the contention that high-GI diets lead to disease. The main epidemiologic studies purporting this contention are the Nurses’ Health Study and the Health Professionals’ Follow-Up Study (16, 17, 54). The Nurses’ Health Study is a large, prospective cohort study of US women followed for several years, the duration depending on the study being reported. The cohort contained 121,700 female registered nurses aged 30–55 y at enrollment, residing in 11 states. Nutritional and outcome data were collected by means of mailed questionnaires. The Health Professionals’ Follow-Up Study is another large, prospective longitudinal study of diet and lifestyle in relation to chronic diseases among 51,529 men aged 40–75 y at baseline in 1986 (54, 90). In the Nurses’ Health Study, in 1980, a 61-item food-frequency questionnaire (FFQ) was used. In 1984, the questionnaire was expanded to 116 items. Similar questionnaires were again used in 1986 and 1990. The 1986 questionnaire was used as baseline and was completed by only 75,543 women. Women with ≥11 questionnaire items left blank, a total energy intake of <2,512 or >14,654 kJ/d, or previously diagnosed disease (changing according to the report) were excluded. The final number of subjects valid for analysis was 65,173.

In the Health Professionals’ Follow-Up Study, the FFQ given in 1986 included 131 items. Men were excluded if 70 of 131 total food items were left blank (even though “almost never” eaten was an option in the questionnaire). Thus, the persons who filled out the FFQs could ignore 61 of 131 items and still qualify. Persons reporting a calculated intake of <800 or >4,200 kcal/d (54) were excluded. Also excluded were persons with a history of a disease that might have induced them to modify their diet. For the diabetes study, 42,759 men were found eligible and were followed for 6 y.

The FFQ required participants to estimate portion sizes and write down how often they ate a particular item of a particular size during the previous year. The authors stated that the reproducibility and validity of the FFQ were acceptable and provided information to support this contention in 5 validation reports (91–95). The validation plan has been the same for both men and women. A very small sample was chosen for the validation: 323 of 51,529 men (95) and 225 of 75,543 women (92). This was clearly not a representative sample, but a convenience sample in the Boston area. Of this sample, not all agreed to participate: only 127 men and 150 women did so. Two 1-wk diet records were kept on 6–7 mo apart by the men and 4 were kept by the women in a given year. The first week’s record was taken ≥3 mo after the first FFQ was administered and the second week’s record ≥2–3 mo before the second FFQ was administered. Of the 1565 unique diet-record food codes, 348 were eliminated, “usually because they were not consumed frequently in this population” (95). Also, it is stated that “because of the small number of subjects (n = 127) relative to the number of food items, we collapsed the individual food items into 40 predefined food groups” (95). Some of the items collapsed into one category were all whole grains, all refined grains, all cold breakfast cereals, all fruit, and all fruit juices. It is difficult to believe that such a wholesale collapse of individual foods into large categories could produce a reliable measure of the GI of a diet. For example, Holt et al (46), who measured the GI of foods and placed them in categories, found a statistically significant difference.
between the foods within such food categories. Pearson correlation coefficients between the FFQs and the dietary records, corrected for week-to-week variation, ranged from 0.45 to 0.74. The actual dietary GI and the global dietary glycemic load were derived from the FFQs as follows:

\[
\text{Average dietary GI} = \frac{[\text{carbohydrate content of each food item}] \times (\text{number of servings/d}) \times \text{(GI)}}{\text{daily carbohydrate intake}}
\]

(1)

Global dietary glycemic load = \((\text{carbohydrate content of each food item}) \times (\text{number of servings/d}) \times (\text{GI})\)

(2)

Salmeron et al (17) stated that “the glycemic index, as a relative measure of glycemic response to a given amount of carbohydrate, does represent the quality of carbohydrate but does not take into account the quantity,” whereas “In contrast, the total glycemic load represents the combination of quality as well as quantity of carbohydrate consumed, and may be interpreted as a measure of insulin demand.” Let us look, then, at how these 2 values are calculated. The carbohydrate content of each food item was taken from food tables; however, we know that the carbohydrate content of a food varies. Clearly, the portion size is crucial to knowing the actual carbohydrate content. How is the portion size a person eats calculated? The person estimates it; the question gives “standard portions.” The person also estimates the number of servings of the food item per year, and this amount is reduced by the investigators to the number of servings eaten per day. Finally, the GI is estimated for the particular food item from a table (for which a reference was not given). This estimate is then divided by the total amount of carbohydrate eaten per day, again derived from the FFQ, consolidating the carbohydrate contents of all foods eaten per year and reduced down to the amount eaten per day.

Thus, 4 very imprecise numbers are derived, 3 of which are then multiplied and divided by the fourth number. This process magnifies the imprecision even more. These values are then used to extrapolate to the effect of these nutrients on the development of disease. In addition, only one year’s FFQ was used for the analysis in the diabetes studies—the one provided shortly after entry into the study. It is assumed that the diet then stays constant for the next 10 or more years, during which the appearance of disease is tracked. The persons being followed in these studies are all health professionals. Is it not possible that many would change their diet depending on the prevailing recommendations of the day? Can one be sure that these cohorts have maintained the same diets that they reported consuming 10 or more years before? In fact, one study suggests that over the period of the study, the nurses’ diets improved significantly (96).

I believe that the final numbers derived for use in these widely quoted studies are extremely imprecise. In a laboratory-based report, the reliability of these measures would never be accepted, and the validation done would be considered inadequate. Tseng (97) identified the validation problem as follows: “validation of FFQ-based dietary patterns against dietary record based patterns with use of scales derived from factor analysis based on the same food items is comparable with validation of a scale against the same scale with individual items measured more accurately. In essence, the validation strategy presumes that the item level data are valid and uses these data rather than an independent indicator of each food pattern.”

Despite the caveats in the methods used to derive the data from these prospective studies, let us look at the results of these studies concerning the development of diabetes. Categorized by quintiles of the GI of the diet eaten, the dietary glycemic load (ie, the measure of insulin demand) of the women was not significantly different across the quintiles \((P < 0.09)\). The average dietary GI showed a significant trend \((P < 0.04)\). In the men, neither the glycemic load \((P = 0.83)\) nor the GI \((P = 0.12)\) was significantly different across the quintiles. These are hardly convincing data.

It is also somewhat puzzling that there was no significant effect of the total amount of carbohydrate eaten on the development of diabetes in these 2 studies. One would think that if the glycemic load were the culprit, the insulin demand would have been greater the greater the carbohydrate intake and significantly correlated with the disease.

The results of several other long-term longitudinal studies do not agree with the above findings about the risk of the development of type 2 diabetes. These studies reported that populations ingesting a high-carbohydrate diet, which results in higher post-prandial glucose concentrations and higher insulin demand, actually have a lower level of insulin resistance, diabetes mellitus, and cardiovascular disease. In the San Luis Valley Diabetes Study (98), for instance, a high-fat, low-carbohydrate diet, which by definition has a lower glycemic load, is associated with a higher incidence of diabetes than is a higher-carbohydrate diet that has a higher glycemic load. Also, in the Iowa Women’s Health Study (99), no significant effect of high-carbohydrate diets on diabetes incidence was found.

Ecologic (100–103) and cross-sectional (98, 104) studies have also shown that a high-fat, low-carbohydrate diet increases the risk of diabetes. A case-control study by Himsworth and Marshall (105) and several prospective studies (106–108) also suggest that a high-fat, low-carbohydrate (ie, a low glycemic load) results in a higher incidence of diabetes.

What about the evidence for the development of CHD? In the Nurses’ Health Study, glycemic load and GI were significantly related to risk of CHD \((P < 0.0001; 16)\). However, in reporting trends in CHD in relation to diet (96), the authors stated that the incidence of heart disease decreased during the study period, yet the glycemic load of the diet increased significantly \((P < 0.001)\). How does these findings fit with their conclusions in the earlier report? Alternatively, the Puerto Rico Heart Health Program (109) showed that persons with a high carbohydrate intake (and thus a greater glycemic load) have a lower risk of CHD. Although the data on the association between the GI and the risk of CHD are intriguing and need to be followed up, the present data seem insufficient to warrant a public health recommendation.

### RANGE OF GIs IN THE POPULATION

The GI quintiles for women in the Nurses’ Health Study (17) and for the men in the Health Professionals’ Follow-Up Study (54) are shown in Table 1. From the lowest to the highest quintile, the difference in GIs for women is only 13 units (from 64 to 77) and for men is 14 (from 65 to 79). The confidence limits for each quintile are wide. Because we know that the GIs for starches cluster in a relatively small range, it seems both impractical and unreasonable to try to move the GI down a few units for the US population. Furthermore, the quintiles reported in these 2 studies indicate that persons who con-
TABLE 1
Median glycemic index quintiles of women in the Nurses’ Health Study and of men in the Health Professionals’ Follow-Up Study

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1 From reference 17.
2 From reference 54.

sume a diet with the highest GI also consume the highest amount of carbohydrates, both in total grams and as a proportion of the total macronutrient content. Can we be sure that changing the GI will have the desired effect if the total carbohydrate intake, and thereby much of the glycemic load of the diet, stays the same?

EPIDEMIOLOGIC STUDIES AND CAUSATION

By its nature, an epidemiologic study can detect an association between 2 variables but cannot prove causation. To make public health decisions about what the optimal diet is for a population, some scientific evidence of cause and effect should be available. Although a certain amount of evidence can be accrued from investigations using animal models, epidemiologic studies, and clinical investigations, only controlled clinical trials can provide proof of causality (110).

Controlled clinical trials are expensive and difficult to conduct. As a result, epidemiologic studies take on more importance because of the lack of more definitive information. However, we must be assured that the methods used in epidemiologic studies are sound and that we can trust the results obtained as being relatively definitive. I do not have faith in the results of the studies mentioned previously that used FFQs. I am not convinced that the methods used in these studies were sound. The database used to derive the GIs is fraught with uncertainty and irreproducibility.

Because of the many uncertainties regarding the validity of the GI for determining what foods are “good” or “bad” for one’s health, I believe it would be a mistake to initiate a public health campaign stating that certain widely consumed carbohydrates should be avoided. Much more definitive data are needed before any such dietary recommendations are made and controlled clinical trials are the best way to proceed.

There are many more worthwhile issues relating to diet and health that merit the focus of a public health effort. The prevention of type 2 diabetes is a critical public health priority given that the prevalence of diabetes in the US population has increased from 8.9% to 12.3% in 11 y (111), and continues to increase (112). The rate of obesity, a primary predictor of diabetes, is skyrocketing (113). As a matter of public health, the message is clear: decrease the incidence of cardiovascular disease, lifestyle changes total energy intakes and increase physical activity (114). To decrease the incidence of cardiovascular disease, lifestyle changes total energy intakes and increase physical activity (114). To decrease the rate of obesity, a primary predictor of diabetes, is skyrocketing (112). The rate of obesity, a primary predictor of diabetes, is skyrocketing (113). As a matter of public health, the message is clear: decrease the incidence of cardiovascular disease, lifestyle changes total energy intakes and increase physical activity (114). To decrease the incidence of cardiovascular disease, lifestyle changes total energy intakes and increase physical activity (114). To decrease the incidence of cardiovascular disease, lifestyle changes total energy intakes and increase physical activity (114). To decrease the incidence of cardiovascular disease, lifestyle changes total energy intakes and increase physical activity (114). To decrease the incidence of cardiovascular disease, lifestyle changes total energy intakes and increase physical activity (114). To decrease the incidence of cardiovascular disease, lifestyle changes total energy intakes and increase physical activity (114).

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