Review

Glycemic Index: Physiological Significance

Amin Esfahani, MSc, Julia M. W. Wong, PhD, Arash Mirrahimi, BSc, Korbua Srichaikul, BSc, David J. A. Jenkins, MD, PhD, Cyril W. C. Kendall, PhD

Department of Nutritional Sciences, Faculty of Medicine, University of Toronto (A.E., J.M.W.W., A.M., K.S., D.J.A.J., C.W.C.K.), Clinical Nutrition & Risk Factor Modification Centre, St. Michael's Hospital (A.E., J.M.W.W., A.M., K.S., D.J.A.J., C.W.C.K.), Toronto, Ontario, College of Pharmacy and Nutrition, University of Saskatchewan, Saskatoon, Saskatchewan (C.W.C.K.), CANADA

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The glycemic index (GI) is a physiological assessment of a food's carbohydrate content through its effect on postprandial blood glucose concentrations. Evidence from trials and observational studies suggests that this physiological classification may have relevance to those chronic Western diseases associated with overconsumption and inactivity leading to central obesity and insulin resistance.

The glycemic index classification of foods has been used as a tool to assess potential prevention and treatment strategies for diseases where glycemic control is of importance, such as diabetes. Low GI diets have also been reported to improve the serum lipid profile, reduce C-reactive protein (CRP) concentrations, and aid in weight control. In cross-sectional studies, low GI or glycemic load diets (mean GI multiplied by total carbohydrate) have been associated with higher levels of high-density lipoprotein cholesterol (HDL-C), with reduced CRP concentrations, and, in cohort studies, with decreased risk of developing diabetes and cardiovascular disease. In addition, some case-control and cohort studies have found positive associations between dietary GI and risk of various cancers, including those of the colon, breast, and prostate.

Although inconsistencies in the current findings still need to be resolved, sufficient positive evidence, especially with respect to renewed interest in postprandial events, suggests that the glycemic index may have a role to play in the treatment and prevention of chronic diseases.

Key teaching points:

- The glycemic index is a quantitative assessment of a food's carbohydrate content through its effect on postprandial blood glucose concentrations.
- Low glycemic index foods are those that elicit a low postprandial glucose response and include legumes (ex. chickpeas, lentils, etc.) and grains such as barley.
- The available scientific evidence, largely supports the notion that low glycemic index diets, through their effect on postprandial glycemia acutely and glycated proteins in the short to intermediate term may have some value in the management and prevention of type 2 diabetes.
- The evidence, although not unanimous, also demonstrates a protective effect for low glycemic index diets against heart disease. Larger, longer RCTs, show that low glycemic index diets were associated with higher serum HDL-C and lower levels of CRP.

INTRODUCTION

With the increasing prevalence of overconsumption and inactivity associated with the Western lifestyle, the increase in chronic diseases and their associated metabolic disorders continues to be a matter of great concern. This has resulted in continued interest in both diet and lifestyle modifications in prevention and treatment. One of the dietary approaches that may have relevance is the glycemic index (GI), a physiological classification of the available carbohydrate content in foods, first proposed in 1981 [1]. Since then, a number of epidemiological and clinical trials have shown that low glycemic index and glycemic load (GL) diets appear protective against chronic diseases, especially those that

Address correspondence to: David J. A. Jenkins, M.D., Ph.D., Department of Nutritional Sciences, Faculty of Medicine, University of Toronto, Toronto, Ontario, M5S 3E2 CANADA. E-mail: cyril.kendall@utoronto.ca

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relate to obesity, such as type 2 diabetes [2–6] and heart disease [7–11]. A recent meta-analysis of observational studies showed that low GI and low GL diets appeared to be protective not only for type 2 diabetes and coronary heart disease (CHD) but also for gallbladder disease and breast cancer [12]. This review will provide a brief overview of some of the current evidence linking the glycemic index with chronic disease.

THE GLYCEMIC INDEX AND GLYCEMIC LOAD

The glycemic index is determined by comparing the postprandial glycemic response of a food with the postprandial glycemic response to the same amount of available carbohydrate from a standard food in the same individual [1]. The original standard was glucose but later bread was used. This is because bread is a commonly consumed carbohydrate food and as such, it was more acceptable from the subject testing standpoint. Generally, 50 g of available carbohydrate from test and standard foods is tested by the same individual unless the volume of the test food is too large, in which case 25 g or less of available carbohydrate portions from both test and control foods is used. The actual glycemic index value is the area under the blood glucose curve (AUC) for the test food, expressed as a percentage of that of the standard control. The glycemic index of a food therefore depends on the food rather than on characteristics of the individual who consumes it [1,13]. If glucose was used as the reference food, the value is multiplied by 100/70 for conversion to the bread scale. Generally, in accordance with the bread scale, low glycemic index foods are those that have a glycemic index value lower than 70, and high glycemic index foods are those with values over 100 [14]. Factors that can affect the glycemic index of a food include the nature of the starch, particle size, pH, and the amounts of fiber, fat, and protein, in addition to cooking method and time [13].

The glycemic load examines the total impact of the dietary carbohydrate on postprandial glycemia. The glycemic load is the product of the glycemic index of the food or diet under study and the grams of available carbohydrate in that food or diet divided by 100 [3]. For a meal, GL is calculated by multiplying the mean glycemic index weighted according to the grams of total available carbohydrate by the grams in the meal or diet.

THE GLYCEMIC INDEX AND WEIGHT LOSS

Currently, in Western nations, obesity has been suggested to be the third most common risk factor for noncommunicable diseases such as heart disease [15]. Over the past 2 decades, the rate of obesity has reached epidemic proportions in developed nations and is increasing in developing ones. For instance, as of 2008, 26.6% of adults in the United States were classified as obese (body mass index [BMI] greater than 30 kg/m^2), and another 36.5% were considered overweight (BMI 25.0 to 29.9 kg/m^2) [16]. Recently, because of the possible link to satiety and metabolism, a number of studies have focused on the role of glycemic index and glycemic load in weight loss, although, as with other aspects of the glycemic index concept, the role of glycemic index in body weight control has been debated [17–20]. Despite the academic debate, major popular books and programs devoted to weight loss use the glycemic index concept as justification for their approach to body weight control (Atkins, Zone, South Beach, Montignac).

In 2007, a meta-analysis [21] that included 6 trials [22–27] concluded that low glycemic index and glycemic load diets resulted in statistically significant reductions of approximately 1 kg in weight, 1 kg in total fat mass, and 1.3 units in body mass index on comparison with control diets (either high glycemic index or low fat) in adolescents and adults ($p < 0.05$ for all 3 outcomes) [21]. Moreover, a recent meta-analysis by Livesey et al. [28], which included results from 23 studies that measured weight loss in low GI/GL diets, showed that body weight fell with reduction in dietary glycemic load and vice versa in studies where (1) subjects are under ''free-living'' conditions (*ad libitum*), and (2) food intake control is limited. However, this beneficial effect is not observed in studies where food intake is controlled [28]. Overall, studies in children and adolescents have demonstrated that the benefits of advice to reduce the glycemic load rather than advice to reduce fat and total calories in the diet is an effective tool in inducing weight loss [23,24,29]. The most recent of these studies have demonstrated that the 30 minute postprandial insulin level is an important determinant of weight loss on a low glycemic load diet, suggesting that the lower the dietary glycemic index, the greater the benefit for those who are overweight [29]. The role of insulin as a mediator is supported by findings in the Nurses' Health Study (NHS) cohort, which showed that in overweight females (BMI greater than 25 kg/m^2) in the second and third tertiles of glycemic load, increasing glycemic load predicted increased CHD risk [7]. Overall, however, long-term, large, randomized clinical trials with various degrees of overweight subjects and differing clinical approaches to weight loss control are required.

THE GLYCEMIC INDEX AND DIABETES

The prevalence of diabetes has increased dramatically over the past 3 decades, and current estimates predict a further 50% increase worldwide by the year 2030 [30]. According to the

American Diabetes Association (ADA), the primary objective in management of diabetes should be regulation of blood glucose levels [31]. Early studies, which looked at the acute impact of low glycemic index foods on postprandial glycemia, consistently demonstrated that low glycemic index foods reduce the peak postprandial blood glucose rise and as such lead to a lower incremental blood glucose area above baseline. Since then, a number of observational and clinical interventions have looked at the role of glycemic index in the management and prevention of diabetes. Most recently, the International Diabetes Federation has raised further awareness of the problems associated with uncontrolled postprandial glycemia [32].

Six epidemiological studies have looked at the effect of dietary glycemic index and GL on the risk of developing type 2 diabetes [2–4,33–35], and 1 trial studied the effect of glycemic index on the risk of developing gestational diabetes [5]. Of these 7 studies, 4 [2–5] showed a significant protective effect against the risk of developing diabetes with the lowest interval of dietary glycemic index intake. The other 3 studies did not find an association between the dietary glycemic index and glycemic load and diabetes [33–35]. Results from all of these studies were pooled in a recent meta-analysis [12], which suggested a protective effect of low glycemic index and glycemic load diets after assessing rate ratios for the risk of developing type 2 diabetes by comparing the highest versus the lowest quintile intakes of dietary glycemic index and glycemic load at 1.40 (95% CI 1.23 to 1.59) and 1.27 (95% CI 1.12 to 1.45), respectively [12].

A recent Cochrane Review that included 11 randomized controlled trials lasting between 4 weeks and 12 months in patients with diabetes (3 trials in type 1 patients, 7 trials in type 2 patients, and 1 trial in both) showed that low glycemic index diets by comparison with high glycemic index or other diets reduce protein markers of glycemic control [6]. Glycosylated hemoglobin (HbA1c) levels were reduced by 0.5% (95% CI −0.8 to −0.2; $p < 0.001$) [6]. This 0.5% reduction is clinically significant as it corresponds to decreases achieved with medication for newly diagnosed patients with type 2 diabetes [36,37]. Furthermore, according to the U.K. Prospective Diabetes Study (UKPDS), a 1% reduction in mean HbA1c levels corresponds to a 21% risk reduction for both deaths related to diabetes and any other endpoints related to type 2 diabetes [38]. Three other meta-analyses over the period of 2003 to 2009 have also indicated that low glycemic index diets improve glycemic control as assessed by glycated protein, serum fructosamine in shorter studies, or HbA1c in longer term studies [28,39,40]. Nevertheless, a recent larger, longer study failed to show a significant effect of a low glycemic index diet on HbA1c [41]. This may be attributed in part to the relatively low HbA1c of participants at baseline (mean 6.1%) and to the fact that they did not yet require oral hypoglycemic agents [41]. In contrast, a 6-month study in 210 type 2 diabetic subjects treated with oral antidiabetic agents, whose mean baseline HbA1c (7.1%) was minimally above the current treatment goal for individuals with longstanding diabetes, showed that a low glycemic index diet reduced absolute HbA1c levels by 0.5% (95% CI −0.61% to −0.39%) in comparison with a high fiber diet (−0.18%; 95% CI −0.29% to −0.07%; $p < 0.001$ between treatments) [42].

Available scientific evidence largely supports the notion that low GI/GL diets, through their effect on postprandial glycemia acutely and glycated proteins in the short to intermediate term, may have some value in the management and prevention of type 2 diabetes.

THE GLYCEMIC INDEX AND HEART DISEASE

Heart disease remains the leading cause of worldwide mortality [15]. Although evidence suggests that low glycemic index and glycemic load diets may indirectly reduce the risk of heart disease by modifying risk factors such as diabetes and obesity, evidence suggests that these diets may have additional protective effects against heart disease by modifying serum lipid levels [9–11]—an effect that has not been shown with most oral antihyperglycemic drugs [43–45]. The epidemiological evidence, although by no means unanimous, has suggested that low GI diets may be protective against heart disease [7,8,11]. A recent pooled analysis of cohort studies concluded that increased consumption of foods with high dietary glycemic index and glycemic load significantly elevated the risk of developing heart disease (relative risk [RR] 1.32; 95% CI 1.16 to 1.48) [46]. However, a number of cohort and observational studies have failed to show a beneficial effect for low glycemic index diets [47–49]. Results from the Zutphen Elderly Study in men suggested that glycemic index and GL are not associated with heart disease (RRs 1.11 and 1.33 for highest vs. lowest tertile of dietary glycemic index and GL, respectively) [47]. However, when the results of this study were pooled with those of the NHS in a recent meta-analysis, glycemic index but not glycemic load was still associated with a protective effect against the risk of developing heart disease (RR 1.25; 95% CI 1.00 to 1.56 for high glycemic index vs. low glycemic index) [12]. Furthermore, even though the study by Levitan et al. [49] did not show an association between glycemic index, glycemic load, and ischemic cardiovascular disease (CVD), investigators did find that the highest quartile of dietary GL increased the risk of hemorrhagic stroke (RR 1.44; 95% CI 0.91 to 2.27; $p = 0.047$).

In addition, observational studies have found a link between glycemic index and glycemic load and biomarkers

of CHD, such as high-density lipoprotein cholesterol (HDL-C). Low serum HDL-C concentrations are associated with a higher risk of developing CHD [50]. Both Ford et al. and Frost et al. found that dietary glycemic index/load was inversely associated with serum HDL-C levels [9,10]. These results were supported by an analysis of the NHS cohort, which showed that dietary GL was inversely linked to serum HDL-C [11]. Low glycemic index/load diets have also been linked to lower levels of C-reactive protein (CRP) [51], a marker of inflammation, elevated levels of which have been linked with the risk of developing type 2 diabetes and CVD [52,53].

The results of dietary interventions have not been as consistent as those of the observational studies. However, these studies show a favorable effect on HDL-C [42,54,55], and reductions in CRP [41,56] and in serum triglycerides and low-density lipoprotein cholesterol have also been reported [26,55,57]. A 2004 meta-analysis of 15 randomized clinical trials (RCTs) by Kelly et al. [58] showed that only total cholesterol and HbA1c were modified by low glycemic index diets in comparison with high glycemic index control; serum LDL-C, serum HDL-C, triacylglycerides, body weight, fasting plasma glucose, and fasting serum insulin were not modified. However, the more recent and longer term trials showing beneficial effects on HDL-C were not included, and most of the included trials were short term, contained a small sample size, and overall were of poor quality [58], emphasizing the need for larger and longer RCTs.

Thus, although not unanimous, the evidence from cohort studies demonstrates a protective effect for low glycemic index/load diets against heart disease. In larger, longer RCTs, some evidence suggests that low glycemic index/load diets were associated with higher serum HDL-C and lower CRP. More studies are required not only to test the effects of low glycemic index and glycemic load diets on serum lipids and CRP, but also to determine the possible mechanisms of action.

THE GLYCEMIC INDEX AND CANCER

In recent years, the dietary glycemic index has been linked with the risk of various cancers, including cancers of the breast, prostate, colon, and pancreas. The suggested reason for the apparent benefit of low glycemic index diets has been lower postprandial hyperglycemia and hyperinsulinemia, which reduce the promotion of transformed cells and the resulting development and growth of tumors [59]. However, much inconsistency is evident in the epidemiological findings.

For instance, in breast cancer, a recent meta-analysis by Mulholland et al. [60], which looked at the effects of glycemic index and glycemic load on the risk of breast cancer in cohort studies, found a nonsignificant RR of 1.14 (95% CI 0.95 to 1.38) and 1.11 (95% CI 0.99 to 1.25) for premenopausal and postmenopausal women for the lowest versus the highest categories of glycemic index intake [60]. However, a meta-analysis by Barclay et al. [12] showed a statistically significant direct relationship between glycemic index and the risk of breast cancer (RR 1.08; 95% CI 1.02 to 1.16), despite calculating a lower RR compared with the study by Mulholland et al. [60]. Similar conflictive findings have been published for colorectal cancer [61,62]. In pancreatic cancer, despite a possible role of hyperglycemia in its origin, none of the 5 cohort studies have found a significant association with glycemic index or glycemic load [63–67]. However, 2 meta-analyses have shown that glycemic index and glycemic load are directly associated with the risk of endometrial cancer [62,68]. Finally, a multicenter, case-control study of Italian men showed that the highest quintile of dietary GI and GL corresponds to odds ratios (ORs) of developing prostate cancer of 1.57 (95% CI 1.19 to 2.07) and 1.41 (95% CI 1.04 to 1.89), respectively [69].

These inconsistencies may be due in part to the limited number of studies in each area and other problems that are inherent in cohort studies, such as consistency in calculating accurate glycemic index and glycemic load values from food frequency questionnaires (FFQs). It may be necessary for future cohort studies to further adjust for additional covariates and to possibly standardize and refine FFQs further for calculating glycemic index and glycemic load values.

MECHANISMS OF ACTION

In general, the metabolic advantages of low glycemic index foods are related to the rate at which glucose is absorbed from the small intestine. Consumption of low glycemic index foods reduces the rate of glucose absorption, which, in turn, induces a lower rise in circulating insulin and related gastrointestinal hormones, such as incretins, gastric inhibitory polypeptide (GIP), and glucagon-like peptide-1 (GLP-1). This lower postprandial but sustained insulin secretion has many advantages, including longer suppression of free fatty acids and blunting of the counterregulatory response that occurs with high blood glucose swings. The reduction in free fatty acid levels improves cellular glucose metabolism, with glucose withdrawn from the circulation at a greater rate. Consequently, blood glucose levels remain closer to baseline, despite continued glucose absorption from the small intestine. The peak postprandial blood glucose rise is therefore reduced, together with the incremental blood glucose area above baseline. This improved blood glucose control is of importance to individuals with insulin resistance (e.g., in obese, sedentary subjects), prediabetes, and diabetes. On the other hand, high glycemic index diets can increase insulin secretion, which may lead to postprandial hyperinsulinemia, possibly perpetuating a vicious cycle with peripheral cell insulin receptor down-regulation. Studies have shown the importance of the 30 minute postchallenge insulin levels in predicting weight loss on low

glycemic load diets [29,70]. Not only does hyperinsulinemia compound the metabolic syndrome, but evidence suggests that with each standard deviation increase in fasting insulin levels, a 60% increase in the chance of developing ischemic heart disease (IHD) is seen in men between the ages of 45 and 76 [71]. Furthermore, high postprandial glucose levels may increase the risk of developing CVD [72].

The lesser studied mechanisms are those that may affect weight loss. Hyperinsulinemia, because of its lipogenic effect, has been linked to obesity [73]. One possible mechanism suggests that the higher postprandial insulin response following a high glycemic index or glycemic load meal may lead to a quicker hunger response and overeating by depleting the metabolic fuels in the body [74]. Another mechanism of action for the beneficial effects of low glycemic index foods may be their effect on satiety. Fifteen short-term studies have shown that low glycemic index foods such as psyllium, guar, oatmeal, and legumes increase satiety and decrease voluntary food intake [75]. However, additional studies are required to test these hypotheses and determine the exact mechanisms by which low glycemic index or glycemic load foods affect appetite control.

CONCLUSION

Despite inconsistencies in the current findings, many observational studies support the notion that low glycemic index diets may be protective against the risks of diabetes and heart disease. For type 2 diabetes, clinical interventions are also supportive of this notion, in demonstrating that low glycemic index diets are effective in maintaining optimal glycemic control. However, longer term interventions are still needed. Additional long-term interventions are also required to determine whether low glycemic index diets can enhance weight loss or modify biomarkers of heart disease, such as LDL particle size, HDL-C, triglycerides, and CRP. Current findings show that low glycemic index and glycemic load diets are more effective than low fat and high glycemic index diets in inducing weight loss. Evidence of an inverse link between dietary glycemic index and serum HDL-C levels is accumulating. A link between dietary glycemic index and various cancers is also being explored. However, future cohort studies, designed to optimally measure dietary glycemic index and glycemic load, are required to supplement the current findings. In diabetes and cardiovascular disease, larger RCTs, properly powered to detect harder endpoints, including alteration in renal function and vascular lesions (intima media thickness [IMT], plaque thickness, and volume), are needed. Overall, a growing body of evidence suggests that the dietary glycemic index may be a useful tool for management of body weight and associated chronic diseases, especially diabetes, heart disease, and possibly cancer.

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