The Glycemic Index

Physiological Mechanisms Relating to Obesity, Diabetes, and Cardiovascular Disease

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The glycemic index was proposed in 1981 as an alternative system for classifying carbohydrate-containing food. Since then, several hundred scientific articles and numerous popular diet books have been published on the topic. However, the clinical significance of the glycemic index remains the subject of debate. The purpose of this review is to examine the physiological effects of the glycemic index and the relevance of these effects in preventing and treating obesity, diabetes, and cardiovascular disease.

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ALL DIETARY CARBOHYDRATES, from starch to table sugar, share a basic biological property: they can be digested or converted into glucose. Digestion rate, and therefore blood glucose response, is commonly thought to be determined by saccharide chain length, giving rise to the terms *complex carbohydrate* and *simple sugar*. This view, which has its origins in the beginning of the century,[1] receives at least tacit support from nutritional recommendations that advocate increased consumption of starchy foods and decreased consumption of sugar.[2]

Throughout the past 25 years, however, the relevance of chain length in carbohydrate digestion rate has been questioned. Wahlqvist et al[3] demonstrated similar changes in blood glucose, insulin, and fatty acid concentrations after glucose as a monosaccharide, disaccharide, oligosaccharide, or polysaccharide (starch) had been consumed. Bantle et al[4] found no differences in blood glucose responses to meals with 25% sucrose compared with meals containing a similar amount of energy from either potato or wheat starch. Nevertheless, the physiological effects of carbohydrates may vary substantially, as demonstrated by marked differences in glycemic and insulinemic responses to ingestion of isoenergetic amounts of white bread vs pasta (FIGURE 1).[5] For this reason, Jenkins et al[6] proposed the glycemic index as a system for classifying carbohydrate-containing foods according to glycemic response. This review examines the hormonal and metabolic events that occur following consumption of foods whose glycemic index differs and how these events might affect risk for or treatment of obesity, diabetes, and cardiovascular disease.

METHODS

A MEDLINE search using the key words *glycemic index* or *glycaemic index* identified a total of 311 citations, including animal and human studies. These citations were examined for relevance to pathophysiological mechanisms affecting body-weight regulation, diabetes, or cardiovascular disease. Articles relating metabolic events in the postprandial state to disease risk were found by additional literature searches and discussions with experts in the fields of nutrition and diabetes. Popular books advocating the use of low–glycemic index,[7-9] reduced carbohydrate,[10] or low-energy-density[11] diets were examined. Interventional studies involving cardiovascular disease–related end points were selected if they controlled for the effects of macronutrient composition.

GLYCEMIC INDEX: A PHYSIOLOGICAL BASIS FOR CLASSIFYING CARBOHYDRATE

Glycemic index is defined as the incremental area under the glucose response curve after a standard amount of carbohydrate from a test food relative to that of a control food (either white bread or glucose) is consumed.[12,13] The glycemic index of a specific food or meal is determined primarily by the nature of the carbohydrate consumed and by other dietary factors that affect nutrient digestibility or insulin secretion.[14] As shown in the TABLE, glycemic index values for common foods differ by more

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than 5-fold.[16] In general, most refined starchy foods eaten in the United States have a high glycemic index, whereas nonstarchy vegetables, fruit, and legumes tend to have a low glycemic index. Coingestion of fat or protein lowers the glycemic index of individual foods somewhat[17,18] but does not change their hierarchical relationship with regard to glycemic index.[19] Despite initial concerns,[20,21] the glycemic response to mixed meals can be predicted with reasonable accuracy from the glycemic index of constituent foods when standard methods are used.[19,22-26] Regular consumption of high–glycemic index meals, compared with isoenergetic and nutrient-controlled low–glycemic index meals, results in higher average 24-hour blood glucose and insulin levels, higher C-peptide excretion, and higher glycosylated hemoglobin concentrations in nondiabetic and diabetic individuals.[27,28] The term *glycemic load*, defined as the weighted average glycemic index of individual foods multiplied by the percentage of dietary energy as carbohydrate, has been proposed to characterize the impact of foods or dietary patterns with different macronutrient composition on glycemic response: thus, a carrot has a high glycemic index but a low glycemic load, in contrast to a potato, in which both are high (Table).[14,29]

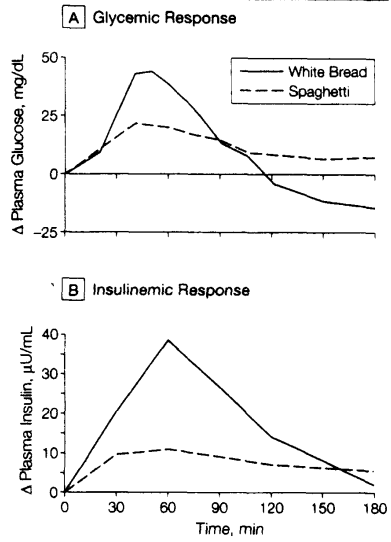
The glycemic index and glycemic load of the average diet in the United States appear to have risen in recent years[30] because of increases in carbohydrate consumption and changes in food-processing technology. What effects might high–glycemic index diets have on health?

ACUTE METABOLIC EVENTS FOLLOWING CONSUMPTION OF A HIGH–GLYCEMIC INDEX MEAL

The body has an obligatory requirement for glucose, approaching 200 g/d, determined largely by the metabolic demands of the brain.[31] Should blood glucose concentration fall below 40 mg/dL (2.2 mmol/L), coma, seizure, or death may ensue. Conversely, blood glucose levels exceeding about 180 mg/dL (10.0 mmol/L) are associated with immediate (glycosuria and calorie loss) and long-term (renal failure, retinopathy, atherosclerosis) consequences.[32] For these reasons, blood glucose concentration is tightly regulated by homeostatic regulatory systems. Hyperglycemia stimulates insulin secretion, promoting uptake of glucose by muscle and adipose tissue. Hypoglycemia elicits secretion of glucagon, epinephrine, cortisol, and growth hormone, counterregulatory hormones that antagonize insulin action and restore normoglycemia.[32]

The rapid absorption of glucose following consumption of a high–glycemic index meal challenges these homeostatic mechanisms, complicating in effect the transition from the postprandial to the postabsorptive state.[23,33-36] Within the first 2 hours after a high–glycemic index meal (FIGURE 2, early postprandial period), integrated incremental blood glucose concentration can be at least twice that after a low–glycemic index meal containing identical nutrients and energy. This relative hyperglycemia, acting in concert with elevated concentrations of the gut hormones glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide, potently stimulates insulin release from pancreatic beta cells and inhibits glucagon release from alpha cells. The resultant high insulin-to-glucagon ratio would tend to exaggerate the normal anabolic responses to eating, including uptake of nutrients by insulin-responsive tissues, stimulation of glycogenesis and lipogenesis, and suppression of gluconeogenesis and lipolysis. Between 2 and 4 hours after a high–glycemic index meal (Figure 2, middle postprandial period), nutrient absorption from the gastrointestinal tract declines, but the biological effects of the high insulin and low glucagon levels persist. Consequently, blood glucose concentration falls rapidly, often into the hypoglycemic range. The physiological significance of this hypoglycemia is demonstrated by a greater fall in glucose oxidation rate after

Figure 1. Glycemic and Insulinemic Responses After Ingestion of Carbohydrates



Responses were measured after ingestion of 50 g of carbohydrate as white bread or spaghetti made from identical ingredients.[5] Qualitatively similar results were obtained after consumption of these foods as part of mixed meals,[22] although nutrient interactions can modulate the magnitude of these responses to some degree.[17,18] Adapted with permission from the *European Journal of Clinical Nutrition*.[5]

Table. Glycemic Index and Glycemic Load Values of Representative Foods*

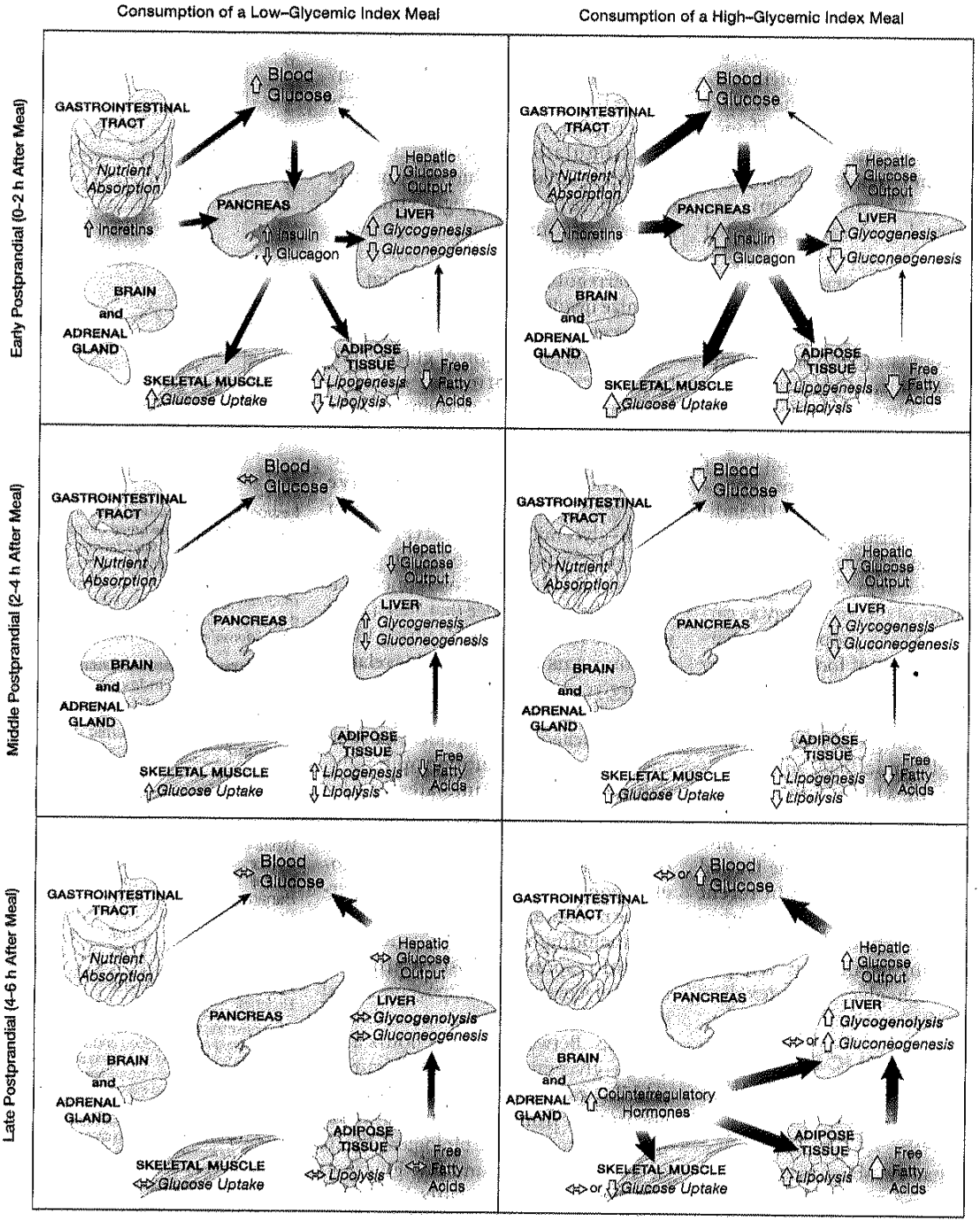
Food	Glycemic Index†	Glycemic Load‡
Instant rice	91	24.8 (110 g)
Baked potato	85	20.3 (110 g)
Corn flakes	84	21.0 (225 mL)
Carrot	71	3.8 (55 g)
White bread	70	21.0 (2 slices)
Rye bread	65	19.5 (2 slices)
Muesli	56	16.8 (110 mL)
Banana	53	13.3 (170 g)
Spaghetti	41	16.4 (55 g)
Apple	36	8.1 (170 g)
Lentil beans	29	5.7 (110 mL)
Milk	27	3.2 (225 mL)
Peanuts	14	0.7 (30 g)
Broccoli	. . .	. . .

*To determine the glycemic index of a specific food, subjects are given a test food and a control food on separate days, each food containing 50 g of available carbohydrate, and changes in blood glucose concentration are measured. Glycemic index is calculated with the trapezoidal rule as the incremental area under the blood glucose curve for 2 hours after the test food is eaten divided by the corresponding area after the control food is eaten, multiplied by 100%. Values for the most commonly consumed carbohydrate-containing foods have been determined and can be obtained from published lists. Ellipses indicate value not computed; the values for most nonstarchy vegetables are too low to measure.

†Glycemic index values are taken from Foster-Powell and Miller[16] and expressed as a percentage of the value for glucose.

‡Glycemic load is calculated as the glycemic index multiplied by grams of carbohydrate per serving size,[15] indicated in parentheses, divided by 100%.

Figure 2. Sequence of Physiological Events After Ingestion of a High–Glycemic Index Meal Compared With a Low–Glycemic Index Meal



Vertical outlined arrows indicate direction and magnitude of change from baseline (preprandial) state indicated by horizontal outlined arrows. Early postprandial period: rapid absorption of carbohydrate after a high–glycemic index meal results in a relatively high blood glucose level and a high insulin-to-glucagon ratio. Middle postprandial period: blood glucose level decreases to below preprandial level, and free fatty acid concentration remains suppressed after a high–glycemic index meal. Late postprandial period: counterregulatory hormones after a high–glycemic index meal restore euglycemia and cause a marked increase in free fatty acid concentration.

consumption of a high– compared with a low–glycemic index carbohydrate during this interval.[37] Free fatty acid, the other major metabolic fuel, is more suppressed after a high–glycemic index meal. Approximately 4 to 6 hours after a high–glycemic index meal (Figure 2, late postprandial period), the low circulating concentrations of metabolic fuels trigger a counterregulatory hormone response that restores euglycemia by stimulating glycogenolytic and gluconeogenic pathways and elevates free fatty acid concentration to levels well above those observed after a low–glycemic index meal. This combination of elevated counterregulatory hormone and free fatty acid levels resembles a state of fasting normally reached only after many hours without food.[38] After a low–glycemic index meal, by contrast, hypoglycemia and its hormonal sequelae do not occur during the postprandial period owing to continued absorption of nutrients from the gastrointestinal tract and rising hepatic glucose output. Thus, consumption of meals containing identical energy and nutrients can produce markedly different physiological responses throughout a 6-hour period.

Although genetic factors would be expected to influence individual response, postprandial hypoglycemia following consumption of high–glycemic index carbohydrate is so common as to be considered normal. For example, mean plasma glucose nadir was below the fasting level in the majority of 650 nondiabetic individuals who had an oral glucose tolerance test and was below 47 mg/dL (2.6 mmol/L) in 10% of the individuals.[39] A similar phenomenon has been observed after consumption of mixed meals containing high–glycemic index foods.[23,40] Moreover, postprandial hypoglycemia may be especially pronounced in obesity.[41]

OBESITY

The decreased circulating concentrations of metabolic fuels in the middle postprandial period after a high–glycemic index meal would be expected to result in increased hunger and food intake as the body attempts to restore energy homeostasis. For example, modest transient decreases in blood glucose concentration, either spontaneous or insulin-induced, were associated with hunger and initiation of feeding in rats and humans.[42,43] Administration of 2-deoxyglucose, a compound that inhibits intracellular glucose use, increased hunger and food intake in nondiabetic subjects.[44] Indeed, insulin-induced hypoglycemia appears to provoke prolonged hyperphagia, persisting well after restoration of normal blood glucose levels.[45] Furthermore, hyperinsulinemia[46] and hypoglycemia[44,45] may preferentially stimulate consumption of high–glycemic index foods, leading to cycles of hypoglycemia and hyperphagia. Weight-loss efforts may exacerbate this phenomenon, as demonstrated by relatively severe postprandial hypoglycemia after overweight subjects on very low-calorie diets consumed high–glycemic index carbohydrate.[47]

Experimental Evidence

There are no long-term clinical trials examining the effects of dietary glycemic index on body-weight regulation. However, numerous animal studies and short-term or small-scale studies in humans have addressed this issue.

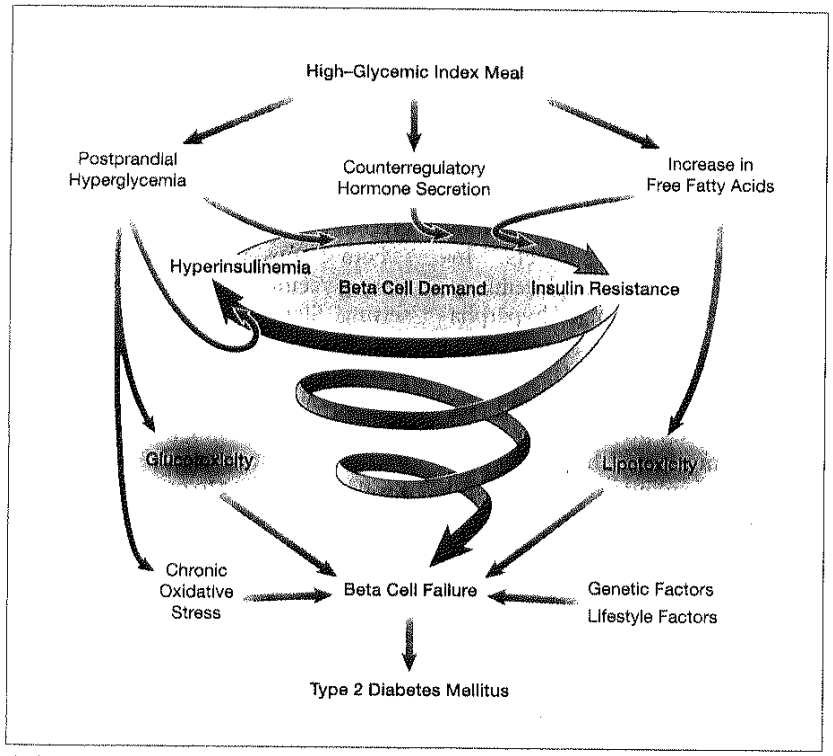
Rats fed amylopectin (a high–glycemic index starch) compared with amylose (a low–glycemic index starch) under nutrient- and energy-controlled conditions for 3 to 5 weeks exhibited physiological changes that would favor fat deposition, including larger adipocyte diameter, increased glucose incorporation into lipids, and greater fatty acid synthase and Glut 4 gene expression in fat tissue.[48-50] By 7 weeks, animals fed a high–glycemic index diet developed increased epididymal fat mass,[51] and by 32 weeks, according to preliminary data, they developed marked obesity.[52]

Among 16 single-day studies in humans, 15 found lower satiety, increased hunger, or higher voluntary food intake after consumption of high– compared with low–glycemic index meals.[53] For example, obese children were given high–glycemic index instant oatmeal or low–glycemic index steel-cut oats with identical energy and macronutrient content at breakfast and lunch, and ad libitum energy consumption was monitored throughout the afternoon. Energy intake was 53% higher after the high– compared with the low–glycemic index meals.[23]

Four groups studied the effects of dietary glycemic index in an outpatient setting. Slabber et al[54] found significantly more weight loss in obese hyperinsulinemic women after 12 weeks of consuming an energy-restricted low– compared with high–glycemic index diet (crossover arm: −7.4 vs −4.5 kg; $P=.04$). According to preliminary data, Bouche et al[55] found lower adiposity by DXA scan in 11 obese men after 5 weeks on an energy- and nutrient-controlled low– compared with high–glycemic index diet (a difference of −0.5 kg; $P<.05$). Spieth et al[56] determined retrospectively that body mass index (BMI) decreased significantly more throughout an average of 4 months in children prescribed an ad libitum low–glycemic index diet compared with those prescribed an energy-restricted low-fat diet, after the effects of confounding factors were controlled (a difference of −1.2 kg/m^2; $P<.001$). In addition, Clapp[57] found less maternal weight gain during pregnancy (11.8 vs 19.7 kg; $P<.01$) and lower placental weight among nonobese women treated with controlled low– compared with high–glycemic index diets. Of particular note, infants born to women in the low–glycemic index group had lower adiposity (301 vs 402 g; $P<.01$).

An interesting parallel can be drawn to α-glucosidase inhibitors, a class of oral hypoglycemic agents that slow digestion of starch in the gastrointestinal tract, in effect lowering glycemic index. These medications not only improve measures of glycemic control, but also produce modest weight loss (although adverse gastrointestinal effects commonly occur).[58] In contrast, most other drugs used in the treatment of diabetes cause weight gain.

Figure 3. High–Glycemic Index Diet and Risk for Type 2 Diabetes Mellitus



The hypothetical model relates a high–glycemic index diet to increased risk for type 2 diabetes mellitus.

DIABETES MELLITUS

FIGURE 3 presents a hypothetical model in which dietary glycemic index alters risk for type 2 diabetes, independent of body weight change, via effects on hyperinsulinemia, insulin resistance, beta cell demand, and ultimately beta cell function.

Calorie for calorie, high–glycemic index meals stimulate more insulin secretion than low–glycemic index meals[27,28] because of relative postprandial hyperglycemia and increased incretin levels. This state of primary hyperinsulinemia may in turn cause insulin resistance, as demonstrated by decreased whole-body glucose disposal after insulin infusion under euglycemic conditions in humans.[59] Indeed, primary hyperinsulinemia produced by insulin treatment of normal rats lowered insulin sensitivity of muscle but increased insulin sensitivity of fat.[60] These physiological changes, similar to those observed after muscle-specific inactivation of the insulin receptor gene, would promote redistribution of metabolic substrates to adipose tissue and, as argued by Kim et al,[61] predispose to diabetes.

Insulin resistance may also occur with a high–glycemic index diet because of the direct effects of hyperglycemia,[62] counterregulatory hormone secretion, and increased late postprandial serum free fatty acid levels.[63,64] Even a modest elevation in blood glucose concentration, less than the difference in postprandial glycemia often observed after consumption of high–compared with low–glycemic index foods, may produce insulin resistance in humans.[62] Insulin resistance, in turn, generally leads to compensatory hyperinsulinemia. Thus, habitual consumption of high–glycemic index meals may initiate a cycle of hyperinsulinemia and insulin resistance that places the beta cell under long-term increased demand.

Several studies demonstrate how increased demand for insulin and hyperinsulinemia itself can directly compromise beta cell function. Sako and Grill[65] produced hyperglycemia by glucose infusion in nondiabetic rats for 48 hours, with and without coadministration of diazoxide, a potassium adenosine triphosphate channel agonist that inhibits insulin secretion. After this treatment, they measured glucose-induced insulin secretion in isolated beta cells. Animals that did not receive diazoxide showed hyperinsulinemia in vivo and marked inhibition of insulin secretion in vitro, whereas diazoxide treatment prevented in vivo hyperinsulinemia and preserved beta cell function in vitro. Del Prato et al[59] showed that long-term insulin infusion under euglycemic conditions in healthy human subjects decreased insulin response to intravenous glucose and decreased insulin sensitivity, as assessed by hyperglycemic clamp study. Conversely, prior somatostatin treatment to achieve beta cell rest increased insulin secretion rate, improved insulin pulse mass, and restored the proinsulin-to-insulin ratio to normal levels in subjects with type 2 diabetes.[66]

In addition to the mechanisms described above, high dietary glycemic index may also impair beta cell function through the direct effects of elevated blood glucose and free fatty acid levels. Hyperglycemia is known to cause beta cell dysfunction, a phenomenon that has been called *glucotoxicity*.[62] For example, Leahy et al[67] studied in vitro islet-cell function in partially pancreatectomized rats that drank either water or a sucrose solution. Compared with the water-treated animals, those treated with sucrose showed a modest 15-mg/dL (0.8-mmol/L) rise in postprandial blood glucose levels and a 75% reduction in glucose-stimulated insulin response. Jonas et al[68] performed 85% to 95% pancreatectomies on rats, resulting in differing degrees of hyperglycemia but no increase in plasma free fatty acid concentrations. Four weeks after surgery, analysis of beta cell messenger RNA (mRNA) showed de-

creased expression of genes associated with glucose-induced insulin release and lower levels of transcription factors involved in differentiation in all groups of animals, even those with minimal hyperglycemia (<100 mg/dL [5.6 mmol/L]). Long-term oxidative stress may compound these glucotoxic effects, as demonstrated by both in vitro and in vivo studies.[69] The increased free fatty acid concentrations in the late postprandial period after a high–glycemic index meal may also impair beta cell function, a process termed *lipotoxicity*.[64]

A variety of genetic and environmental factors are known to affect risk for type 2 diabetes. The studies described above suggest that a high–glycemic index diet might increase risk in susceptible individuals by overstimulation, glucotoxicity, and lipotoxicity, 3 critical metabolic factors thought to contribute to beta cell failure.[70]

Experimental Evidence

Six studies compared the effects of high–glycemic index diets with those of nutrient- and energy-controlled low–glycemic index diets in either nondiabetic or diabetic rats. After 3 weeks, rats treated with a high–glycemic index diet showed greater Glut 4 gene expression in fat tissue and lower maximal insulin-stimulated glucose oxidation.[48,49] Hyperinsulinemia without insulin resistance developed by 7 weeks,[51] and insulin resistance developed by 8 to 12 weeks, as assessed by an intravenous glucose tolerance test.[71,72]

In humans, consumption of high–glycemic index meals compared with energy- and nutrient-controlled low–glycemic index meals adversely affects glucose tolerance at a subsequent meal.[73] Net posthepatic glucose appearance was substantially higher 4.5 hours after ingestion of high– compared with low–glycemic index carbohydrate, suggesting resistance to insulin-stimulated uptake of glucose by the liver.[74] However, studies of 3 to 4 weeks' duration of whole-body insulin resistance with diets differing in glycemic index yielded inconsistent results.[75,76]

There are no long-term interventional studies examining the effects of dietary glycemic index in preventing diabetes mellitus, although 3 observational studies address this issue. The Nurses' Health Study[29] and Health Professionals' Follow-up Study[77] found that the risk of diabetes was higher among individuals in the highest quintile of glycemic index or glycemic load compared with those in the lowest quintile, after adjustment for BMI and other potentially confounding variables. By contrast, no meaningful associations were found between glycemic index or glycemic load and diabetes risk among women in the Iowa Women's Health Study.[78]

Management of Type 1 and Type 2 Diabetes

A low–glycemic index diet may in theory improve management of diabetes by lowering early postprandial hyperglycemia and decreasing risk for postabsorptive hypoglycemia. Since 1988, 13 interventional studies have examined this possibility, although some were apparently underpowered (subject number: 6-104; duration: 12 days to 12 months). Twelve studies found improvement in at least 1 measure of glycemic control (hemoglobin A_{1c}, glycated serum proteins, or blood glucose level) with the low– vs high–glycemic index diet,[79-90] 1 found no difference between diets,[91] and none found improvement with the high– vs low–glycemic index diet. One of these studies reported a lower number of hypoglycemic events with the low–glycemic index diet.[89] In addition, quality-of-life measures were higher among children who had type 1 diabetes and were counseled to follow a low–glycemic index diet compared with those who received standard dietary advice.[90] An observational study found that glycemic index was positively related to hemoglobin A_{1c} among 2810 patients with type 1 diabetes mellitus in Europe.[92] Recently, the American Diabetes Association, citing methodological issues with some of these studies, concluded that there is insufficient evidence of substantial long-term benefit to recommend use of glycemic index in the management of diabetes.[93] Other professional associations do recognize a role for glycemic index in this regard.[13,94-96]

CARDIOVASCULAR DISEASE

The higher postprandial blood glucose and insulin levels found in a high–glycemic index diet may affect risk for cardiovascular disease (CVD) through the physiological mechanisms discussed below.

Postprandial Hyperglycemia

Postprandial hyperglycemia has recently been recognized as an important risk factor for CVD not only among persons with diabetes, but also among the general population.[97] Balkau et al[98] examined 20-year mortality in 3 European cohorts and found an odds ratio (OR) of 1.6 for mortality among those in the highest quintile of blood glucose level 2 hours after an oral glucose tolerance test. de Vegt et al[99] found that 2-hour, but not fasting, blood glucose concentration was independently associated with all-cause and cardiovascular mortality in a population without diabetes. Temelkova-Kurktschiev et al[100] showed that postchallenge glucose and glycemic spikes were more strongly associated with intima-media thickness than fasting glucose or glycosylated hemoglobin levels in nondiabetic subjects.

Postprandial hyperglycemia appears to increase CVD risk by producing oxidative stress.[101,102] In vitro studies have shown that glucose causes oxidation of membrane lipids, proteins, lipoproteins, and DNA and activates inflammation. In vivo, hyperglycemia increases reactive oxygen species and lowers antioxidant concentrations, changes that are associated with increased blood pressure, accelerated blood clot formation, and reduced endothelium-dependent blood flow.[101-105] Of particular relevance, the adverse effects of hyperglycemia on endothelial function and other CVD-related outcomes occur rapidly following consumption of glucose or mixed

meals that induce high postprandial glycemia.[104,106] Administration of antioxidants can prevent or reverse these adverse effects.[104,105] Thus, it is reasonable to hypothesize that habitual consumption of high–glycemic index meals increases the risk for CVD, at least in part by hyperglycemia-induced oxidative stress.

Hyperinsulinemia

A high–glycemic index diet may also affect the risk for CVD by increasing insulin levels (incremental area under the insulin curve may be 2-fold greater after macronutrient-controlled high– compared with low–glycemic index mixed meals[22,26]). Hyperinsulinemia is believed to mediate, in part, the increased risk for heart disease associated with the insulin resistance syndrome (also known as syndrome X or the metabolic syndrome) through independent effects on blood pressure, serum lipids, coagulation factors, inflammatory mediators, and endothelial function.[107-109] For example, the OR of developing ischemic heart disease increased by 60% for each 1-SD increase in fasting insulin level among men aged 45 to 76 years, after BMI and other risk factors were controlled.[110]

Experimental Evidence

Thirteen interventional studies have examined the effects of dietary GI on serum lipids under macronutrient-controlled conditions (FIGURE 4).* Because of the lack of statistical detail and methodological differences, confidence intervals cannot be estimated, nor can a formal meta-analysis be provided. Nevertheless, the low–glycemic index diets resulted in lower triglyceride levels and low-density lipoprotein cholesterol levels and lower ratio of total to high-density lipoprotein (HDL) cholesterol in most of these studies. In one study, marked reduction of plasminogen activator inhibitor 1, a novel CVD risk factor, was also observed.[88] Of 6 observational studies, 5 demonstrated higher HDL cholesterol levels, lower triglyceride levels, or lower myocardial infarction rates among individuals in the lowest category of glycemic index or glycemic load compared with those in the highest category, after adjustment for potentially confounding factors.[92,113-116] Two of these studies directly compared glycemic index and glycemic load with respect to serum lipid concentrations: one found that glycemic load had a greater effect[116]; the other, that both had similar effects.[113] The sixth observational study found no significant association between glycemic index and heart disease.[117]

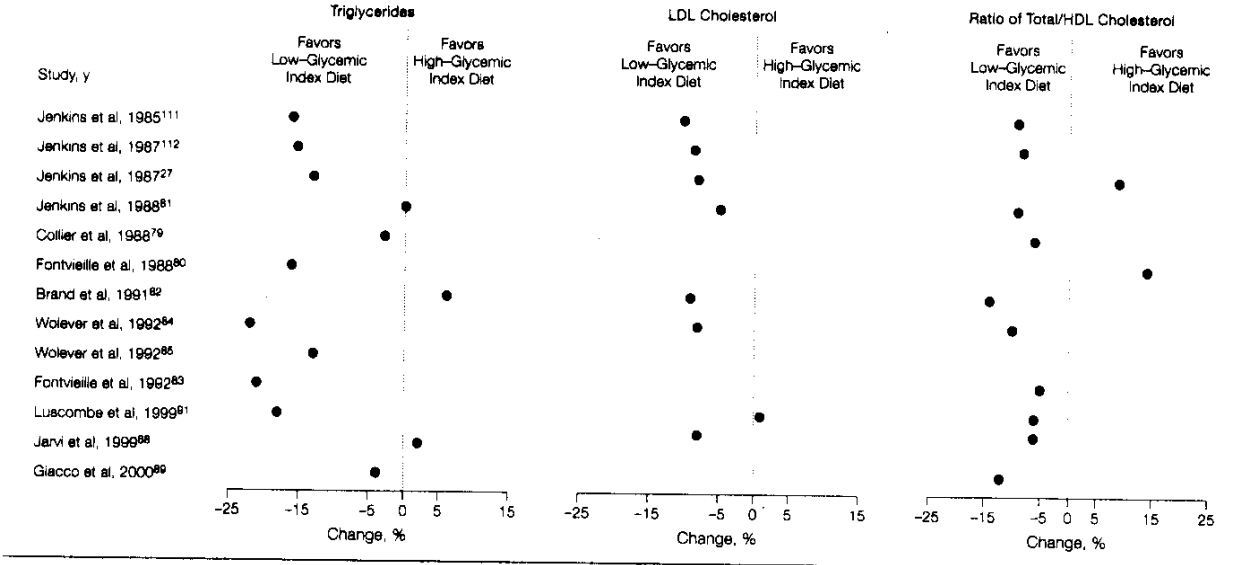
*References 27, 79-85, 88, 89, 91, 111, 112.

CONTROVERSIES

The clinical relevance of glycemic index has been vigorously debated in recent years. Some experts argue that any beneficial effects of low–glycemic index diets on insulin resistance and related CVD risk factors are small in comparison with that of reduced-carbohydrate diets.[118] Another concern is that the concept of glycemic index might be too complicated to be practical[119] or that potentially simpler principles, such as energy density, effectively incorporate many of the advantageous aspects of low–glycemic index diets.

In response to these concerns, the following points should be considered. First, several dozen interventional studies have described statistically and clini-

Figure 4. Interventional Studies Examining the Effects of Dietary Glycemic Index on Serum Lipids



The data are depicted as percentage of change in lipid concentration after a low– compared with a high–glycemic index diet. LDL indicates low-density lipoprotein; HDL, high-density lipoprotein.

cally significant improvements in end points related to obesity, diabetes, or CVD among free-living subjects consuming self-selected low- vs high–glycemic index diets. Second, observational studies link glycemic index to disease risk within prevailing dietary patterns. Third, several studies suggest that the beneficial effects of a low–glycemic index diet may be independent of, or additive to, that of other dietary manipulations involving carbohydrate content[116] or energy density.[23] Fourth, low–glycemic index diets have no known adverse effects, in contrast with low-fat diets, for example, that may adversely affect serum HDL cholesterol and triglyceride concentrations.[120] Fifth, whereas the concept of glycemic index may be complex from a food science perspective, its public health application can be simple: increase consumption of fruits, vegetables, and legumes, choose grain products processed according to traditional rather than modern methods (eg, pasta, stone-ground breads, old-fashioned oatmeal), and limit intake of potatoes and concentrated sugar. Indeed, these recommendations would tend to promote diets high in fiber, micronutrients, and antioxidants and low in energy density. Thus, the physician should consider this concept a practical guide, although routine measurement of the glycemic index and glycemic load of patients' diets must await development of applicable computer programs.

Other questions remain unresolved: How do the long-term benefits of low–glycemic index and low–glycemic load diets compare with each other and with those of diets focused on other nutritional properties? To what extent do associated factors (eg, fiber, micronutrients, or antioxidants) contribute to the observed protective effects of low–glycemic index diets? How does glycemic index interact with genetic and lifestyle risk factors in the initiation and progression of disease? Mechanistically oriented studies, multicenter clinical trials, and prospective epidemiological analyses are needed to address these issues.

CONCLUSION

The rate of carbohydrate absorption after a meal, as quantified by glycemic index, has significant effects on postprandial hormonal and metabolic responses. High–glycemic index meals produce an initial period of high blood glucose and insulin levels, followed in many individuals by reactive hypoglycemia, counterregulatory hormone secretion, and elevated serum free fatty acid concentrations. These events may promote excessive food intake, beta cell dysfunction, dyslipidemia, and endothelial dysfunction. Thus, the habitual consumption of high–glycemic index foods may increase risk for obesity, type 2 diabetes, and heart disease, a hypothesis that derives considerable support from laboratory studies, clinical trials, and epidemiological analyses. Despite areas of continuing controversy, clinical use of glycemic index as a qualitative guide to food selection would seem to be prudent in view of the preponderance of evidence suggesting benefit and absence of adverse effects.

Finally, the physiological mechanisms considered here were proposed more than 75 years ago in THE JOURNAL. Seale Harris, a colleague of Fredrick Banting, speculated that "one of the causes of hyperinsulinism [and hypoglycemia] is the excessive ingestion of glucose-forming foods and that, as the result of overactivity induced by overeating, the islands of Langerhans become exhausted and . . . (diabetes) follows. It is possible that the hunger incident to hyperinsulinism may be a cause of overeating, and, therefore, the obesity that so often precedes diabetes."[121]

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