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

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Considerable epidemiologic evidence links consuming lower glycemic index (GI) diets with good health, particularly upon aging. The GI is a kinetic parameter that 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 two 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.

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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 (CHOs) has been associated with reduced risk of coronary heart disease (CHD), type 2 diabetes, AMD, and some types of cataract even in the approximately 90% of the US population that is nondiabetic. Slowly digested CHOs release glucose into the blood more gradually than rapidly digested CHOs. Thus, the tissues that appear to benefit from CHOs that are digested more slowly are those that 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, this review summarizes results from clinical and epidemiologic studies that relate risk for common age-related diseases to...
glycemic index (GI) and glycemic load (GL). Issues and concerns that require resolution before the GI concept is reconsidered as a guide to food choice are also discussed.

The GI is widely known, but its use has been controversial. Methodologically, GI is defined as the incremental area under the curve (AUC) of blood glucose response that occurs within a 2-hour period and is 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 with different GI scores are to be distinguished from diets that 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. A high-CHO diet in which the majority of CHO is 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 United States, high-CHO diets are most often dominated by high-GI foods, but in Scandinavian countries, high-CHO diets include many low-GI staples. This may result in geographic or ethnic differences in the associations between dietary GL and risk for diseases.

**DIETARY GLYCEMIA AND RISK FOR TYPE 2 DIABETES**

With greater availability of energy-rich foods and the rising prevalence of obesity, the incidence of type 2 diabetes and associated complications are increasing alarmingly. In 2007, type 2 diabetes afflicted 8% of the US population and was associated with annual expenditures of $159 billion/year; by 2025, its incidence in the United States is expected to increase by 30%, with 22.8 million people affected. 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. Thus, dietary factors that decrease plasma glucose and insulin demand could plausibly decrease the risk of type 2 diabetes.

In 7 of the 11 prospective epidemiologic studies included in this review that examined the relation between GI and risk of type 2 diabetes, positive associations were reported (Figure 1). The GI was also positively associated with diabetes (Figure 2), and this finding was confirmed based on 20 years of follow-up. Methodological difficulties might explain the null findings of the remaining four studies. One possible reason for the lack of association in the Iowa Women’s Study is that the diagnosis of diabetes was recorded based
only on self report without confirmation. 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 in their study. 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-analysis summarizing studies of GI and GL in relation to the risk of type 2 diabetes, Barclay et al. calculated 40% and 27% higher summary RRs when comparing the highest with the lowest quartiles for 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’s on comorbidities of diabetes has been investigated. Importantly, individuals 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 7.4% (95% CI, 8.8–6.0) lower 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 beneficial effect of a low-GI diet on improving glycemic control in diabetes was further confirmed. The analysis also concluded that episodes of hypoglycemia were significantly fewer with low-GI diets in comparison with 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 monounsaturated 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 nondiabetics from low-GI diets and that low-GI diets confer additional advantage compared to high-fiber diets.

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

Figure 2  Studies relating glycemic load to type 2 diabetes. Data derived from references numbered in X-axis. Reference 8: 5th vs. 1st quintile. Reference 13: 5th vs. 1st quintile. Reference 14: 10th vs. 1st decile. Reference 33: 5th vs. 1st quintile. Reference 34: Meta-analysis. Reference 24: 5th vs. 1st quintile. Reference 32: 3rd vs. 1st tertile. Reference 11: 5th vs. 1st quintile. Reference 12: 5th vs. 1st quintile. Reference 31: 5th vs. 1st quintile.
Animal tests

In rats in which diabetes was modeled by partial pancreatectomy, feeding of a high-GI versus a low-GI diet for 18 weeks resulted in decreased glucose tolerance and plasma adiponectin, doubled body fat, increased plasma triglyceride concentrations, and exacerbated fibrosis of the pancreatic islets.53

Epidemiologic evidence regarding glycemic index/glycemic load and cardiovascular disease

It has been reported that over 16 million people in the United States are affected by CHD, and in 2006 CHD caused approximately 20% of deaths in the United States and was associated with costs of approximately $165 billion.54 Insulin resistance increases multiple risk factors for cardiovascular disease (CVD), which is a broad category of circulatory diseases that 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.55 The relations between GI and GL and incidence of CVD have been examined in five prospective studies (Figures 3 and 4), and GL was related to a higher risk than GI. In a large US cohort of females, a high dietary GL was associated with markedly increased risk of CHD, independent of conventional CHD risk factors, over 10 years of follow-up4 and a 90% increased risk after 20 years of follow-up (Figure 3).2 In a Dutch female cohort, there was a 47% increased risk of CVD in women followed up for 9 years (Figure 3).15 However, results from a much smaller study following 646 elderly Dutch men for 10 years did not corroborate these observations (Figure 3).56 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, 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) were found to increase the overall risk of CHD in women but not in men after a median of 7.9 years of follow-up.57 In a cohort of 36,246 Swedish men aged 45–79 years without diabetes or prior cardiovascular disease, dietary GI and dietary GL were not associated with ischemic cardiovascular disease or mortality after 8 years of follow-up, 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.23 Compared with other US cohorts, such as the Nurses’ Health Study (NHS) cohort, these Swedish men had much higher cereal fiber intake (6.2 g per 1,000 kcal compared with approximately 2–3 g per 1,000 kcal in the NHS) and amounts of physical activity (approximately twice as much as the NHS cohort). In a meta-analysis of CVD,34 there were 25% higher summary RR scores 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 levels58–61 and increased insulin resistance, metabolic syndrome,62 and C-reactive protein.63 Another meta-analysis

![Figure 3](image-url)
also listed foods with high-GI or -GL values as harmful factors.64

Intervention studies regarding glycemic index/ glycemic load and metabolic risk factors for coronary heart disease

No randomized trials in humans using CHD as the endpoint have been performed to date; however, evidence indicates that diets high in CHOs can increase plasma levels of triglycerides and reduce HDL cholesterol, both of which are risk factors for CHD.65 Further, partial replacement of CHOs with either protein or unsaturated fat improved CVD risk factors.66,67 Three controlled intervention studies found that low-GI diets reduced levels of plasminogen-activator inhibitor-1 (PAI-1), a marker of thrombogenicity, in overweight68 as well as diabetic adults.69,70

AGE-RELATED MACULAR DEGENERATION AND CATARACT

Age-related macular degeneration (AMD) blinds 7% of the elderly population in the United States and, at present, there is no widely practicable treatment for the 500,000 people affected or those who will be stricken.71,72 Cataract, or opacification of the eye lens, afflicts over 50% of the elderly worldwide, and in the less developed world there is insufficient capacity to surgically remove the clouded lens. In the United States, the annual direct and indirect costs associated with AMD and cataract amount to approximately $15 billion. By 2020, it is anticipated that the numbers of people blinded from AMD or who will need medical attention due to cataract will double to 3 and 30 million, respectively.73 These data provide a clear mandate to try to avert these epidemics. Importantly, recent epidemiologic studies consistently indicate that consuming a low-GI diet is associated with reduced risk for AMD onset and progression in apparently healthy people (Figure 5).4,6,7,16 A high-GI diet was associated with an approximate 2.7-fold increased risk for early AMD indicators in a Boston female cohort4 and an over 40% increased risk for later stages of AMD in a large US cohort.6 Furthermore, the risk for AMD progression was 10% higher for those in the upper 50% of a GI group than those in the lower 50%.7 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 years if people consumed a low-GI diet.6,7 This could result in the prevention of over 100,000 cases of AMD-related blindness in the United States in 5 years. Similarly, in an Australian cohort followed for 10 years, a higher GI diet was related to a 69% increased risk for early AMD,4,7,16 Interestingly, consumption of 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).74,75

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 (Figures 6 and 7). Risk for cortical opacities was related to the quantity of CHOs but not to
GI in two US cohorts.3,5 In comparison, Tan et al.17 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 of CHOs,17 a 29% increased risk for moderate opacities was related to higher GI in a large American cohort.5 The difference between CHO measures and associated pathologies may suggest subtle pathophysiologic mechanistic differences as well as differences in composition, structure, homeostatic system, microenvironment, and function between metabolically different regions within tissues.

Mechanistic links between dietary hyperglycemia and loss of glucose homeostasis are evolving. Among the

![Glycemic index and age-related macular degeneration](image1)

**Figure 5** Studies relating glycemic index to age-related macular degeneration. Data derived from references numbered in X-axis. Reference 4: 3rd vs. 1st tertile. Reference 6: Large drusen, 5th vs. 1st quintile. Reference 6: Advanced AMD, upper vs. lower 50%. Reference 7: All AMD progression, upper vs. lower 50%. Reference 7: Advanced AMD progression, 5th vs. 1st quintile. Reference 16: Indistinct soft or reticular drusen incidence, 4th vs. 1st quartile. Reference 16: Early AMD incidence, 4th vs. 1st quartile.

![Carbohydrate nutrition and cortical cataract](image2)

**Figure 6** Studies relating carbohydrate nutrition to cortical cataract. Data derived from references numbered in X-axis. Reference 3: Early opacity, total carbohydrate: 3rd vs. 1st tertile. Reference 3: Early opacity, dietary glycemic index: 3rd vs. 1st tertile. Reference 5: Moderate opacity, total carbohydrate: 4th vs. 1st quartile. Reference 5: Moderate opacity, dietary glycemic index: 4th vs. 1st quartile. Reference 17: Incident cataract, total carbohydrate: 4th vs. 1st quartile. Reference 17: Incident cataract, dietary glycemic index: 4th vs. 1st quartile.
major etiological mechanisms is damage due to glycation by various sugars or their metabolites. Such glycation renders proteins cytotoxic and insoluble.\textsuperscript{76–78} Glycated proteins accumulate in drusen, which are precursors of AMD, as well as in cataractous precipitates.\textsuperscript{79} 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,\textsuperscript{80–82} which are etiologically related to AMD and cataract.

**METHODOLOGIC ISSUES REGARDING GLYCEMIC INDEX MEASUREMENT**

**Comparison of glycemic index and other measures of carbohydrate intake**

There are several ways to measure the carbohydrate content of foods, particularly as it affects physiology and biochemistry. Whereas the 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 high GIs or that “complex” CHOs such as whole grains or high-fiber foods have low GIs.\textsuperscript{83} Examined here are ways in which numerous methodological factors may alter measures of glycemic responses, and it is emphasized that the factors used to classify glycemic responses are not necessarily the same factors that are important for measuring GI.\textsuperscript{22,84,85}

**Subjects and the GI measure.** 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 database, with complete and accurate dietary data, is used to compare subjects within the same cohort. Furthermore, the GI result should be repeated several times in appropriate groups of 10 or more subjects with normal gastrointestinal function, using standardized conditions, and with an average within-subject coefficient of variation of less than 30% and averaged results.\textsuperscript{84,86} Using such conditions, two interlaboratory studies involving 28 laboratories around the world\textsuperscript{85,87} 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.\textsuperscript{88}

**Test meals.** It is recommended that 50 g of 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

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{carbohydrate_nutrition_and_nuclear_cataract.png}
\caption{Studies relating carbohydrate nutrition to nuclear cataract. Data derived from references numbered in X-axis. Reference 3: Early opacity, total carbohydrate: 3rd vs. 1st tertile. Reference 3: Early opacity, dietary glycemic index: 3rd vs. 1st tertile. Reference 5: Moderate opacity, total carbohydrate: 4th vs. 1st quartile. Reference 5: Moderate opacity, dietary glycemic index: 4th vs. 1st quartile. Reference 17: Incident cataract, total carbohydrate: 4th vs. 1st quartile. Reference 17: Incident cataract, dietary glycemic index: 4th vs. 1st quartile.}
\end{figure}
formulation of the food, including the amount of a food consumed, the size of the food particle swallowed, viscosity, extent of digestion and absorption, addition of other components such as fat, cooking times and temperatures, etc.; variations in these parameters may account for some inconsistencies among GI measurements for the same food item. Although GI is usually tested on individual foods, there are descriptions of methods that estimate the GI and GL of meals and habitual diets. The timing of ingestion and associated liquid are also factors in GI measures. Liquid meals (250 mL) should be consumed within 5–10 min and solids and semisolids should be ingested within 10–15 min. Subjects should drink at least 250 mL of 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 min 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., coefficient of variation < 3%.

Calculations. A recent study showed that over 50% of laboratories did not report correct values for the AUC. The GI value of each test food should be the mean of the following values: 100 × (AUC elicited by the test food)/(AUC elicited by the reference food) in the same subject. Values that are more than 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 understanding of the mechanisms and facilitate the development of dietary guidelines and potential therapeutic agents. For example, it has been discovered that individuals with bilateral AMD progression are more affected by GI than those with unilateral AMD progression. Susceptibility biomarkers will be useful for elucidating the underlying mechanisms and can be used to identify high-risk populations. Clearly, it is essential that future studies address environment-GI, nutrient-GI, and 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 use the GI as a way to help choose healthier foods, particularly individuals who are interested in diminishing their risk for type 2 diabetes, CVD, and age-related eye diseases. Studies have 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. Foods with intact whole grain should not be confused with whole wheat, however, since the GI of whole wheat may not differ significantly from that of 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 who consumes it, they could, in principle, be useful for helping consumers make more informed food choices if they were included on food labels. However, in light of the significant procedural concerns noted in the methodological issues section of this article, the practice is not currently recommended in the United States.

There are additional hurdles that must be overcome before GI measures are listed on food labels. One primary requirement is the publication of internationally accepted standards for GI measurement. Consumer education about using this metric in choosing foods is also essential. For example, consumers should be aware that GI is most informative when the food’s 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 its GI value. Indeed, because it is possible to “game” the GI, by replacing CHOs with unhealthy fats, products may need to meet nutritional composition requirements to be eligible for GI testing. Additional concerns, such as clarifying the effects of food processing on GIs and the variability of a food’s GI when it is eaten with different foods, can be allayed through scientific research. More comprehensive GI tables reflecting different local foods would be advantageous. 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 outlined above has been gathered, intensive public education programs will be essential to effectively encourage people to adhere to healthier eating habits. The combined collective data from long-term epidemiologic studies and randomized trials using metabolic indicators of glucose metabolism as endpoints provide strong evidence that
optimizing dietary CHOs will reduce the risk of type 2 diabetes, CHD, AMD, and, probably, cataract. Encouragingly, this benefit can be achieved without the need for new technology and with modest dietary and behavioral changes. Greater understanding of the processes and mechanisms regulating rates of digestion and rates of glucose removal, including insulin responses, will also inform the use of GI measures.99,100

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