Informing food choices and health outcomes by use of the dietary glycemic index

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Abstract

Considerable epidemiologic evidence links consuming lower glycemic index (GI) diets with good health, particularly upon aging. The GI is a kinetic parameter which reflects the ability of carbohydrate (CHO)-contained in consumed foods to raise blood glucose in vivo. Newer nutritional, clinical, and experimental data link intake of lower dietary GI foods to favorable outcomes of chronic diseases, and compel further examination of the record. Based upon the new information there are 2 specific questions: 1) should the GI concept be promoted as a way to prolong health, and 2) should food labels contain GI information? Further, what are the remaining concerns about methodological issues and consistency of epidemiological data and clinical trials that need to be resolved in order to exploit the benefits of consuming lower GI diets? These issues are addressed in this review.

Introduction

Most people desire a long, healthy and productive life. Average life expectancy has increased in many parts of the world, but projections suggest alarming increases in the...
numbers of people who will be afflicted by age-related diseases such as type 2 diabetes, coronary heart disease (CHD), age-related macular degeneration (AMD) and cataracts. Given the personal and societal burdens associated with health-compromised longevity, as well as lack of adequate medical care in many parts of the world, it is imperative to find means to extend healthy life, preferably at low cost. Recent studies indicate that the types or quality of carbohydrate foods consumed by an individual have a major impact on health. Specifically, consuming diets that favor slowly-digested carbohydrates (CHO) has been associated with reduced risk of coronary heart disease (CHD), type 2 diabetes, AMD and some types of cataract even in the ~90% of our population that is nondiabetic.\textsuperscript{1–17} Slowly-digested CHOs release glucose into the blood more gradually than rapidly-digested CHO. Thus, the tissues that appear to benefit from more slowly digested CHO are highly oxygenated with rapid blood flow, such as the heart, brain and retina, and those in low oxygen tension without direct blood supply, such as the eye lens.

The metabolic diversity of the tissues that are affected by dietary CHO intake suggests that the relationship between dietary CHO and cellular homeostasis is of fundamental physiological importance. Moreover, these benefits may be achieved with only minor modification of CHO intake. To facilitate the evaluation and choice of CHO-containing foods that optimize health we summarize results from clinical and epidemiologic studies that relate risk for common age-related diseases to glycemic index (GI) and glycemic load (GL). We will also discuss issues and concerns which require resolution before the GI concept is reconsidered as a guide to food choice.

GI is widely known,\textsuperscript{18, 19} but its use has been controversial.\textsuperscript{20–22} Methodologically, GI is defined as the incremental area under the blood glucose response curve (AUC) within a two hour period elicited by a portion of food containing 50 g of available CHO, relative to the AUC elicited by 50 g glucose. Thus, the GI is a kinetic parameter that reflects the potency of foods to raise blood glucose and rates of glucose clearance. The GI of a particular diet is determined by averaging the GI values of the food items, statistically weighted by their carbohydrate contribution. Diets with the same amount of CHO but that have different GI are to be distinguished from diets which have higher or lower amounts of CHO but for which GI may be the same. A related metric, GL, is defined as GI×w/100, where w is the grams of available CHO contained in the amount of food consumed.\textsuperscript{8} A high CHO diet in which the majority of CHOs are derived from high GI foods, has the highest GL. However, it is likely that high-GL diets have differential physiologic effects from country to country. For example, in the US high-CHO diets are most often dominated by high-GI foods, but in Scandinavian countries high-CHO diets include many low-GI staples.\textsuperscript{23} This may result in geographic or ethnic differences in associations between dietary GL and risk for diseases.\textsuperscript{24}

**Dietary glycemia and risk for type 2 diabetes**

With greater availability of energy-rich foods and the rising prevalence of obesity, type 2 diabetes and associated complications are increasing alarmingly. Currently afflicting 8% of our population and associated with annual expenditures of $159 billion/y in 2007, a 30% increase to 22.8 million Americans is expected by 2025.\textsuperscript{25} The global prevalence of type 2 diabetes is expected to rise to 329 million affected people by 2030. Type 2 diabetes is characterized by insulin resistance and reduced responsiveness of the pancreatic islet cells to glucose, ultimately leading to hyperglycemia and the development of clinical diabetes. In animal models, hyperglycemia contributes to insulin resistance and defects in insulin secretion.\textsuperscript{26–28} Thus, dietary factors that decrease plasma glucose and insulin demand could plausibly decrease the risk of type 2 diabetes.
Positive associations were obtained in seven of the eleven prospective epidemiologic studies that examined the relation between GI and risk of type 2 diabetes (Fig. 1). The GL was also positively associated with diabetes (Fig. 2) and this finding was confirmed based on 20 years of follow-up. Methodological difficulties might explain the four studies with null findings. Stevens et al. used an abbreviated food questionnaire that deliberately focused on dietary fat rather than carbohydrate. Sahyoun et al. included only 99 cases of diabetes. The Whitehall II study used dietary information collected from only one baseline questionnaire to relate to diabetes incidence in 13 years.

In a recent meta-analyses summarizing studies of GI and GL in relation to risk of type 2 diabetes, Barclay calculated 40% and 27% higher summary RRs when comparing the highest with lowest quartiles of GI (95% CI: 1.23, 1.59; P < 0.0001) and for GL (95% CI: 1.12, 1.45; P < 0.0001), respectively. All the studies included in this meta-analysis were adjusted for fiber. Findings from the Black Women’s Health Study and the Shanghai Women’s Health Study provide valuable evidence that the adverse effects of GI and GL also apply to non-Caucasian ethnic groups. In summary, although not every study found positive associations between GI and GL and risk of type 2 diabetes the overall epidemiologic evidence strongly supports a positive relationship.

Although there have been no clinical trials to determine whether low-GI or low-GL diets can prevent diabetes, the effect of dietary CHO on comorbidities of diabetes has been investigated. Importantly, those who develop diabetes are unable to compensate for increased age-related insulin resistance by secreting more insulin. In normal subjects and subjects with impaired glucose tolerance, as well as in patients with diabetes or CHD, low-GI diets limit reductions in insulin sensitivity and reduce insulin secretion. Further, a meta-analysis of 14 randomized trials of people with diabetes indicated that glycated proteins (HbA1c or fructosamine) were reduced 7.4% (95% CI, 8.8-6.0) more on a low-GI diet compared to a conventional diet with a higher GI after adjusting for baseline differences. In another meta-analysis of 11 relevant randomized controlled trials, the benefit of a low-GI diet on improving glycemic control in diabetes is further confirmed. The analysis also concluded that episodes of hypoglycemia were significantly fewer with low- compared to high-GI diets. In a recent trial among patients with type 2 diabetes, a low-GI diet, compared with a high-fiber control diet, improved HbA1c. However, neither a lower GI diet nor a lower CHO (higher mono-unsaturated fat) diet improved HbA1c in patients with near-normal HbA1c and only the lower-GI diet elicited sustained reductions in postprandial glucose and C-reactive protein. These data suggest that diabetics gain more salutary advantage than non-diabetics from low-GI diets and low-GI diets confer additional advantage compared to high-fiber diets.

Acarbose is a drug which can delay CHO digestion by inhibiting intestinal glucosidase and thus mimic the effect of a low-GI diet. Use of acarbose, reduced diabetes risk in a randomized trial. This data also implies that an aspect of low-GI diets other than high fiber is related to their salutary advantage. Overall, available experimental evidence corroborates the findings from epidemiologic studies that low GI/GL are associated with reduced risk of type 2 diabetes.

Animal Tests

Rats in which diabetes was modeled by partially pancreatectomy, feeding of a high- versus low-GI diet for 18 weeks showed decreased glucose tolerance and plasma adiponectin, doubled body fat, increased plasma triglyceride concentrations and exacerbated fibrosis of the pancreatic islets.
Epidemiologic evidence regarding GI/GL and cardiovascular disease

Over 16 million people are affected by CHD, the cause of ~20% of deaths and associated costs of ~$165 billion in the US in 2006. Insulin resistance increases multiple risk factors for cardiovascular disease (CVD), a broad category of circulatory diseases which affect the heart and blood vessels. These risk factors include dyslipidemia, hypertension and hyperglycemia, and many of the same dietary factors that are related to enhanced risk for diabetes also appear to be related to higher risk of CHD. The relation between GI and GL and incidence of CVD has been examined in five prospective studies (Fig. 3 and Fig. 4). GL has been related to a higher risk than GI. In a large female American cohort, a high dietary GL was associated with markedly increased risk of CHD, independent of conventional CHD risk factors over 10 years of follow-up and a 90% increased risk after 20 years of follow-up (Fig. 3). In a Dutch female cohort, there was a 47% increased risk of CVD in women followed up for 9 years (Fig. 3). However, results from a much smaller study following 646 elderly Dutch men for 10 years did not corroborate these observations (Fig. 3). In a cohort of Italian men (n=15 171) and women (n= 32 578) originally recruited to the European Prospective Investigation into Cancer and Nutrition study, after a median of 7.9 years of follow-up, high dietary GL (RR=2.24; 95% CI: 1.26, 3.98) and high carbohydrate intake from high-GI foods (RR=1.68; 95% CI: 1.02, 2.75) increase the overall risk of CHD in women but not men. In a cohort of 36 246 Swedish men aged 45–79 y without diabetes or prior cardiovascular disease, after 8 years of follow-up dietary GI and dietary GL were not associated with ischemic cardiovascular disease or mortality, but dietary GL was associated with a greater risk of hemorrhagic stroke (RR = 1.44 comparing extreme quartiles; 95% CI: 0.91, 2.27; P for trend = 0.047). The authors concluded that the discrepancies between these findings and those of previous studies may be due to variations in the associations by sex or to differences in dietary contributions to GI and GL. Compared with other US cohorts, such as the NHS cohort, these Swedish men had much higher cereal fiber intake (6.2 g per 1000 kcal compared with ~2–3 g per 1000 kcal in the NHS) and physical activity (approximately twice as much time as the NHS). In a meta-analysis of CVD, there were 25% higher summary RRs for GI. Corroborating the epidemiologic data above, high-GI or GL diets were found to be strongly and inversely associated with risk factors for CHD, including reduced HDL levels and increased insulin resistance, metabolic syndrome and C-reactive protein. Another meta-analysis also lists foods with a high GI or GL as harmful factors.

Intervention studies regarding GI/GL and metabolic risk factors for coronary heart disease

There have not been randomized trials in humans using CHD as the end point, however, evidence indicates that diets high in CHO can increase plasma levels of triglycerides and reduce HDL cholesterol, both of which are risk factors for CHD. Further, partial replacement of CHO with either protein or unsaturated fat improved CVD risk factors. Three controlled intervention studies show that low-GI diets reduced levels of plasminogen-activator inhibitor-1 (PAI-1), a marker of thrombogenicity, in overweight as well as diabetic adults.

Age related macular degeneration and cataract

Age-related macular degeneration (AMD) blinds 7% of our elderly and at present there is no widely practicable treatment for the 500,000 people affected or those who will be stricken. Cataract, or opacification of the eye lens, afflicts over 50% of our elderly and in the less developed world there is insufficient capacity to surgically remove the clouded lens. In the US the annual direct and indirect costs associated with AMD and cataract are approximately $15 billion. By 2020 it is anticipated that the number of people blinded from AMD or who will need medical attention due to cataract will double to 3 and 30 million,
respectively. These data provide a clear mandate to avert these epidemics. Importantly, recent epidemiologic studies consistently indicate that consuming low-GI diets is associated with lower risk for onset and progress of AMD in apparent healthy people (Fig. 5). A high-GI diet was associated with ~2.7-fold increased risk for early AMD indicators in a Boston female cohort and an over 40% increased risk for later stages of AMD in a large American cohort. Furthermore, the risk for AMD progression was 10% higher for those in the upper 50% of GI group than those in the lower 50%. It was estimated that 20% of existing cases could have been eliminated and 7.8% of new advanced AMD cases would be prevented in 5 y if people consumed a low-GI diet. This could save over 100,000 cases of AMD-related blindness in the US in 5 years. Similarly, in an Australian cohort followed for 10 years, a higher GI was related to 69% increased risk for early AMD. Interestingly, consuming low-GI diets appears to provide ophthalmic benefit in addition to that gained from consuming higher levels of antioxidants (including vitamins C and E, and lutein/zeaxanthin), zinc, and omega-3 fatty acids (including docosahexaenoic acid and eicosapentaenoic acid).

The risk for the two major forms of cataract, cortical and nuclear, was found to be associated with CHO nutrition but the specifically correlated measure of CHO is inconsistent across studies (Fig. 6 and Fig. 7). The risk for cortical opacities was related to the quantity of CHO but not GI in two American cohorts. In comparison, Tan et al. observed a 77% greater risk for developing cortical cataract in an Australian cohort with a higher dietary GI. As for nuclear cataract, while the Australian cohort showed no association with either the quantity or GI, a 29% increased risk for moderate opacities was related to a higher GI in a large American cohort. The difference between CHO measures and associated pathologies may suggest subtle pathophysiologic mechanistic differences as well as differences in composition, structure, homeostatic system, micro-environment, and function between metabolically different regions within tissues.

Mechanistic links between dietary hyperglycemia and loss of glucose homeostasis are evolving. Among the major etiological mechanisms is damage due to glycation by various sugars or their metabolites. Such glycation renders proteins cytotoxic and insoluble. Glycated proteins accumulate in drusen, which are precursors of AMD, as well as in cataractous precipitates. Such glycation can also compromise the proteases that are involved in the recognition and removal of glycated proteins. Together these dysfunctions render cells more vulnerable to oxidative and inflammatory stresses which are etiologically related to AMD and cataract.

Methodologic Issues regarding GI measurement

Comparison of GI and other measures of CHO intake

There are several ways to measure carbohydrate content of foods, particularly as it affects physiology and biochemistry. Whereas total CHO content of a food sums simple sugars, starch, resistant starch, fiber, etc, in terms of chemical composition, the GI indicates the extent to which the CHO in the food alters glucose levels in blood. It is incorrect to assume that all simple sugars have a high GI or that “complex” CHO, whole grains or high fiber foods have a low GI. Here we examine why numerous methodological factors may alter measures of glycemic responses and we emphasize that factors which are used to classify glycemic responses are not necessarily the same factors that are important for measuring GI.

Subjects and the GI measure—The use of the GI is predicated on the GI being a property of the food, not a property of the subject in whom it is measured. The subjects can be thought of as the analytical instruments used to measure GI. Many of the concerns raised...
by researchers regarding inconsistencies in GI measurements may be mitigated if the same
data base, with complete and accurate dietary data, is used to compare subjects within the
same cohort. Furthermore, the GI result should be repeated several times on appropriate
groups of 10 or more subjects with normal gastrointestinal function, using standardized
conditions, and with an average within-subject coefficient of variation (CV) of less than
30% and the results averaged. Using such conditions, two inter-laboratory studies
involving 28 laboratories around the world showed that the current method for
measuring GI is reliable enough to be able to distinguish a low-GI food (GI 55 and below)
from a high-GI food (GI 70 and above).

It has been shown that the GI values obtained for the same foods are roughly similar in an
ethnically and physiologically wide variety of subjects.

**Test Meals:** It is recommended that 50 g available CHO be used as a test portion. Available
CHO is defined as total CHO minus dietary fiber and other CHO that does not get absorbed
in the intestine. GI values reflect the context and formulation of the food including the
amount of a food consumed, size of the food particle swallowed, viscosity, extent of
digestion and absorption, addition of other components such as fat, cooking times and
temperatures, etc and variations in these parameters may account for some inconsistencies
of GI measurements for the same food item. Although GI is usually tested on individual
foods, there are methods described whereby the GI and GL of meals and habitual diets can
be estimated. Timing of ingestion and associated liquid are also factors in GI measures.
Liquid meals (250ml) should be consumed within 5–10 minutes and solids and semisolids
should be ingested within 10–15 minutes. Subjects should drink at least 250 ml with each
test meal.

**Blood sampling and analysis:** It is recommended that blood samples for GI measures be
obtained from finger-prick capillary blood samples the morning after an overnight fast
(immediately before starting to eat) and at 15, 30, 45, 60, 90 and 120 minutes after starting
to eat the test meal. Glucose in whole blood, serum or plasma (consistent method for all
tests) should be measured with an acceptable analytical precision, i.e. CV<3%.

**Calculations:** A recent study showed that over 50% of laboratories did not report correct
values for AUC. The GI value of each test food should be the mean of the values of: 100×
(AUC elicited by the test food)/(AUC elicited by the reference food) in the same subject.
Values which are >2 standard deviations from the mean should be excluded. Final GI values
should be expressed on the glucose scale, i.e. the GI of glucose = 100.

**Advantages of surrogate markers:** Additional biomarkers that reflect GI exposure or
susceptibility and surrogate endpoints for clinical diseases may be helpful. For
example, in normal weight healthy Japanese women, HbA1c has been shown to correlate
with the GI of the diet and could be used as a predictor of CVD risk. The discovery of
more biomarkers will contribute to our understanding of the mechanisms and facilitate the
development of dietary guidelines and potential therapeudic agents. For example, we found
that individuals with bilateral AMD progression are more affected by GI than those who had
unilateral AMD progression. Susceptibility biomarkers will be useful to elucidate the
underlying mechanisms and can be used to identify high-risk populations. Clearly, it is
essential that future studies address environment-GI, nutrient-GI, gene-GI interactions, as
well as competing risks among diseases on GI-disease associations to identify individuals
who are particularly susceptible to the adverse effect of high GI/GL diets.
Conclusion

It appears that concepts and methods regarding the GI are sufficiently mature to recommend preparing the population to implement it as a way to help choose healthier foods, particularly to those who are interested in diminishing risk for type 2 diabetes, CVD and age-related eye diseases. Our studies estimated that one can move from the higher to the lower risk group for AMD by daily replacing small quantities of white bread or potatoes with small amounts of foods with lower glycemic indices, such as foods with whole intact grains.\textsuperscript{74} Foods with intact whole grain should not be confused with whole wheat, the GI of which may not differ significantly from white flour based products. The benefit of consuming low-GI diets appears very attractive when such benefits can be gained by such a modest dietary change. Since the GI and GL are devised to measure the glycemic property of a food, regardless of its consumers, they could, in principle, be useful to include on food labels to allow consumers to make more informed food choices. However, in light of the significant procedural concerns noted in the methodological Issues section this is not recommended in the United States at present. There are additional hurdles that must be overcome before adapting GI measures on food labels. First, internationally accepted standards for GI measurement should be published. Consumer education about using this metric in choosing foods is essential. For example, consumers should be aware that GI is most informative when the primary constituent is CHO, not other nutrients. In attempts to alter the GI/GL of a food, the impact of the replacement macronutrient should be indicated together with the GI value. Indeed, because it is possible to “game” the GI, by replacing CHO with unhealthy fats, products may need to meet nutritional composition requirements to be eligible for GI testing. Additional concerns, including clarifying effects of processing the food on GIs, and variability of the GI of a food when it is eaten with different foods,\textsuperscript{94, 95} etc., can be allayed through scientific research. More comprehensive GI tables reflecting different local foods would be advantageous.\textsuperscript{19, 94, 96, 97} No single constituent or characteristic can be used to completely define the healthfulness of a food. “Dietary pattern” research may give valuable information about how to adjust or calibrate the dietary GI formulas.

After sufficient information regarding the issues above have been gathered, intensive public education programs will be essential to more effectively encourage people to adhere to healthier eating habits.

The combined collective data from long-term epidemiologic studies and randomized trials with metabolic indicators of glucose metabolism as endpoints provides strong evidence that optimizing dietary CHO will reduce the risk of type 2 diabetes, CHD, AMD and, probably, cataract. Encouragingly, this benefit can be achieved without needs for new technology and with modest dietary-behavior change. Greater understanding of processes and mechanisms which regulate rates of digestion and rates of glucose removal, including insulin responses will also inform the use of GI measures.\textsuperscript{98, 99}

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References


Fig. 1.
Studies relating glycemic index to type 2 diabetes.
Fig. 2.
Studies relating glycemic load to type 2 diabetes.
Fig. 3.
Studies relating glycemic index to cardiovascular disease.
Fig. 4.
Studies relating glycemic load to cardiovascular disease.
Fig. 5.
Studies relating glycemic index to age-related macular degeneration.
Fig. 6.
Studies relating carbohydrate nutrition to cortical cataract.
Fig. 7.
Studies relating carbohydrate nutrition to nuclear cataract.