Glycemic index and heart disease

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ABSTRACT  A diet high in carbohydrates with high glycemic indexes (GI) and glycemic load were linked to risk of coronary heart disease development in women in a large prospective study. Two cross-sectional studies showed that low-GI diets are associated with high HDL-cholesterol concentrations, especially in women. In a tightly controlled study of patients with type 2 diabetes, serum total cholesterol, LDL cholesterol, and apolipoprotein B concentrations fell more significantly after a low-GI diet than after a high-GI diet. In the same study, plasminogen activator inhibitor-1 concentrations were reduced by 58% after the low-GI diet. Insulin-stimulated glucose uptake by adipocytes was significantly higher in patients undergoing coronary artery bypass graft surgery after 4 wk of consuming a low-GI diet than after consuming a high-GI diet. The effects of low-GI diets may be mediated by changes in postprandial fatty acid concentrations or by hormonal signals from adipocytes, but a possible association of low-GI diets with some other dietary factor such as chromium must not be excluded. Proof of the clinical value of low-GI diets awaits prospective trials, which should include short-term observations covering periods of metabolic stress induced by surgery as well as long-term trials with clinical endpoints.  Am J Clin Nutr 2002;76(suppl):286S–9S.

KEY WORDS  Glycemic index, glycemic load, CHD, HDL cholesterol, PAI-1, TNF-α, insulin sensitivity, postprandial nonesterified fatty acids, chromium

INTRODUCTION

Dietary carbohydrates with different chemical compositions (eg, sugars, oligosaccharides, starches, and nonstarch polysaccharides) and physical structures are digested and absorbed at different rates in the human small intestine and therefore give rise to different blood glucose and insulin responses. In 1981 Jenkins et al (1) defined an index designed to describe the effect of any one carbohydrate food on the area under the blood glucose curve (over 2 h after a 50-g carbohydrate portion) compared with a standard. This “glycemic index” (GI) was initially reported against standards of white bread, but because the structure of white bread, and therefore the blood glucose response to it, varies by country, oral glucose is becoming the standard. The GI has a clear potential application in dietary management of type 1 diabetes, and much effort since 1981 has focused on determining the extent to which lowering GI in the diets of persons with diabetes is beneficial and learning the practical limitations of doing this. Because diabetes predisposes patients to vascular disease, a potential role for GI in diet therapy for patients with coronary heart disease (CHD) needed to be investigated. Several questions must be answered to establish a justifiable use of GI in diet therapy in patients with established CHD and those predisposed to CHD through adverse risk-factor patterns. Is there any evidence that low-GI diets reduce the risk of CHD? At present, no epidemiologic study with the prospective intent to measure dietary GI has been conducted, but retrospective analysis of existing cross-sectional and prospective studies now underway is possible.

Intervention by reduction of dietary GI may modify risk factors during short- and long-term studies. Is the evidence limited to observations of blood lipid fractions or have other, more recently identified risk factors, been investigated? Insulin-stimulated glucose uptake may be at the heart of this topic. Reduced insulin-stimulated glucose uptake may contribute to long periods of hyperinsulinemia, during which adverse blood lipid and fibrinolytic profiles prevail and contribute to the atherosclerotic process (2). Does lowering dietary GI increase insulin-stimulated glucose uptake? Furthermore, if this can be achieved in clinical practice, can such a change be shown to have any demonstrable short- or long-term clinical benefits?

Finally, it must be remembered that no single dietary characteristic can be changed without altering another. Whereas no published reports specifically address the issue, a reasonable hypothesis is that, in Western populations, a low-GI diet is a marker for a healthy lifestyle. In the United Kingdom, persons who consume low-GI diets tend to have higher incomes, be better educated and more physically active, and smoke less than those persons who consume high-GI diets, and the lowest dietary GI values are seen in women rather than in men (AR Leeds, unpublished observations, 1999; 3).

EPIDEMIOLOGIC STUDIES

Prospective studies

Epidemiologic evidence that a high glycemic load from dietary carbohydrates increases risk of CHD was first reported in 2000 by Liu et al (4), using data from 10 y of follow-up on 75,000 women aged 38–63 y who were recruited in 1984. The
glycemic load, which is an expression of the GI of the diet multiplied by the quantity of carbohydrate, was calculated from dietary data obtained by using a validated food-frequency questionnaire. During the 10-y follow-up, 208 fatal and 553 nonfatal myocardial infarctions occurred. Dietary glycemic load was directly associated with risk of CHD after adjustment for smoking, age, total energy intake, and other CHD risk factors. The GIs of the quintiles were 72, 75, 77, 78, and 80 (against bread standards), and the glycemic loads were 117, 145, 161, 177, and 206 g/d—not particularly wide ranges. The relative risk of CHD was ≈ 2 in the upper tertile of glycemic load in the women with body mass indexes (in kg/m²) of 23–29 and >29, suggesting a relation between GI and load and obese and overweight. This study has been criticized for relying on food-frequency data.

Cross-sectional studies

Frost et al (3) then undertook a retrospective analysis of 7-d weighed records of 1420 British adults taken in 1986–1987 in Britain’s first cross-sectional dietary survey, calculating GIs of the diets and relating them to cardiac risk factors. The results showed a significant negative correlation between serum HDL cholesterol and GI. The relation was strongest in women (P < 0.0001, for men P = 0.02) in whom the difference in the HDL cholesterol between the highest GI quintile (GI = 92) and the lowest (GI = 77) was 0.25 mmol/L, a difference that might be expected to be linked to a 29% reduction of CHD morbidity (3). In an associated article, Katan (5) noted that people who “eat lots of beans,” that is, those who consume low-GI diets, differ from those at the other end of the GI scale in many ways, and that multivariate analysis as used by Frost et al (3) did not fully eliminate confounding factors, including those that were measured in the study. Results consistent with the findings of Frost were reported by Ford and Liu (6), who studied data from nearly 14000 US subjects aged >20 y. The subjects were participants in the third National Health and Nutrition Examination Survey (NHANES III) conducted in 1988–1994. Ford and Lui reported an inverse relation between dietary GI and plasma HDL cholesterol concentrations. After adjustments for other variables, the HDL concentrations for the lowest and highest GI quintiles were 1.36 and 1.26 mmol/L, respectively.

INTERVENTION STUDIES

Studies of nondiabetic persons with hyperlipidemia

Dyslipidemia that is associated with insulin sensitivity characterized by high triacylglycerol and high LDL-cholesterol concentrations might be expected to respond to changes achieved with low-GI diets. In an early study, Jenkins et al (7) showed that different subtypes of patients with dyslipidemia responded differently to low-GI diets. Thirty subjects were treated with a control high-GI diet for 1 mo, then with a low-GI diet for 1 mo, and finally by a high-GI diet for 1 mo. Six subjects with a type IIa hypercholesterolemia showed little change in values, whereas 24 subjects with a variety of types (IIb and IV) characterized by hypertriglyceridemia showed significant decreases in triacylglycerol (by ≈20%), in LDL cholesterol (by 7–10%), and in total cholesterol (by 7–9%). Although great effort had been made to control changes in other dietary variables, there were inevitably small but significant changes in soluble fiber, total energy, fat, and total carbohydrate intakes, making it difficult to be absolutely certain that the observed changes were attributable to the very great reduction in GI, from 84 to 73.

Studies of patients with diabetes mellitus

Most other published works on GI and blood lipids reported findings in subjects with type 2 diabetes. In a carefully controlled study reported by Wolever et al (8), 15 patients with type 2 diabetes were treated with a low-GI diet (GI = 60) for 2 wk and a high-GI diet (GI = 87) for 2 wk. In subjects receiving the low-GI diet, area under the glucose curve after a standard breakfast was reduced by 29%, urinary C peptide (reflecting insulin secretion) was reduced by 30%, and plasma fructosamine was significantly reduced (P = 0.044), compared with subjects receiving the high-GI diet. Total blood cholesterol was significantly reduced after the low-GI diet (P = 0.017), but a reduction in plasma triacylglycerol was not significant. In 1999, Jarvi et al (9) reported a tightly controlled crossover study in which 20 patients with type 2 diabetes were randomly assigned to receive low-GI (GI = 57) and high-GI (GI = 83) diets for 24 consecutive days. Body weights were maintained throughout the study period by adjusting energy intake. Subjects’ insulin sensitivity, which was measured at the beginning and end of the study period by using a euglycemic clamp procedure, were higher after both diets but were more so after the low-GI diet. Fasting plasma insulin concentrations were lower after both diets, as were fructosamine, glycated hemoglobin, and fasting plasma glucose concentrations. Serum total cholesterol (P = 0.002), LDL-cholesterol (P = 0.003), and apolipoprotein B (P = 0.006) concentrations were significantly lower after the low-GI diet than after the high-GI diet. HDL-cholesterol concentrations were lower after both diets. However, the area under the nonesterified fatty acid (NEFA) curve was, if anything, higher after the low-GI diet than after the high-GI diet. In this study, plasminogen activator inhibitor-1 (PAI-1) was significantly reduced, by 58% (P < 0.01), after the low-GI diet, but was unchanged after the high-GI diet. The authors attributed the change (the first evidence of a beneficial effect of low-GI diet on fibrinolysis) to the lowered prevailing insulin concentrations. The authors concluded that, in patients with type 2 diabetes, a strictly controlled diet in which most starchy foods had low GIs resulted in a considerably improved metabolic profile compared with a high-GI diet.

Studies of patients with coronary artery disease

Prospective intervention studies to determine the effect of low-GI diets on insulin sensitivity, either in vivo or in vitro (in biopsy specimens), would help to determine how insulin sensitivity causes some of the changes of biomarkers described above. Frost et al (10) recruited 60 patients awaiting coronary artery bypass grafting (CABG) and 30 control patients awaiting valve surgery and with no evidence of coronary artery disease for determination of in vitro insulin sensitivity (measured with labeled glucose uptake by using adipocytes from pretestinal tissue). Insulin-stimulated glucose uptake in the patients with coronary artery disease was significantly lower (P < 0.05) than that in the control patients. Subsequently, 32 patients awaiting CABG were randomly assigned to receive either low- or high-GI diets for 4 wk before surgery, at which point biopsy specimens from pretesternal subcutaneous fat were used to study insulin stimulated glucose uptake (11). At the same time, the relation of the in vitro method to hyperglycemic clamp measures was studied in a group of 16 patients with CABG. The relation of insulin-stimulated glucose uptake in adipocytes correlated significantly with results.
from the clamp \( r = 0.72, P < 0.02 \), and insulin-stimulated glucose uptake of adipocytes after the low-GI diet was significantly higher than that after the high-GI diet \( P < 0.05 \). There was also a significant reduction in insulin incremental area after the low-GI diet \( P < 0.05 \). However, HDL-cholesterol concentrations did not change significantly.

**Studies of patients with a family history of coronary artery disease**

To investigate the effect of a low-GI diet in preoperative patients without established arterial disease but with a family history of heart disease, 28 women awaiting abdominal surgery for gynecologic conditions were recruited (12). The subjects were categorized according to presence or absence of family history of heart disease. Sixteen subjects with positive family history were randomly assigned to receive a low- or high-GI diet \( n = 8 \) per diet), and 14 subjects without such a history were likewise randomly assigned \( n = 7 \) per diet). In vivo insulin sensitivity was measured by using a short insulin tolerance test (SITT), and in vitro studies were done on adipocytes removed from the subcutaneous and omental regions at surgery. Because the adipocyte cytokine tumor necrosis factor \( \alpha \) (TNF-\( \alpha \)) may play a role in insulin sensitivity, its production in vitro from adipocytes was also studied. A significant difference between the decrease in glucose (during the SITT) before and after the low-GI diets in both those with and without a family history of CHD was shown \( P < 0.03 \) and \( P < 0.05 \), respectively), indicating in both cases increased sensitivity to insulin. Glucose uptake by adipocytes increased significantly during the low-GI diet compared with high-GI diet in both subcutaneous and abdominal adipocytes \( P < 0.03 \) and \( P < 0.05 \), respectively). TNF-\( \alpha \) production by adipocytes was significantly greater in the subjects with a family history of CHD than in the control subjects. However, no difference in TNF-\( \alpha \) production was shown after the low- and high-GI diets, but it must be noted that the diets were designed to achieve weight maintenance. Reduction of TNF-\( \alpha \), which in other experimental contexts has been shown to be related to insulin resistance (13), may be dependent on the reduction of adipose tissue mass. The findings confirmed the increased insulin-stimulated glucose uptake in vivo in human subjects after 4 wk of dietary intervention with low-GI diet. Could a reduction in postprandial NEFAs be a major effect of low-GI diets? Low-GI diets have been shown to be associated with lower postprandial NEFA concentrations (10) which may be associated with increased glucose uptake by muscle, reduced VLDL synthesis, and in turn reduced small dense LDL-cholesterol (14) and increased HDL-cholesterol concentrations. Studies on mechanisms should distinguish clearly between experimental designs in which adipose mass is deliberately maintained and those in which adipose mass is decreased. In free-living situations, an effect of low-GI diets in reducing adipose mass might be an important mechanism in increasing insulin sensitivity, mediated by TNF-\( \alpha \) or the recently described Resistin (15).

**INTERPRETIVE ISSUES**

Another overlooked component of a low-GI diet may bear some consideration. Carbohydrate-drink meals that generated large postprandial hyperglycemic responses in adult subjects also increased urinary chromium losses (16). Also, chromium depletion has been shown to be associated with hyperglycemia and dyslipidemia (17). It may be possible that persistent consumption of high-GI meals causes a gradual depletion of body-tissue chromium concentrations. The insulin receptor tyrosine phosphatase is activated by chromium (18); therefore, chromium status may influence insulin sensitivity. It may be useful to know the chromium contents of low-GI compared with high-GI diets, and whether its bioavailability differs in the diets. At this stage, no published studies have linked dietary GI and chromium status.

Because population studies have focused only on groups in the Western world, where dietary GIs in the middle-to-high range are prevalent, relations between dietary GI and markers of vascular risk and morbidity and mortality outcomes have only been observed at that GI range. Further studies of low-GI subgroups within these populations may be rewarding. Prospective, controlled, intervention trials with a duration >4 wk are indicated to determine whether increased tissue and whole-body sensitivity to insulin is sustained over time and whether there is a reduction in fatal or nonfatal myocardial infarction. Low-GI dietary intervention is inexpensive and the benefit may be great.

**CONCLUSION**

GI is a dietary variable that can be manipulated easily and with good patient compliance, thus achieving a reduction in average dietary GI values from \( \approx 70 \) to just less than 60. Reductions of this magnitude have been shown to increase insulin-stimulated glucose uptake after 4 wk of dietary treatment and to improve some markers of risk of vascular disease. Low-GI diets may reduce plasma fatty acids and may suppress production or release of signaling hormones from adipose tissue, in turn tending to reverse dyslipidemia and insulin resistance. Proof of the clinical value of low-GI diets in heart disease awaits prospective trials in persons with established disease and in those with an adverse pattern of risk factors for vascular disease.

**REFERENCES**