Glycemic Index

The State of the Science, Part 3—Role in Cardiovascular Disease and Blood Lipids

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The effects of carbohydrate quality, as characterized by glycemic index (GI) and glycemic load (GL), have become a topic of interest in assessing diet’s impact on chronic disease including cardiovascular disease. This review focuses on the role of GI or GL with respect to coronary heart disease, stroke, and key blood lipid biomarkers. The main body of this review emanates from the white paper completed for the Wheat Foods Council. In addition, findings from relevant papers published since the completion of the white paper will be added. Overall, the findings are mixed. In some studies, there are associations found between the risk of coronary heart disease and stroke and high-GI or high-GL diet. However, roughly an equal number other studies fail to show such associations. In some cohorts, gender, body weight, or other differences such as dietary patterns may impact the associations. The most consistent associations are those observed between GL and blood lipids. High dietary GL is associated with increased triglyceride levels. However, the associations for GI and various lipid biomarkers are less consistent. There are several potential reasons for the inconsistencies for GI and various lipid biomarkers are less consistent. One stems from the variability of the GI and GL measurement. Other difficulties stem from (a) the application of table values for GI and GL to diets, especially those from food frequencies, and (b) the fact that diet quality of low-GI or low-GL diets replete with fruits, vegetables, nuts, and whole grains may vary as GI or GL varies. Such diets have many constituents such as dietary fiber that lower cholesterol and mitigate risks independently. The findings of this review concur with those from the evidence-based review prepared for the 2010 Dietary Guidance Advisory Committee, which stated that data in the literature were inadequate to come to a firm conclusion about the relationship of GI or GL to cardiovascular disease. Nutr Today. 2013;48(2):61–67

Coronary heart disease (CHD) ranks as the number 1 cause of death in the United States. Therefore, dietary strategies to prevent and manage this disease are of great interest. After decades of linking the quality and quantity of fat in the diet to increased risk of CHD, the focus has widened to include other dietary components as possible culprits in increasing CHD. Carbohydrate (CHO) quality and quantity are among components that have received greater scrutiny. Particular concern stems from CHO’s effects on the glycemic response as measured by the glycemic index (GI) or the glycemic load (GL) and whether these might be linked to CHD, cardiovascular disease (CVD), or its biomarkers.

This article is part of a series that emanates from a white paper on GI and GL and their role in health and disease prepared for the Wheat Foods Council. The review updates an initial white paper for the Wheat Foods Council published in 2004. This narrative review series has as its primary focus those papers published after the first review. This includes MEDLINE entries between 2005 and 2011 of the following types of studies: retrospective (case control), cross-sectional, prospective (cohort), nested case control, randomized controlled trials (RCTs), and meta-analysis of prospective of RCTs. The different types of studies are explained in the Table. Each of these types of studies is subject to confounding errors that result from the fact that diets with the same GI or GL be constituted very differently. The first article in the series not only defines GI and GL and outlines details regarding their methods, variability, strengths, and limitations but also discusses potential confounding and sources of error. The second article assesses GI and GL in relation to body weight, weight loss, and weight maintenance. This article, the third in the series, looks at GI and GL with respect to CHD and CVD risk and their biomarkers such as blood lipids and markers of inflammation. References for the initial white paper were generated from a MEDLINE search with glycemic index or glycemic load (also glycaemic) as search terms coupled with the following other search terms: coronary heart disease, cardiovascular disease, weight maintenance, and metabolic syndrome.
### Types of Studies Considered and the Strength of Their Evidence

<table>
<thead>
<tr>
<th>Study Type</th>
<th>What It Is</th>
<th>Strengths</th>
<th>Weaknesses</th>
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<tr>
<td>Retrospective (normally case control)</td>
<td>A comparison of a physiological characteristic or disease or its marker with past eating behaviors.</td>
<td>• Compares people with the disease (cases) with matched controls and therefore can look at diseases that may be relatively rare. • No amount of time is required for subjects to develop the symptoms.</td>
<td>• May not have accurate memories of what was eaten, especially because participants may have their intake colored by the disease and control volunteers may be more likely to have health habits and diets that are healthier.</td>
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<td>Cross-sectional</td>
<td>A comparison of eating patterns and diseases at 1 moment in time.</td>
<td>• These can be large, representative, and relatively cheap.</td>
<td>• The particular sample day may not reflect overall intake.</td>
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<td>Prospective cohort</td>
<td>Follows a large number of usually healthy people over time. Allows for diets of those who contract the disease to be compared with those who do not.</td>
<td>• Diets can be assessed at various points throughout the follow-up time period. • Diets are usually not altered as a result of the study.</td>
<td>• Results show associations and not causation. • There can be significant confounding because a number of diet and health changes can work together to cause the outcome. If these are not adequately adjusted for, the conclusions may be wrong. • Individuals at risk for disease may alter their patterns, and if they still contract the disease, the altered pattern may show up as causative when it is not. • Time periods must be very long. • A variable not measured or considered may be key.</td>
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<td>Nested case control</td>
<td>Compares the role of diet and disease in a subset of participants in a prospective cohort.</td>
<td>• Not subject to biased recall as in an ordinary case control study. • Samples are smaller, making the study more cost-effective.</td>
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<td>RCT</td>
<td>Compares the effect of intervening with a specific dietary or health strategy in a group that is randomly assigned to receive a specific treatment.</td>
<td>• Variables can be controlled. • Optimally, blinding is a good idea, although this is often difficult with diet.</td>
<td>• Subjects may not comply with the proscribed dietary change. • Other important variables may be missed. • Expensive, so trial might be not carried on long enough. • Optimally, blinding is a good idea, although it is often difficult when dietary changes are involved.</td>
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<td>Meta-analysis</td>
<td>Surveys studies from the scientific literature and tries to gain greater numbers of subjects by systematically analyzing results from several large cohort studies and RCTs.</td>
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Abbreviation: RCT, randomized control trial.

disease, cardiovascular disease, stroke, cholesterol or triglyceride, and serum lipids. Any citations added after the completion of the white paper were searched using the same method and also included the evidenced-based review prepared as part of the 2010 Dietary Guidelines Advisory Committee (DGAC) deliberations.4
GI, GL, AND CHD: EPIDEMIOLOGICAL STUDIES

Interest in a possible relationship between GI and GL and CHD risk was sparked when results from a small intervention study in subjects with increased triglyceride (TG) levels suggested that controlling the GI or GL of CHO foods would help lower serum lipids and could therefore potentially lower CHD and CVD risk. Subsequently, the relationship between CHD and GI and GL has been assessed in a number of large prospective cohorts. In 1 such cohort, the Harvard Nurses’ Health Study, a prospective cohort of more than 88,000 women older than 45 years, the relationship was measured at several time points during the study follow-up. After 10 years of follow-up, nurses in the quintile ingesting diets with the highest GI were associated with having increased risk of CHD compared with those in the quintile with diets having the lowest GI. Glycemic load was associated with increased CHD risk only in those whose body mass index (BMI) was 23 kg/m² or greater. Data from the 20-year follow-up showed that women with diets in the top decile of GI had a higher risk of CHD than did those in the lowest decile. Data from following European cohorts showed a mixed picture with respect to the link between GI and CHD risk in both men and women. Neither GI nor GL was related to increased risk of myocardial infarction (MI) or risk of heart failure in women (48–83 years old) in the Swedish Mammography Cohort (n = 36,234). The relationship was unchanged when the weight of the women was considered. However, in middle-aged Dutch women who were part of the European Prospective Investigation into Cancer and Nutrition (EPIC) (n = 15,714), GI was associated with increased risk of CHD, but only in women with BMI greater than 25 kg/m². For the female Italian cohort of the EPIC project (n = 32,578 women), both dietary CHO and GL increased CHD risk for the quartile of women ingesting diets having the highest amount of CHO. For the women in this study, increasing CHO intake from high-GI foods was also significantly associated with greater risk of CHD. No such increase in CHD risk was observed with increasing CHO intake from low-GI foods.

The role of GI and GL for men seems to be somewhat different than for women. For older and middle-aged men, neither GI nor GL was related to (a) the incidence of coronary disease in older men in the Zutphen cohort (n = 646, ages 64–84 years), (b) the rate of MI or cardiovascular death in Swedish men both with and without a history of diabetes and coronary disease (n = 36,246, ages 45–79 years), (c) the risk of CHD in the Italian cohort of the EPIC project (n = 15,171), or (d) acute risk of MI in the Kuopio (Finland) Ischaemic Heart Disease Risk Factor Study (n = 1,891 men) in the cohort overall. Further analysis of the data in the Finnish men showed that there was an effect of body weight.

Both GI and GL were associated with increased risk of MI in overweight Finnish men, and the association became more pronounced if the men were physically inactive.

POTENTIAL CAUSES OF DIFFERENCES AMONG STUDIES

The GI or GL calculated as a result of food frequencies may not capture differences in diet composition. Foods rich in dietary fiber from fruits, vegetables, nuts, and whole grains also tend to have a low or medium GI, thus making it nearly impossible to separate the impact of GI and GL on CHD from the impact of these nutritious, fiber-rich foods. In fact, diets with the same GI or GL can be composed of markedly different foods and nutrients. One study tried to use modeling to assess the impact of dietary changes. When high-GI CHO foods were substituted for saturated fats—a known CHD risk factor—in Danish women and men (n = 53,644), the risk of MI for both men and women increased. Substitution with either low- or medium-GI CHO had no such impact. Although these findings are interesting, the switch to a low-GI CHO foods may change both macronutrients and micronutrients, especially the amount of known confounders such as increased dietary protein, fiber, and minerals such as magnesium known to impact CHD.

Another potential cause of variability is the problem caused by using published values to assign GI or GL to diets from food frequencies where factors known to alter GI such as cooking methods, variety, and ripeness may not be known, making the assignment of GI or GL inaccurate. A further problem may be due to very different intakes among countries. For example, foods that have little or no impact on GI or GL, such as coffee or fish, may affect CHD risk and may not be reflected by simply assigning a dietary GI or GL. Factors inherent to the various cohorts may need to be considered, such as gender, ethnicity, physical activity, or metabolic differences caused by genetics or fat pattern distribution, especially visceral fat and gender. Although existing studies show inconsistency, there may be a trend for women to be more at risk for CHD when diets are high in GI or GL. This seems to be different by country and by body weight in some countries. Gender may have impact because of differences in men’s and women’s processing of CHO. For instance, it has been established in a variety of populations that impaired fasting glucose is more prevalent in men and impaired glucose tolerance is more prevalent in women. This could impact the effects of GI and GL. In addition, differences in men’s and women’s overall CHD risk and fat deposition patterns could be related to some of the GI and GL impacts. Another potential impact on the conclusions is publication bias. This could occur in either direction. Studies showing no association often do not get published, but studies that show associations but fail to identify confounders may present problems in the published body of work.
Further studies relating either GI or GL and CHD are needed, especially those that (a) control for fiber and microconstituents, to see if there is a relationship and how it is impacted by diet and subject characteristics, (b) improve the consistency of the measure, or (c) reduce errors in assigning GI and GL values to diets from published tables. The lack of consistency with respect to GI and GL and risk of coronary disease was stated in the 2010 DGAC. They concluded that data in the peer reviewed, scientific literature on human subjects were inadequate to come to a firm conclusion about the relationship of GI or GL to CVD.4

GI, GL, AND STROKE RISK
The relationship between GI and GL and the risk of stroke also shows lack of consistency among studies. The following studies showed no association between GI and the risk of stroke: in women in the US Nurses’ Health Study,19 in men in a large Swedish cohort,13 and in either gender in a Dutch cohort.10 In 1 mixed-gender Japanese cohort (n = 12,000 men and 15,000 women), higher GI diets were associated with a trend toward lower stroke risk in men but a higher risk in women.20 Those Japanese women whose diets had the highest GI had twice the risk of stroke compared with those women whose diets had the lowest GI. Although GI was not related to stroke risk overall in Swedish men or in the Dutch men and women, GL was related in both these cohorts to cerebrovascular accident in the Dutch10 and to hemorrhagic stroke in Swedish men.13 In a Japanese cohort, GL was also related to increased risk of mortality from hemorrhagic stroke in women.20 In the Nurses’ Health Study, GI was not associated with increased stroke risk overall, but it was related to increased risk in those women who were overweight (BMI >25 kg/m2).19 In the Australian Blue Mountain Eye Study (n = 2712), both GI and GL were associated with deaths from stroke.21 In this study, diet quality was shown to have an impact. Associations became much stronger if diets were both high in GI and low in cereal fiber. Findings about stroke risk and its relationship with either GI or GL indicated that GL may increase stroke risk in some populations, but not all studies. Similar inconsistency occurred with respect to GI. This inconsistency is exemplified by 2 critical reviews on the subject. One review, a meta-analysis of 37 prospective cohort studies, found that there was not a significant relationship to GI. However, the relative risk for increased CVD between the highest versus the lowest quintile of dietary GL was 1.41.22 In contrast, the paper prepared for the 2010 DGAC addressed the question “What is the relationship between glycemic index or glycemic load and body weight, type 2 diabetes, cardiovascular disease, and cancer?”4 The Committee concluded with respect to CVD, based on an evidence-based review that assessed many of the same primary research studies as in Barclay et al22 (but no meta-analysis, to prevent double counting) and stated the following: “Due to limited evidence, no conclusion can be drawn to assess the relationship between either glycemic index or load and cardiovascular disease.”4 Both reviews considered human studies from the peer reviewed literature, so it is interesting and confusing that the conclusions are different. Perhaps, the inconsistent effects caused by diet differences and in some studies gender, ethnicity, and body weight seem could account for the discrepancy. These and other factors need further study to clarify the relationship of dietary GI and GL to impact stroke and other CVD risk.

GI, GL, AND BIOMARKERS ASSOCIATED WITH CHD AND OTHER CVDS
Postprandial glucose and insulin are known to be related to blood lipids and severity of CHD.23,24 Such relationships suggest that GI or GL, which affect postprandial glucose or insulin excursions, might also affect blood lipids.

GI, GL, and Total and Low-Density Lipoprotein Cholesterol
Studies looking at GI and GL and low-density lipoprotein (LDL) give mixed results. Glycemic index was not related to LDL and total cholesterol in either gender in the Framingham Offspring Study (n = 2941) and Japanese female farmers (n = 1349) eating traditional diets.25,26 However, there was an association between GI and LDL cholesterol in middle-aged Japanese factory workers of both genders (n = 2257 men and 1598 women)27 and for both menopausal and postmenopausal women in the Women’s Health Study.28 The mean LDL concentration was 122 mg/dL for those in the quintile eating diets with the lowest GI and 127 mg/dL for those eating diets with the highest GI.28 The differences are small, and thus, there are arguments as to their practical importance. Glycemic load was related to increased LDL cholesterol level in the following groups: middle-aged Japanese factory workers, Japanese female farmers, and in men the Insulin Resistance Atherosclerosis Study (n = 1026), a multiethnic, middle-aged cohort of men and women with normal or impaired glucose tolerance.26,27,29 Thus, GI was linked to total and LDL cholesterol in 2 of 4 cohorts, with no consistent effect of gender or urban setting across the cohorts. Glycemic load was linked in all 3 cohorts and was not impacted by gender or other differences in the cohorts.

GI, GL, and TG and High-Density Lipoprotein Cholesterol
Glycemic load was associated with higher TG level in 8 cohorts: the Framingham Offspring Study25; the Women’s Health Study28; the Cooper Center Longitudinal Study of women (n = 1775) and men (n = 9137)30; a small Massachusetts cohort of healthy, middle-aged, mostly white,
well-educated men and women (n = 574)\textsuperscript{31}; middle-aged Japanese factory workers\textsuperscript{27}; Japanese female farmers eating a traditional diet\textsuperscript{26}; the Whitehall cohort of more than 10,000 white UK civil servants (70% men/30% women)\textsuperscript{32}; and in rural and urban men and women in India (n = 2043).\textsuperscript{33} In all but 1 study, GI was inversely associated with high-density lipoprotein (HD) cholesterol. In the Women’s Health Study, GI was unrelated to HDL, but it was related to the LDL-to-HDL ratio.\textsuperscript{28}

Dietary factors and/or BMI was shown to affect the relationship between GI and blood lipids in the Whitehall cohort. The association weakened when dietary fiber and CHO intake were added to the model but was strengthened when BMI and waist-to-hip ratio were considered.\textsuperscript{32} Gender, race, and ethnicity seem to impact GI’s and/or GI’s effect on blood lipids. For rural and urban Indians, high-GL diets were associated with a greater drop in HDL level in men than in women.\textsuperscript{33} Glycemic load was positively related to total and LDL cholesterol in men in the Insulin Resistance Atherosclerosis Study and had an inverse relationship with HDL.\textsuperscript{29} This was not observed in women. However, it was noted that the dietary intakes varied by gender, with men consuming more total digestible CHO and the CHO’s had higher GI’s than those eaten by women. Because studies show that energy-adjusted dietary GL and total CHO intake are highly correlated, this begs the question whether the blood lipid increases are caused by high dietary GL or simply total CHO intake.\textsuperscript{34} In the aggregate, studies suggest a trend toward an association of GI and increased TG and lowered HDL levels, with a less clear picture of the impact on total and LDL cholesterol. Furthermore, the effect and degree of impact vary among studies and seem to be affected by race, ethnicity, BMI, and, in some cases, gender.

The practical significance of the observed differences in lipid levels for those in the highest intake groups and the lowest has been questioned in some cases. One study showed that the difference in HDL between those in the category with the lowest versus the highest GI was extremely small. In another study, the mean difference in the TG concentration between the top and bottom quintiles was 12 mg/dL for GI and 13 mg/dL for GL. Because the reference range for TG as defined by the American Heart Association is up to 150 mg/dL and borderline high is 150 to 200 mg/dL, some argue that small differences are not practically important. Others argue that small differences when looking at cardiovascular risk of large populations may have important health impacts.

**GI, GL, AND BLOOD LIPIDS: INTERVENTION STUDIES**

Intervention studies, such as epidemiological studies, also fail to show a consistent pattern. Low-GI foods lowered serum TG levels and improved blood lipids in 2 RCTs: (a) in a trial of 73 obese, young adults where a low-GL diet, compared with a low-fat diet, increased HDL cholesterol and lowered TG levels\textsuperscript{35} and (b) in the Ontario Cardiac Rehabilitation Pilot Project (n = 120). In this large trial of free-living Canadians, those on the low-GL diet showed greater improvement in HDL and a larger decrease in TG levels than did the 1434 controls eating according to the Canadian Food Guide.\textsuperscript{36} However, in 2 RCTs, there were no improvements in blood lipids. In 40 overweight subjects with poorly controlled diabetes, a low-GI diet did not improve blood lipid profiles over that seen in subjects eating diets constructed according to recommendations of the American Diabetes Association.\textsuperscript{37} Similarly, a low-calorie, low-GL diet did not give better lipid profiles for 26 obese children than a low-calorie, high-GI diet did.\textsuperscript{38} (In both these studies, although there were no positive effects on lipids, some nonlipid outcomes were improved with the low-GI diet.)\textsuperscript{37,38}

Several potential mechanisms have been put forward as to how low-GI or -GL diets might influence risk factors. First, the amount of dietary CHO can influence the balance of small and large LDL particles. Small, dense LDL particles are known to be more atherogenic than the large, less dense particles. Because low-GL diets may have a smaller percentage of calories from CHO and a larger percentage from fat, this may affect LDL particle size.\textsuperscript{39} Furthermore, such diets have also been shown to keep HDL levels high. The strong correlation between GI and level of CHO might explain why the relationship between dietary GI and lipid risk factors shows greater consistency than seen with GI. Because quality, proportion, and type of CHO can decrease chylomicron production, this might also influence blood lipids.\textsuperscript{40} Fat levels may change in a low-GI or -GL diet, and this might influence blood lipids independently of the GI or GL of the diet. Higher levels of dietary heart-healthy fats, such as those in fish, nuts, seeds, olives and olive oil, and avocados, may lower CHD risk and help create a better blood lipid profile. Thus, this is another dietary aspect that can change simultaneously with changes in GI and GL.

Carbohydrate quality and quantity are also associated with markers of inflammation such as C-reactive protein (CRP). It is postulated that because markers of inflammation are strongly correlated with coronary disease, then dietary patterns that reduce CRP and other proinflammatory substances may be an important aspect of prevention. Inflammation markers have been associated with dietary GI or GL in some,\textsuperscript{27,41} but not all, studies.\textsuperscript{42} (This will be addressed in a subsequent paper in the series.) Low GI was associated with low CRP in another large cohort. However, the effect was small.\textsuperscript{22} Some studies show an association between increased markers of inflammation and GL in obese individuals (BMI > 30 kg/m\textsuperscript{2}).\textsuperscript{42} Thus, there is a theoretical
basis for a low-GI or -GL diet and a potential impact on CVD. However, because low-GI and -GL diets have factors beyond their glycemic response that can impact CVD, confounding exists.

CONCLUSION

The literature assessing the role of CHO quality as measured by GI and GL in impacting the risk of CHD and stroke shows associations in some of the epidemiological studies and no associations in others. There is a trend that low GL may be useful in preventing stroke, but not all studies substantiate this effect. However, there is a fair degree of consistency showing that CHOs that are also low in GI may improve lipid risk biomarkers by lowering TG levels and keeping HDL levels high. There is less consistency among various cohorts with respect to total and LDL cholesterol.

The lack of consistency across studies continues to beg questions about the methodology for determining GI and GL and the methodology of assigning GI and GL values to foods and diets from food frequencies and other instruments used to reflect dietary intake. Furthermore, other changes in diet quality, such as the amount of that change as GI and GL change, can alter CHD biomarkers and CHD risk. The lack of agreement among epidemiological evidence in different studies and conflicting outcomes among intervention studies also give pause about forming a conclusion. Confounders among and within cohorts, including impacts of gender, body weight, and metabolic state and diet, seem to have an impact, but the current state of the literature does not show these to be same across cohorts. This may indicate that cohorts in future studies need to be parsed into groups by various characteristics such as fasting glucose or BMI to assess the impact of such factors and potential interactions. The state of the current literature looking at the link between GI and GL and CVD gives no reason to alter conclusions made in the DGAC report stating that the data were inadequate to come to a firm conclusion about the relationship of GI or GL to CVD.

REFERENCES


