Effects of Glycemic Load on Metabolic Health and Type 2 Diabetes Mellitus

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Abstract

A large body of epidemiologic evidence has demonstrated that the combination of a Western diet and lifestyle is primarily responsible for the increased metabolic disease risk, such as obesity, type 2 diabetes mellitus (T2DM), and metabolic syndrome, noted in society today. Thus finding optimal intervention strategies to combat these growing epidemics is imperative. Despite some controversy, a growing body of literature indicates that one aspect of diet that likely affects phenotypic outcomes and metabolic disease risk is the glycemic load (GL). This brief review will provide an overview of the GL concept, discuss epidemiologic work investigating relationships between both GL and metabolic risk factors, as well as intervention studies that have assessed the impact of GL on phenotypic outcomes related to T2DM and cardiovascular disease. Overall, a low dietary GL may be protective against metabolic disease and should be considered as a healthful dietary component.

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Introduction

Obesity, type 2 diabetes mellitus (T2DM), and metabolic syndrome are major health care concerns,[1–4] so finding optimal intervention strategies to combat these growing epidemics is imperative. A large body of epidemiologic evidence has demonstrated that the combination of a Western diet and lifestyle is primarily responsible for increased metabolic disease risk, such as T2DM.[5,6] For example, ecological studies have documented that people who migrate to countries with a more sedentary lifestyle and "Westernized" diet have greater risk of developing T2DM than their counterparts who remain in their native countries.[7] Also, populations undergoing Westernization in the absence of migration, as found in the North American Indians[8] and Western Samoans,[9] have experienced dramatic increases in T2DM prevalence. In prospective cohort studies, it has been estimated that

80–90% of the total risk of T2DM could be eliminated by the adoption of a healthier diet and lifestyle.[10] Several randomized clinical trials, including the Daqing Diabetes Study,[11] the Finnish Diabetes Prevention Study,[12] and the Diabetes Prevention Program[13] have demonstrated that T2DM is largely preventable through diet and lifestyle modifications. Nevertheless, much controversy exists regarding nutritional intervention strategies needed to ameliorate metabolic disease risk.

Early on, it was established that fat intake,[14] and later, specifically saturated fat,[15] contributed to coronary heart disease (CHD), while carbohydrates appeared to be a "safe" nutrient to consume. What followed was a greater focus on research examining the roles of dietary fat in the development of a host of metabolic diseases, including T2DM and CHD, and led to population-wide increases in carbohydrate consumption. However, dietary guidelines failed to acknowledge differences in carbohydrate quality, and much of the increase in carbohydrate intake in the United States over the past few decades[16] may be attributable to refined-carbohydrate products.

Traditionally, dietary carbohydrates have been categorized as simple or complex based on the number of simple sugar units per molecule, and there is a general perception that complex carbohydrates have smaller effects on blood glucose than do simple carbohydrates. However, this is not true; in fact, some complex carbohydrates raise blood glucose more than simple ones. An appreciation for differences in the effects of natural state versus refined plant carbohydrates began to emerge in the 1970s with Burkitt and Trowell's[17] attribution of differences in disease patterns to loss of plant-cell walls (i.e., "dietary fibers") in the Western world. A few years later, Jenkins and colleagues[18] pioneered the glycemic index (GI) concept, which acknowledged that because of the differences in chemical structure, physical form, fiber content, degree of processing (refining and gelatinization), and other factors, different carbohydrates are likely to have heterogeneous biological functions and health effects (discussed in detail elsewhere[19]), such as their abilities to induce plasma glucose and insulin responses. At a population level, the increasing intake of dietary carbohydrates with high GI, including refined grains, has been associated with increased risks for obesity, T2DM, CHD, and other diseases. Moreover, individual responses to the adverse metabolic effects of a high-GI diet are influenced by the degree of underlying insulin resistance, which, in turn, is determined primarily by physical activity, genetics, degree of adiposity, as well as other dietary factors.

The Development of the Glycemic-Load Concept

From a historical perspective, the development of GI and glycemic load (GL) can be viewed as an extension of the original fiber hypothesis, suggesting that slow digestion and absorption of plant-based foods may have an impact on metabolic profiles and ultimately affect the risk of metabolic disease. The aforementioned GI measures the blood glucose response to carbohydrate ingestion by summing the incremental area under the curve for blood glucose, measured at specific times, following intake of a standard weight of carbohydrate.[20,21] Each unit of GI represents the equivalent of 1 g of carbohydrate from glucose or white bread. Several factors influence the GI of a food, including organic acids, tannins, fiber content, ratio of amylose to amylopectin, amount of processing, and physical nature of dietary starch.[22] Overall, the higher the GI value, the greater the blood glucose response per standard weight of carbohydrate. Typically, foods with a low degree of starch gelatinization, such as pasta, and those containing a high level of viscous soluble fiber, such as whole grain, oats, barley, and rye, have slower rates of digestion and lower GI values. For foods that contain a mix of carbohydrates and other components, GI is calculated as a weighted mean of GI values for each of the components.[23–25] One of the strengths of GI is that it is a relative measure; a person's glycemic response to a test food is a percentage of that same person's response to the standard carbohydrate. Averaging this relative measure across hundreds of individuals reduces the effects of interindividual variation. Thus GI values predict the ranking of blood glucose responses of any one individual to a range of foods, as shown for groups that vary by weight and insulin resistance.[20] However, the concept and utilization of GI has not gone without controversy, particularly with regard to the utility of values for mixed meals. Nevertheless, studies have shown that fat and protein intakes do not greatly affect relative differences between foods and that the correlation between GI for mixed meals and average GI for individual component foods range from 0.84 to 0.99.[20,26,27]

Although the GI measures the quality of a carbohydrate, it does not account for quantity of carbohydrate and thus cannot capture the entire glucose-raising potential of dietary carbohydrate. The GL[28] adjusts the GI value of foods for the amount of carbohydrates contained in the food. Glycemic load, a concept validated by Brand-Miller and associates,[29] is calculated as the product of GI and the amount of dietary carbohydrate. For an individual

food, the GL is therefore more relevant than the GI. For example, in some popular diets, although some fruits and vegetables like beets have been disparaged because of their high GI values, the amount of carbohydrate is low in these foods and has little effect on blood glucose or insulin concentrations, leading to a very low GL. It should be acknowledged that for the GL, glycemia is measured for only 2 h, which does not take into consideration metabolic effects that may occur during the late postprandial phase, i.e., 4 to 6 h after meal ingestion.

Glycemic Load and Metabolic Risk Factors

Since 2000, the GL of foods has been incorporated into the assessment of long-term dietary GL for each participant in several large epidemiologic studies. For example, a strong positive association was noted between dietary GL and fasting triglyceride (TG) levels in a random sample of 280 women who participated in the Nurses' Health Study (NHS),[30] and the direct relation between dietary GL and fasting TG levels appeared to differ significantly by body mass index (BMI) categories, suggesting that differential dietary effects may occur based on current obesity and/or health status. Dietary GL was also inversely associated with high-density lipo-protein (HDL)-cholesterol levels. A similar analysis of National Health and Nutrition Examination Survey-III data showed a significant inverse association between dietary GL and HDL.[31] Healthy women from the NHS subjects in the highest quintile of dietary GL had 14.1% and 16.1% higher C-peptide than did subjects in the lowest quintile after further adjustment for total fat or carbohydrate intake, respectively. In contrast, subjects with high intakes of cereal fiber had 15.6% lower C-peptide after control for other covariates.[32] Dietary GL was independently negatively associated with HDL-cholesterol and positively associated with fasting TG and fasting glucose in a female Japanese population, in which white rice was a major contributor to the diet.[33] Additionally, the Framingham Offspring Study noted that intakes of dietary fiber and whole grains were inversely associated, whereas dietary GI and GL were positively associated with homeostasis-model assessment for insulin resistance (HOMA-IR).[34] It should be acknowledged that not all have noted that dietary GL is related to metabolic factors, as in a Dutch population; dietary GI but not GL was related to metabolic risk factors, likely due to the high correlation between GL and carbohydrate intake.[35]

Several studies have noted improved metabolic and cardiovascular risk factors with low-GI/GL diet interventions. For example, Dumesnil and coworkers[36] noted that an *ad libitum* low-GI diet led to reductions in both fasting and postglucose load insulin, a decrease in TG, and an increase in low-density lipoprotein (LDL) particle diameter, all while spontaneously decreasing energy intake and hunger and increasing satiety relative to an energy-matched American Heart Association phase 1 diet. Frost and colleagues[37] noted improved *in vivo* as well as both subcutaneous and omental adipocyte insulin sensitivity after consumption of a low-GI diet versus a high-GI diet.

Many of the changes noted with low-GI/GL diets may be independent of body weight. For example, a low-GL diet given to obese young adults for 12 months led to lower TG and plasminogen activator inhibitor 1 (PAI-1) independent of body weight change compared to conventional energy restriction.[38] McMillan-Price and associates[39] noted that, despite similar weight loss, a low-GI diet elicited greater reduction in fat mass compared to a high-GI diet. Furthermore, Pereira and coworkers[40] noted that, compared to a conventional energy-restricted low-fat diet, a low-GL diet led to smaller reductions in resting metabolic rate and hunger and greater reductions in insulin resistance, TG, C-reactive protein (CRP), and mean arterial pressure, independent of changes in body composition. Additionally, sedentary, insulin resistant individuals may be particularly prone to the adverse effects of high dietary GL and hence may benefit more from a low-GL diet. For example, in the CALERIE Trial,[41] greater weight loss was noted with a low-GL diet in overweight subjects with high insulin secretion as compared with low insulin secretion. This may be explained, in part, by differences in postprandial substrate use.[42] Dietary GI was also associated with a 6-year change in weight loss in women, but not men, suggesting that gender differences may exist.[43]

High dietary GL is also associated with increased concentrations of inflammatory cytokines. Liu and colleagues[44,45] demonstrated that dietary GL was directly related to plasma levels of CRP, independent of BMI, total energy intake, and other known coronary risk factors, and the association was stronger among women with BMI > 25 kg/m^2. In the Women's Health Initiative, lower plasma levels of interleukin-6 (IL-6) and tumor necrosis factor-alpha receptor-2, but not CRP, were associated with lower dietary GL.[46] Other groups have noted that dietary GI or GL is associated with lower CRP, tumor necrosis factor receptor-2 (TNF-R2),[47] and adiponectin.[48,49] Lopez-Garcia and associates[50] noted in the NHS that a prudent as compared to a Western dietary pattern was associated with CRP and IL-6 levels.

These effects may be mediated, in part, by diet-induced hyperglycemia, which may stimulate macrophages and lymphocytes to secrete cytokines.[51] On the other hand, both low- and high-GI meals induced monocyte activation in overweight women.[52] Prior studies noted elevated concentrations of nuclear-factor kappa-B (NF-κB) after high-GI carbohydrate consumption, whereas the anti-diabetes drug, acarbose (an α-glucosidase inhibitor), reduced postprandial mononuclear NF-κB activation.[53] These data suggest that exacerbation of pro-inflammatory processes may be yet another mechanism whereby a high intake of rapidly digested and absorbed carbohydrates increases the risk of CHD and T2DM, particularly among overweight individuals who are prone to insulin resistance. Along these lines, Pittas and coworkers[54] noted in a 6-month intervention study that a low-GL diet tended to decrease CRP more in overweight young adults.

Population studies have noted that markers of endothelial function (i.e., E-selectin, soluble-intracellular adhesion molecule-1, and soluble-vascular cell adhesion molecule-1) are associated with dietary patterns.[50] However, endothelial function has not been assessed directly, and intervention studies have not tested this, although cursory work has indicated low-GI diets have produced better cardio-vascular-related outcomes.[55] It is plausible that a conventional high-GL diet may induce endothelial dysfunction since hyperglycemia induces oxidative stress.[56] In support of this hypothesis, oral glucose induces endothelial dysfunction,[57,58] and malondialdehyde and F2-isoprostanes are positively associated with dietary GL.[59] Additionally, recent data indicate that, acutely, a high-fiber meal may improve endothelial function,[60] leading to the possibility that a low-GL diet may improve endothelial function.

Glycemic Load, Type 2 Diabetes Mellitus, and Coronary Heart Disease

Early on, it was noted in the NHS that dietary GL was positively associated with the risk of T2DM[61] and that women with the combination of high dietary GL and low cereal fiber intake were at an even higher risk of T2DM (relative risk = 2.50, 95% confidence interval, 1.14–5.51). Similar findings have also been observed in men in the Health Professionals Follow-Up Study (HPFS).[62] In a subsequent related study, dietary GI and cereal fiber were significantly associated with an increased and decreased risk of T2DM, respectively, but dietary GL was not significantly associated with risk in the overall cohort.[63] In the Shanghai Women's Health Study[64] and the Black Women's Health Study, dietary GI and GL were positively (as well as cereal fiber, inversely for the latter) associated with T2DM. In the latter, stronger associations were noted among women with a BMI < 25, with incident risk ratios for the highest versus lowest quintile being 1.91, 1.54, and 0.41 for dietary GI, GL, and cereal fiber, respectively.[65] However, others, such as the Atherosclerosis Risk in Communities (ARIC) Study[66] and the Health, Aging, and Body Composition (Health ABC) Study,[67] noted no significant associations of intake of total dietary fiber, dietary GI, or GL with incident T2DM. However, the ARIC Study[66] did note borderline significance when dietary GL was treated as a continuous variable and adjusting for cereal fiber, and the Health ABC Study[67] had a somewhat shorter duration and smaller sample size than the earlier studies that found an association. Two other studies did not note an association, but only a single dietary measurement was obtained. In the Melbourne Collaborative Cohort Study,[68] the authors mentioned that the reproducibility of the dietary questionnaire used was only fair, and in the Iowa Women's Health Study,[69] ascertainment of T2DM outcome was documented to be poor. Analysis of the entire NHS database also indicated that dietary GL was significantly associated with CHD risk independent of other CHD risk factors,[70] and the adverse effect of a high-GL diet on CHD risk was more evident in women with BMIs > 23 kg/m^2, whereas no association was found among women with BMIs < 23 kg/m^2.

One of the major likely contributors to the improvements associated with a low-GL diet is whole grain consumption. Processing whole grains into white flour actually increases the caloric density by ~10%, reduces the amount of dietary fiber by ~80%, and reduces the amount of dietary protein by ~30%, leaving nearly pure starchy carbohydrate with fewer nutrients.[16] Qi and associates[71] noted that, in women with T2DM, higher intakes of whole grains, bran, and cereal fiber were associated with decreasing trends of CRP and TNF-R2.[47] In the HPFS, high whole grain, but not refined grain, intake was associated with a 42% relative risk reduction in T2DM risk after confounder adjustment. Intake of refined grains was not significantly associated with risk of T2DM. After further adjustment for cereal fiber intake and dietary GL, the association between whole grains and T2DM was attenuated and the trend no longer significant.[72] Several randomized feeding trials provide some causal explanations by linking the intake of high-fiber whole grain foods to favorable metabolic intermediates (including smaller postprandial responses of glucose and insulin, improved serum lipid profiles, and lower oxidative stress[73–76]) and lower risk of T2DM (as reviewed by Liu[77]) and CHD.[78]

Intervention studies have documented beneficial effects of low-GI or GL diets in patients with T2DM. In T2DM patients treated with a low-GI diet (GI = 60) compared to a high-GI diet (GI = 87) for 2 weeks, area under the curve for glucose after a standard breakfast was reduced by 29%, urinary C-peptide was reduced by 30%, and plasma fructosamine was significantly reduced.[79] In randomized crossover studies in subjects with T2DM, Jarvi and coworkers[80] noted reduced serum total cholesterol, LDL-cholesterol, apolipoprotein B, and PAI-1 after a low-GI diet, independent of body weight, and Jimenez-Cruz and colleagues[81] noted improved hemoglobin A1c (HbA1c) on a low-GL compared with a high-GL, high-fiber diet. Later, in T2DM patients fed a low-GI diet for 1 year, CRP was 30% lower, and 2 h postload glucose was lower in the low-GI group than in a low-carbohydrate diet group, despite no significant weight difference between the groups.[82] This group went on to note increased disposition index, an index of β-cell function,[83] replicating the group's earlier findings in subjects with impaired glucose tolerance.[84] Additionally, Jenkins and associates[85] noted a modest reduction in HbA1c and an increase in HDL-cholesterol in subjects with T2DM being treated with hypoglycemic agents with a low-GI diet as compared with a high cereal fiber diet.

Despite the aforementioned data, some have questioned the clinical utility of the concepts of GI and GL because of lack of evidence that they are reliable and predictable measures of the glycemic effect and insulin demand of different diets.[86–88] The extent to which different dietary carbohydrates can modify many metabolic risk factors such as adipokines, endothelial function, and inflammation is largely unknown and requires further study.

Summary

The U.S. food supply has become reliant on highly refined carbohydrates as significant sources of energy since these carbohydrate-dense foods are economical and easily consumed in fast-food restaurants or otherwise highly processed and prepackaged foods. The quality of these carbohydrates is considerably different from those consumed before the beginning of the 20th century since the refining process has altered their compositions. The public health campaign to lower fat in the United States unfortunately has been translated by food manufacturers and consumers into a potentially harmful set of food choices. Consequently, instead of replacing high-fat foods with fruits, vegetables, legumes, and whole grain foods, consumers have often increased their consumption of low-fat or fat-free varieties of naturally high-fat foods, as well as refined-sugar-laden products. The result has been an increase in refined carbohydrate and sugar consumption, leading to a U.S. dietary pattern early in the 21st century, consisting largely of refined products such as white bread, white rice, processed cereals, soda, and other sugary beverages and snacks.

A large body of evidence now indicates that dietary carbohydrates low in GL, i.e., from fruits, vegetables, and whole grains, are preferable for long-term health. Without any drastic change in regular dietary habits, for example, one can simply replace high-GI grains with low-GI grains and starchy vegetables with less starchy ones and cut down on sugary beverages that are often nutrient poor and high in GL. We should encourage the use of GI and GL concepts in conjunction with caloric density and nutrient composition since the classification of carbohydrates incorporating GI is more accurate than the "simple versus complex" classification for predicting glucose and insulin responses. Even without consideration of its effects on weight changes, a low-GL diet can create a more favorable glucose and insulin profile as well as a variety of metabolic and cardiovascular risk factors in overweight and T2DM individuals. Unfortunately, long-term studies in humans are lacking, and exact dietary recommendations will, in the future, be best approached in an individualized fashion, based on diet–gene interactions that are likely critical for understanding the relationships between dietary GL and risk of metabolic diseases such as T2DM.

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