Glycemic Index: The State of the Science, Part 3:
Glycemic Index, Glycemic Load and Markers of Coronary Risk and Cardiovascular Disease

PART 3

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Introduction

Coronary Heart Disease (CHD) ranks number one as the cause of death in the United States. Therefore, dietary strategies to prevent and manage this disease are of great interest. After decades of near obsession about the quality and quantity of fat in the diet and their role as the culprit in CHD, the focus has widened to include other dietary components including the amount and quality of the carbohydrate (CHO).

One way the quality of the CHO can be assessed is the glycemic response. There have been a number of studies trying to link the glycemic response by measuring the glycemic index (GI) or the glycemic load (GL) and to see if these dietary qualities impact on coronary heart disease (CHD) or its biomarkers. This paper emanates from a White Paper for the Wheat Foods Council (WFC) (1) and summarizes key findings from it. These findings are considered along with conclusions from the evidenced-based review prepared as part of the 2010 Dietary Guidelines Advisory Committee (DGAC) deliberations (2) and with some studies published since the White Paper.

The first paper in the series defines GI and GL and outlines details regarding their methods, variability, strengths and limitations. (1,3) The second paper assesses GI and GL in relation to body weight, weight loss and weight maintenance. This, the third article in the series, will look at GI and GL with respect to cardiovascular disease (CVD) and disease biomarkers for CVD such as blood lipids and markers of inflammation.

GI/GL and Risk of Cardiovascular Disease

Findings from studies on dietary GI and GL and CVD risk give confusing picture with some studies showing a relationship and others not. This inconsistency was reflected in the conclusions of the evidence-based review prepared for the 2010 DGAC, which stated that data in the literature were inadequate to come to a firm conclusion. (2) This paper will look at details from epidemiological and intervention studies from the DGAC review, the WFC White Paper and some papers added to the literature since the review was completed.

GI, GL and CHD – Epidemiological Studies

The relationship between GI and GL and CHD risk has been assessed in a number of large prospective cohorts ever since an initial, small intervention study suggested that controlling the GI or GL of CHO foods would help address disease CHD risk factors. (4)

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One such prospective cohort study is the Nurses’ Health Study. (5) Data from this cohort of women over 45 years old has been assessed at several time points. In the first assessment that occurred 10 years after data collection began, analysis showed that diets high in GI were associated with increased risk of CHD. However, diets high in GL were associated with increased CHD risk only in women whose body mass index (BMI) was 23 or greater. (5) Analysis after 20 years showed that the decile of women ingesting the highest GL had a higher risk of CHD than the decile ingesting the lowest GL. (6) Positive associations such as those observed in the Nurses’ Health Study between GI and CVD risk were also seen in the Dutch subset of the European Prospective Investigation into Cancer and Nutrition (EPIC) (n=15,714) study. In this study dietary GI was related to CVD in both genders, but GL was associated with CVD risk only in overweight women. (7) Somewhat similar data were also seen in women in the Italian subset of the EPIC project (n=15,171 men and 32,578 women). Those women in the quartile ingesting the highest GL had more than twice the risk of CHD than women in the quartile with the lowest GL. Interestingly, none of these associations was observed in men. (8)

**GI, GL and Cardiovascular Disease and Gender**

Since several of the studies seemed to show an association of GI or GL and CVD and women, especially overweight women, one has to ask the question, “Is gender the key to understanding the impact of GI and GL?” This might be the case as other studies have shown that neither GI nor GL was associated with CVD in men. For example, neither GI nor GL was associated with incidence of CHD in a Dutch cohort of older men (64-84-year-old men in the Zutphen study (n=646). (9) Also there was no association between dietary GI and dietary GL and myocardial infarction (MI), or cardiovascular or all-cause mortality in Swedish men aged 45-79 years with (n=4617) or without (n=36,246) a prior history of coronary disease and diabetes. (10, 11)

However the effects of gender are not consistent across all studies. In the Swedish Mammography Cohort (n=36,234 women aged 48-83 years), there were no statistically significant associations of either dietary GI or GL with MI or risk of heart failure in either normal weight or overweight women. (12, 13)

**GI, GL, and Cardiovascular Disease and Other Dietary Components.**

Overall dietary composition may impact CVD risk since foods and patterns of food can impact risk. This can be confounded by the fact that a diet with the same overall GI or GL can be comprised of markedly different foods and nutrients, all of which can impact coronary risk. One study in a cohort of 53,644 Danish women and men tried see if the quality of CHO would impact CHD risk if it was substituted for a known coronary risk factor, saturated fats (SF). (14) These data indicate that when CHOs with high-GI values were substituted for SF, the risk of MI increased. If CHOs with low-GI values were substituted, there was a non-significant inverse association between GI and risk of MI, and if CHOs with medium-GI values were substituted, there was no measurable effect. Gender was not a factor in this cohort. (14)
GI, GL and Stroke Risk

Some large cohort studies have tried to see if the relationship between GI and GL and the risk of stroke gave any clearer outcome than that observed between GI and GL and CHD. GI was not associated with the risk of stroke for women in the US Nurses’ Health Study. (15) However, GL was associated with stroke risk, but only in women who were overweight (BMI > 25). (15) GI was not related to stroke risk in the mixed gender Dutch cohort, (7) but dietary GL was associated with stroke risk. In the Australian Blue Mountain Eye Study (n= 2,712), there was an association between both GI and GL and deaths from stroke. (16) The association became much stronger if diets were high in GI and low in cereal fiber. In a cohort of 36,246 Swedish men, there was no association found between with GI or GL and ischemic stroke or all cause mortality, but there was with hemorrhagic stroke. (10) So, as with CHD, the relationship between GI and GL and the risk for stroke is not consistent across studies. Further research is needed to assess the impact of other dietary components such as dietary fiber, the effect of overweight and possible interactions with gender or other metabolic factors.

GI and GL and Risk of CVD – Summary

The overarching view of the studies and reviews on this subject shows the lack of consistency among the studies and agreement about what the findings mean. For example, two critical reviews came to different conclusions. A meta-analysis of 37 prospective cohort studies calculated the relative risk (RR) for increased CVD between the highest versus the lowest quintile of dietary GI was 1.25 (17). In contrast, an evidence based review (2) for use by the 2010 Dietary Guidelines Advisory used many of the same studies and was published at approximately the same time stated that data in the literature were inadequate to come to a firm conclusion on the impact of dietary GI or GL on CVD risk. Since some studies show a positive effect, more research is needed to see if this is merely due to dietary GI or GL or other aspects of the diet that change as GI and GL change. Since there seems to be possible effects body weight, gender, ethnicity, cultural diet patterns and other lifestyle factors, studies must be carried out that can assess the effect dietary GI or GL has on CVD risk.

GI, GL and Biomarkers Associated with Cardiovascular Disease

Since data on GI and GL and their relationship to CVD are not clear, it may be instructive to see if there is a clearer pattern that exists between dietary GI and GL and markers of CHD risk such as blood lipids. Early intervention studies posited such a relationship because changing the foods in the diet from high GI to moderate GI lowered LDL and total cholesterol and lowered triglycerides (TG) in a small study.

The relationship between GI and GL on blood lipids has been addressed in several large, prospective epidemiological studies with varying results. For example in the Framingham Offspring Study (n=2941), there was no relationship between GI or GL and LDL and total cholesterol. (18) In the Insulin Resistance Atherosclerosis Study (IRAS) (n= 1026 multiethnic, middle-aged adults with normal or impaired glucose tolerance), both dietary GL and CHO were associated positively with total and LDL cholesterol in men only. (19) But in menopausal and postmenopausal women in the Women’s Health Study, GI was related to LDL cholesterol but the differences between the top and bottom quintiles were small. (20) The mean LDL concentration for those in the quintile with the lowest dietary GI was 122 mg/dl and for those in the highest was 127mg/dl.

The relationship between GI and GL and HDL cholesterol and raising TG seems to be more consistent than the relationship of dietary GI and GL and LDL cholesterol. This was true in the Whitehall cohort of over 10,000 white UK civil servants (70% men), dietary GI and GL were associated inversely with HDL cholesterol, and GI was associated directly with TG. However, it should be pointed out that factoring in
the total amount of dietary CHO and fiber markedly decreased strength of the association between HDL and GI and rendered the association between GL and HDL no longer significant. (21) In the Framingham Offspring Study, GI was directly related to TG and inversely related to HDL cholesterol. (18) In the Women’s Health Study, there was also a significant decrease in HDL as GI increased. There was also an association between the LDL:HDL ratio and the dietary GI. However, there was no significant relationship between GL and HDL, but GL was directly related to the LDL:HDL ratio. In this cohort the changes were small, but the differences were highly significantly different. (20) The question that must be asked is whether these highly significant small differences shown in a large cohort are of practical impact in clinical impacts for the reduction of CVD risk.

GI, GL, Gender and Blood Lipids

As with the relationship of overall risk for CVD and GI and GL, several studies point to the possibility that different genders, racial and ethnic groups may show different associations between blood lipids and dietary GI or GL. In the IRAS study comprised of multiethnic, middle-aged adults with normal or impaired glucose tolerance, both dietary GI and CHO were associated positively with total and LDL cholesterol, and inversely with HDL in men. However, in women, associations were limited to TG. (19)

Perhaps other dietary differences such as impaired glucose tolerance had an impact. Also it was noted that men in this cohort consumed more digestible CHOs, and that the CHO was higher in both GI and GL than it was in women. In a cohort of Japanese factory workers, (22) no significant associations were observed between GI and serum lipids in men or women. However, GL was inversely associated with HDL-cholesterol in both genders. In this study GL was positively associated with LDL-cholesterol and TG in women only. Also in a cohort of 1,349 Japanese women farmers eating a traditional diet, both GI and GL were associated with elevated TG levels, and GL was associated with lower HDL cholesterol. However, LDL was not related to either GI or GL. (23) In India the direction of the change in HDL was the same but the magnitude was different. Men eating a diet with a high GL diet showed a greater drop in HDL than women. (24) No gender effects were seen in a study of 574 healthy middle-aged mostly white, well-educated adults from central Massachusetts. Higher total CHO intake, GI and GL were associated with higher TG and lower HDL levels in both genders in this cohort. (25)

Thus, it can be seen that there may be a trend toward higher GI and/or GL elevating TG and lowering HDL. However, the effect is not seen in all studies. In some cases the difference in HDL between those in the category eating the lowest versus the highest was as small as 0.06 mmol/L. Thus the question about whether the difference is practically significant as well as statistically significant must be addressed. A similar question can be asked about the relationship between GI and GL and TG. High GI (not GL) was associated directly with TG levels in several studies. In some of these, the mean difference in the concentration between the top and bottom quintiles was 12 mg/dL for GI and 13 mg/dL for GL. It is not clear whether this relatively small significant difference in mean TG levels is clinically important when the normal range as defined by the American Heart Association for triglyceride is up to 150 mg/dL and borderline high is 150 to 200 mg/dL. Some argue that these differences when looking at cardiovascular risk of large populations may be significant, while others question whether this is practically significant.

GI, GL and Blood Lipids: Intervention Studies

Some, but not all, intervention studies show that low GI foods can lower serum TGs and improve blood lipids. In a randomized trial of obese young adults, the low GL diet, compared to a low-fat diet, raised HDL cholesterol and lowered TGs. (26)
In the Ontario Cardiac Rehabilitation Pilot Project, the 120 subjects on the low GL diet showed greater improvement in HDL and drop in TGs than the 1434 ‘controls’ eating according to the Canadian Food Guide. However, in a randomized, controlled trial with 40 poorly controlled overweight diabetics, a low GI diet did not improve blood lipid profiles over that seen with the American Diabetes Association diet, but did have some other positive outcomes. Similarly, hypocaloric low GI diet did not give better lipid profiles for obese children than a hypocaloric high GI diet, but some non-lipid outcomes were improved.

**GI and GL and Potential Mechanisms**

Several mechanisms have been suggested as possible ways that low GI diets can decrease coronary risk factors. First, the amount and type of dietary CHO can influence the balance of small and large LDL particles. Small, dense LDL particles are known to be more atherogenic than large, less-dense particles. Low GI diets that have a smaller percentage of calories from CHO and a larger percentage from fat have been shown to keep HDL levels high. Second, the proportion and type of CHO can decrease chylomicron production. Third, markers of inflammation such as C-reactive protein have been associated with dietary GI or GL in some, but not all studies. In the latter study, there was an association between elevated markers of inflammation and GL in obese individuals (BMI > 30). Low GI was associated with low C-reactive protein (CRP) in another large cohort, however, the effect was small. The authors of the latter study argued that since markers of inflammation are strongly correlated with coronary disease, then dietary patterns, which reduce CRP and other pro-inflammatory substances, may be important for prevention.

**Conclusion**

Promoters of the low GI concept show that diets moderate in fat and low in saturated fat and CHOs with low GI are important for controlling complications of cardiovascular disease. Data point to the fact that low GI/GL may be associated with lower blood lipids and TG and higher HDL levels and lower markers of inflammation. The findings, while positive, are not consistent in all studies and may be affected by interactions between diet and subjects. In terms of overall CHD and CVD risk, evidence is not strong enough to alter conclusions made in the Dietary Guidelines Report. Proof of the clinical value of low GI/GL diets with respect to CVD awaits further clinical trials with subjects segmented by gender, age, lipid profile, BMI and other factors.

More research is needed on the role of GI and GL with respect to all cardiovascular diseases. Low GI and GL diets that contain components – whole grains, dietary fiber, fruits and vegetables, nuts, and the right fats – that lower CVD disease risk – should be recommended for all. Further proof is needed to understand if it is the GI or GL of these diets or other inherent attributes of these healthy diets and food combinations.
References

3. Jones, JM NT paper in press


