

Glycemic index, glycemic load, and risk of type 2 diabetes¹⁻³

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ABSTRACT The possibility that high, long-term intake of carbohydrates that are rapidly absorbed as glucose may increase the risk of type 2 diabetes has been a long-standing controversy. Two main mechanisms have been hypothesized, one mediated by increases in insulin resistance and the other by pancreatic exhaustion as a result of the increased demand for insulin. During the past decade, several lines of evidence have collectively provided strong support for a relation between such diets and diabetes incidence. In animals and in short-term human studies, a high intake of carbohydrates with a high glycemic index (a relative measure of the incremental glucose response per gram of carbohydrate) produced greater insulin resistance than did the intake of low-glycemic-index carbohydrates. In large prospective epidemiologic studies, both the glycemic index and the glycemic load (the glycemic index multiplied by the amount of carbohydrate) of the overall diet have been associated with a greater risk of type 2 diabetes in both men and women. Conversely, a higher intake of cereal fiber has been consistently associated with lower diabetes risk. In diabetic patients, evidence from medium-term studies suggests that replacing high-glycemic-index carbohydrates with a low-glycemic-index forms will improve glycemic control and, among persons treated with insulin, will reduce hypoglycemic episodes. These dietary changes, which can be made by replacing products made with white flour and potatoes with whole-grain, minimally refined cereal products, have also been associated with a lower risk of cardiovascular disease and can be an appropriate component of recommendations for an overall healthy diet. *Am J Clin Nutr* 2002;76(suppl):274S–80S.

KEY WORDS Diabetes, carbohydrate, insulin, glucose, prevention, fiber, insulin resistance

INTRODUCTION

Because diabetes is fundamentally a condition of disordered glucose metabolism, it is reasonable to ask whether the type of dietary carbohydrate can influence the risk and course of this disease. In popular literature, sucrose has been portrayed as a particularly dangerous component of the diet despite clear metabolic evidence that many forms of starch have similar effects on blood glucose and insulin concentrations. In response, some professional organizations have taken the position that the form of carbohydrate has little clinical relevance (1). However, many metabolic studies now have shown that food sources of carbohydrate vary greatly in their rate of absorption and effects on blood glucose and insulin concentrations. One way of quantifying this variation

in response to dietary carbohydrate is the glycemic index, pioneered by Jenkins et al (2). Operationally, the glycemic index is the incremental area under the curve of blood glucose produced by a standard amount of carbohydrate in a food, usually 50 g, relative to the incremental area produced by the same amount of carbohydrate from a standard source, usually white bread or glucose. The concept of the glycemic index can also be applied to whole meals or overall diet. For example, in a crossover study of 6 healthy adults, Jenkins et al (3) found that a low-glycemic-index diet containing mainly intact whole grains significantly reduced C-peptide concentrations (a 32% reduction) compared with a high-glycemic-index diet containing primarily refined grain products. Because the amount of carbohydrate in a food or overall diet can vary, we have also introduced the concept of glycemic load, which is the amount of carbohydrate multiplied by its glycemic index. Whether the glycemic index or load of foods or the overall diet has relevance to human health has been a topic of contention, partly because of the lack of long-term studies (4–7). Only recently have data become available from large, long-term epidemiologic studies relating dietary glycemic index or glycemic load to risk of type 2 diabetes, coronary heart disease, and obesity. In this short review, we examine evidence relating dietary glycemic index and glycemic load to type 2 diabetes incidence and the role of the form of dietary carbohydrate in the management of diabetes. Although we focus on dietary glycemic index and load, we appreciate that other aspects of carbohydrate-containing foods, such as fiber and micronutrient content, may also have important health consequences and should be considered in making decisions about diet.

POTENTIAL MECHANISMS FOR REDUCING INCIDENCE OF TYPE 2 DIABETES

From our current understanding of the development of type 2 diabetes, the incidence of this condition should be reduced either

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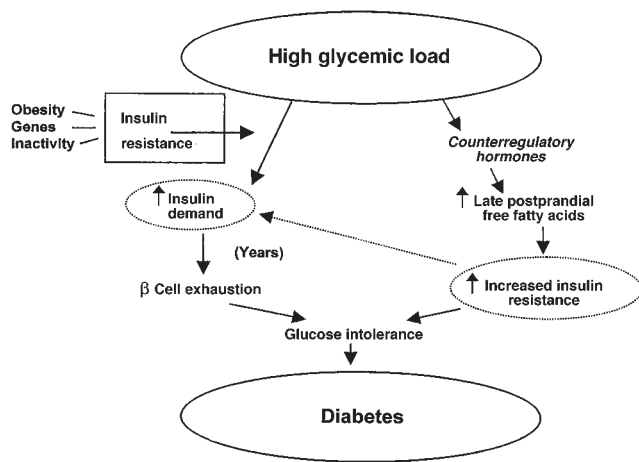


FIGURE 1. Potential mechanisms whereby high-glycemic-load diets could increase risk of type 2 diabetes.

by decreasing insulin demand or by improving insulin sensitivity, the mechanisms of which are depicted in **Figure 1**. Over a period of years, hyperglycemia leads to loss of pancreatic β cell function that can result in glucose intolerance and ultimately an irreversible state of diabetes. The mechanism for this phenomenon is not entirely clear, and it has not been fully resolved whether this loss of pancreatic function results primarily from excessive secretion of insulin (ie, β cell exhaustion) or toxicity to β cells because of hyperglycemia. Nevertheless, either mechanism would predict that a diet that produces higher blood glucose concentrations and greater demand for insulin would increase the risk of type 2 diabetes. By definition, high-glycemic-index forms of carbohydrate are foods that produce high concentrations of blood glucose and increased insulin demand and that, therefore, could plausibly contribute to higher risk of type 2 diabetes. The individual response to a given carbohydrate load is influenced by the degree of underlying insulin resistance, which is, in turn, determined primarily by degree of adiposity, physical activity, genetics, and other aspects of diet. Thus, it might be expected that the adverse metabolic effects of high-glycemic-index foods would be exacerbated in sedentary, overweight, or genetically susceptible persons.

Available evidence also suggests that a high intake of high-glycemic-index carbohydrates can increase insulin resistance, at least in the short term. Feeding rats a diet with a high glycemic index (consisting of amylopectin or glucose) produced more rapid and severe insulin resistance than did feeding rats a low-glycemic-index diet (amylose) (8, 9). In a detailed study among 28 women with and without a history of coronary heart disease, Frost et al (10) randomly assigned one-half of the women to consume high- or low-glycemic-index diets for 3 wk. Insulin resistance measured in vivo and in cultured adipocytes was greater in women consuming the high-glycemic-index diet, and these adverse effects were greatest among those with a history of coronary disease, who had a greater degree of insulin resistance at baseline. The adverse effects of the high-glycemic-index diet appeared to be due to an increased production of free fatty acids in the late postprandial state, presumably as a result of a depression in blood glucose below baseline (reactive hypoglycemia) and possibly mediated by increases in counterregulatory hormones (cortisol, glucagon, and growth hormone) (11).

In a smaller study, Kiens et al (12) did not find an increase in insulin resistance in 7 healthy, lean young men after the subjects had consumed a high-glycemic-index diet. In addition to the small sample size, the low underlying degree of insulin resistance in this group of lean young men may have contributed to the lack of an observed effect. Another recent crossover study involving 11 overweight subjects showed that insulin sensitivity, as measured by the euglycemic hyperinsulinemic clamp, improved after subjects consumed a whole-grain diet compared with a refined-grain diet for 6 wk, independent of body weight (13).

Additional evidence of an adverse effect of high-glycemic-index diets on insulin resistance derives from a series of second meal studies. In this design, breakfasts of constant macronutrient composition but differing in the glycemic index of the carbohydrate are provided, and the glucose and insulin responses to a standardized lunch are measured. Consistently, these studies show that the glucose and insulin responses are greater when the same lunch is fed after the high- compared with the low-glycemic-index breakfasts (14–17). Again, the underlying mechanism appears to be related to the increases in late postprandial free fatty acids after the consumption of a meal with a high glycemic index. This mechanism is supported by studies conducted by Jenkins et al (18), who showed that lipid metabolism could be improved by dividing meals into small snacks (nibbling), thus simulating the slow release of carbohydrates.

ASSESSMENT OF GLYCEMIC INDEX AND GLYCEMIC LOAD IN EPIDEMIOLOGIC STUDIES

Although the results of metabolic studies suggest that long-term consumption of low-glycemic-index carbohydrates should reduce the risk of type 2 diabetes, evaluation of this hypothesis in human populations is important. This might be done in the context of a randomized trial, but as yet, no such trials have been conducted. The feasibility of such a trial is unclear because it would require a large number of subjects and many years of follow-up. Large, prospective epidemiologic studies in which other risk factors for type 2 diabetes can be measured and accounted for are thus the best available alternative.

In metabolic studies, the effects of the glycemic index are typically evaluated by keeping the macronutrient intake constant and varying the glycemic index of carbohydrates. For realistic diets of mixed foods, the total dietary glycemic index can be calculated as a weighted average of the glycemic index values of the individual foods, with the weights corresponding to each food's carbohydrate content. In the early 1980s, 3 studies from Reaven et al (19–21) showed that when individual carbohydrate foods are consumed as part of a mixed meal, differences in glycemic responses between foods no longer exist. These authors postulated that such findings are due to the effects of fat and protein on glycemic responses (22). These studies led a National Institutes of Health consensus conference on diet and exercise in type 2 diabetes to reject the use of the glycemic index (23). Since then, numerous studies aimed at addressing these issues have been conducted, and abundant data now support the importance of the glycemic index in the context of mixed meals (24–27). In particular, studies have shown that although fat and protein affect the absolute glycemic response, they do not affect the relative differences between carbohydrate-containing foods (24, 28, 29). Studies using standardized methods have indicated that the correlation between the glycemic index of mixed meals and the

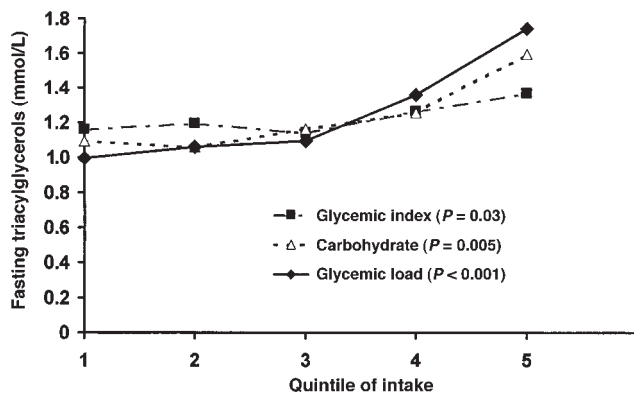


FIGURE 2. Fasting plasma triacylglycerol concentrations according to glycemic index, carbohydrate intake, and glycemic load in the Nurses' Health Study (6).

average glycemic index values of individual component foods ranges from 0.84 to 0.99 (24, 26, 27). Thus, although other aspects of diet may add to variation in glucose and insulin responses, the effect of these other sources of variation does not appear to seriously affect the validity of calculated glycemic index values for mixed meals under realistic conditions.

Although the dietary glycemic index is directly relevant in metabolic studies in which the total carbohydrate content is held constant, in free-living populations the amount of carbohydrate (eg, as a percentage of energy) and its composition varies among individuals. Because the glucose and insulin responses depend on both the quantity and quality of the carbohydrate, we have used the dietary glycemic load, ie, the amount of carbohydrate multiplied by its glycemic index, to represent both of these dimensions of carbohydrate intake (30). For an individual food, it is intuitively obvious that the glycemic load will be more relevant than the glycemic index. For example, in some popular diets, carrots have been condemned because they have a high glycemic index. However, the amount of carbohydrate is so low in a carrot that eating a carrot will have little effect on blood glucose or insulin concentrations, which are better predicted by the glycemic load value for a carrot, which is very low. For calculating the total dietary glycemic load, the glycemic load scores from all foods are added. From a statistical perspective, the glycemic load also presents an interaction, as does any cross-product. This is physiologically relevant and makes sense intuitively because this interaction implies that the glycemic index is more important when the total carbohydrate content of the diet is high.

Because the physiologic relevance of the glycemic index has been questioned (4, 7), we recently conducted a study in which we used fasting plasma triacylglycerol as a marker of adverse metabolic response (6). In many metabolic and long-term studies, high carbohydrate intake has been shown to increase fasting triacylglycerol concentrations and reduce HDL-cholesterol concentrations (31), but fasting triacylglycerol is most sensitive to these dietary changes. We therefore examined the cross-sectional relations between fasting triacylglycerol concentrations and total carbohydrate intake, total dietary glycemic index, and glycemic load in a group of postmenopausal women, controlling for total energy intake, body mass index, and several other determinants of triacylglycerol concentrations (Figure 2). Each of these variables was significantly associated with fasting triacylglycerol, but the

association was strongest with glycemic load, which includes the contributions of both total carbohydrate intake and glycemic index and their interaction with each other. Triacylglycerol concentrations were nearly two-fold higher among women in the highest glycemic load quintile than among those in the lowest quintile. In a multivariate analysis, glycemic load predicted triacylglycerol concentrations independent of carbohydrate intake. In addition to documenting the physiologic importance of glycemic index and load, these data provide objective evidence of the validity of our questionnaire to measure these variables.

INTERACTION BETWEEN UNDERLYING INSULIN RESISTANCE AND DIETARY GLYCEMIC LOAD

Jeppeson et al (32) showed in a group of 10 postmenopausal women that the adverse metabolic effects on glucose and lipid metabolism of high carbohydrate intake, compared with similar energy intake from monounsaturated fat, are strongly correlated with an individual's underlying degree of insulin resistance. Because obesity is a major determinant of insulin resistance, we used the data described above to examine the association between glycemic load and fasting triacylglycerol concentrations separately among women with body mass indexes (in kg/m^2) <25 and ≥ 25 (Figure 3). As hypothesized, the slope for increasing glycemic load was nearly 4 times greater among women with a higher body mass index. This finding has major implications because it suggests that the effects of the same diet can vary greatly among individuals and populations, depending on their levels of adiposity and physical activity. In addition, because metabolic studies are frequently conducted among young, healthy, and lean subjects (often graduate students out of convenience), the adverse consequences of high-glycemic-load diets may often be underestimated.

DIETARY GLYCEMIC INDEX AND LOAD IN RELATION TO INCIDENCE OF TYPE 2 DIABETES

To evaluate the hypothesis that high dietary glycemic load would increase the risk of type 2 diabetes, we used data from our large prospective studies of women (Nurses' Health Study) and

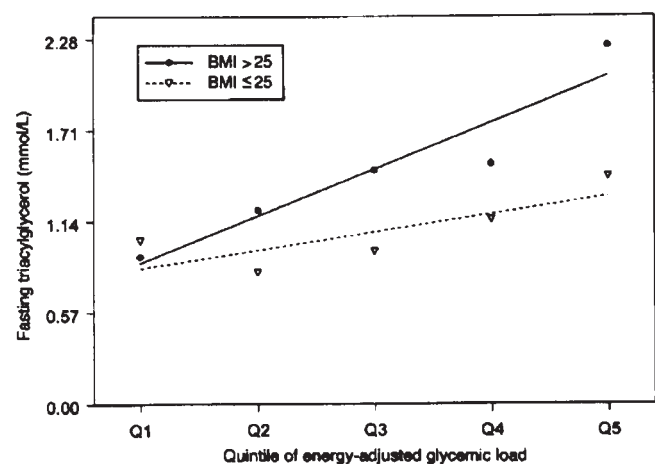


FIGURE 3. Glycemic load in relation to fasting triacylglycerol concentrations among women with BMI (in kg/m^2) ≤ 25 or > 25 . Reproduced with permission (6).

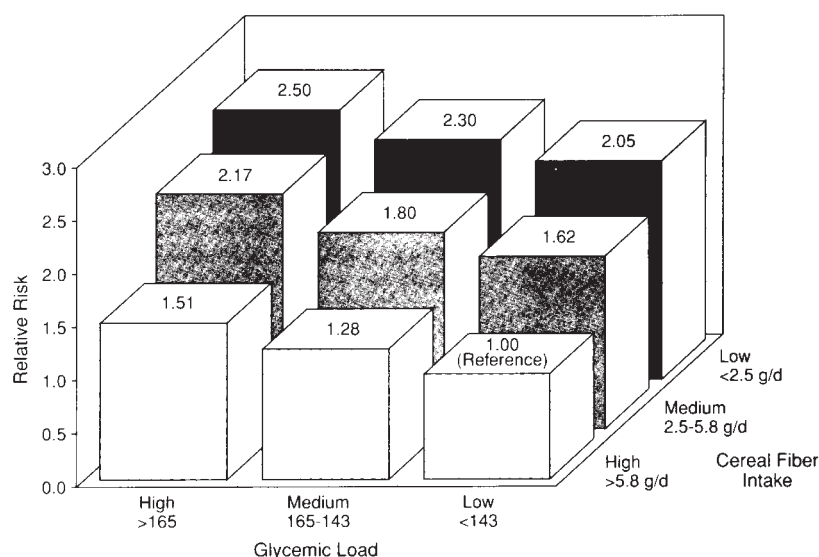


FIGURE 4. Glycemic load and cereal fiber intake in relation to relative risk of type 2 diabetes among women. Reproduced with permission (30).

men (Health Professional's Follow-up Study) (30, 33). In our first evaluation of dietary factors and risk of type 2 diabetes, we used a 61-item food-frequency questionnaire completed by 84360 women in 1980 to assess nutrient and food intakes in relation to incidence of diabetes from 1980 to 1986 (34). Although neither total carbohydrate nor total fat intake was related to risk of diabetes, we did observe that intakes of white bread and potatoes were associated with significantly higher diabetes risk, suggesting that the standard definitions of macronutrients had failed to capture important information about diet. Using an independent follow-up period from 1986 to 1992, we computed total dietary glycemic index and glycemic load scores for the 65173 women who completed the 1986 dietary questionnaire, and we related these to the 915 cases of type 2 diabetes diagnosed through 1992 (30). After adjustment for age, body mass

index, alcohol intake, physical activity, and cereal fiber intake, women in the highest quintile of glycemic load had a 40% greater risk of diabetes than did women in the lowest quintile (P for trend = 0.003). Because cereal fiber was also associated with risk, but in an inverse direction, we classified women jointly by glycemic load and cereal fiber intake (Figure 4). Compared with women with high intake of cereal fiber and low dietary glycemic load, those with low cereal fiber intake and high glycemic load had a 2.5-fold higher risk of diabetes.

We saw similar relation among the 42759 men participating in the Health Professional's Follow-up Study who were initially free of diabetes (33). For those in the extreme categories of glycemic load and cereal fiber intake, the relative risk was 2.17 (Figure 5). More recently, we updated the follow-up of the Nurses' Health Study from 1980 through 1986, which included

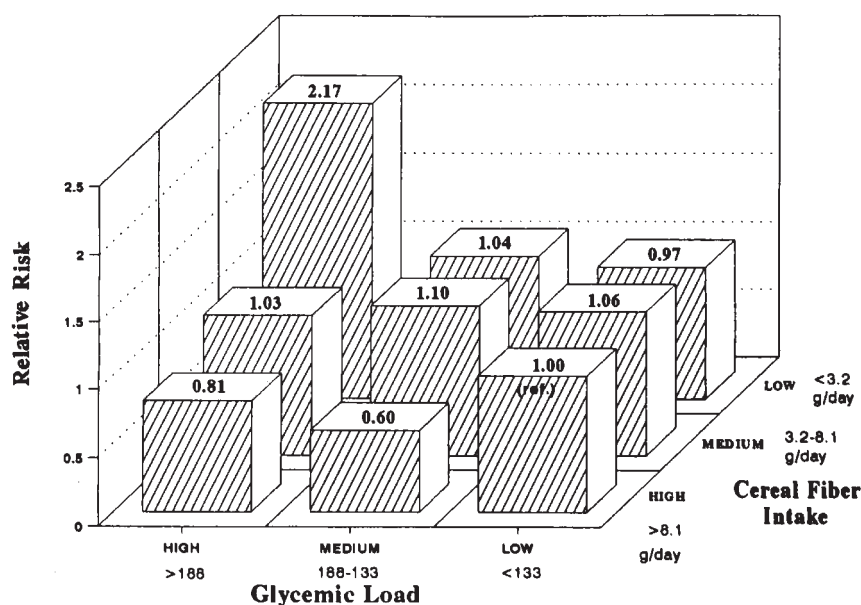


FIGURE 5. Glycemic load and cereal fiber intake in relation to relative risk of type 2 diabetes among men. Reproduced with permission (33).

TABLE 1
Food predictors of type 2 diabetes

Nurses' Health Study (1980–1986) (34)	Nurses' Health Study (1986–1992) (30)	Health Professionals Follow-up Study (33)
French-fried potatoes (+)	French-fried potatoes (+)	French-fried potatoes (+)
Potato chips (+)	Cooked potatoes (+)	White bread (+)
White bread (+)	Cola beverages (+)	White rice (+)
Cola beverages (+)	White bread (+)	Carbonated beverages (+)
Noncarbonated beverages (+)	White rice (+)	Cold breakfast cereal (–)
White rice (+)	Cold breakfast cereal (–)	Yogurt (–)
Pasta (+)	Yogurt (–)	
Dark bread (–)		

3300 incident cases of type 2 diabetes and used 5 assessments of diet. This confirmed the association with glycemic load reported earlier, which was statistically highly robust ($P < 0.001$) (35).

To further understand the types of diets associated with risk of type 2 diabetes, we also examined specific foods contributing appreciably to carbohydrate intake (Table 1). The patterns were similar in these 3 independent datasets, with potatoes, white bread, and soda beverages being associated with increased risk and cold breakfast cereal being associated with reduced risk. We also recently reported the relation between whole-grain consumption, another way of expressing the quality of carbohydrate that reflects both glycemic index and cereal fiber content, and the risk of type 2 diabetes among women in the Nurses' Health Study (36). After control for body mass index and for other risk factors for type 2 diabetes, women in the top quintile of whole-grain consumption (median: 2.7 servings/d) had a 27% lower risk of diabetes than did those in the lowest quintile (median: 0.13 servings/d; relative risk = 0.73; 95% CI: 0.63, 0.89; P for trend < 0.0001). The ratio of refined to whole grains was also significantly associated with risk of diabetes (P for trend = 0.01).

In the other large study that sought to examine carbohydrate consumption in relation to risk of type 2 diabetes, Meyer et al (37) followed 35988 women who completed the same dietary questionnaire used in the Nurses' Health Study for 6 y. They found, as in the Nurses' Health Study, that total carbohydrate was not related to risk of diabetes. However, whole-grain consumption and cereal fiber intake, but not refined grain intake, were inversely associated with diabetes incidence. Although the

study provided support for the form of carbohydrate being important, dietary glycemic index or load per se was not significantly related to risk of diabetes. The lack of association with glycemic index or load may have been related in part to use of a single measure of dietary intake and self-reported diabetes without confirmatory information.

GLYCEMIC INDEX AND MANAGEMENT OF DIABETES

In managing the diets of diabetic patients, the major objectives are to reduce hyperglycemia, prevent hypoglycemic episodes in insulin-treated diabetes, and reduce the risk of complications, particularly cardiovascular disease. From the evidence among nondiabetics, the consumption of slowly absorbed carbohydrates that produce lower peaks in blood glucose appears to be an advantage in maintaining glycemic control. Although this has been an area fraught with controversy, a review of randomized trials among persons with diabetes suggests that the consumption of low- rather than high-glycemic-index carbohydrates is advantageous with regard to the first objective (5) (Table 2). In 8 of 9 studies conducted among persons with both type 1 and 2 diabetes, glycemic control, assessed by measurement of glycosylated proteins, was significantly improved when subjects consumed diets with a low glycemic index (17, 38–46). The weighted mean difference for low- compared with high-glycemic-index diets was 10% (range: 0–27% among studies), corresponding to a reduction in glycated hemoglobin from 8% to 7.2%. Although the long-term implications are not proven, the

TABLE 2
Effect of low-glycemic-index (GI) diet on blood glucose control in diabetes¹

First author and reference	Diabetes	Duration	Change in diet GI	Change in glycosylated proteins
		<i>wk</i>	<i>absolute value (%)</i>	<i>%</i>
Collier, 1988 (38)	Type 1 ($n = 7$)	6	–12 (15)	–27 (F) ²
Fontvieille, 1988 (39)	Type 1 ($n = 8$)	3	–14 (23)	–22 (F) ²
Jenkins, 1988 (40)	Type 2 ($n = 8$)	2	–23 (26)	–6.6 (F) ²
Calle-Pascual, 1988 (41)	Both 1 and 2 ($n = 24$)	4	–7 (12)	0 (H)
Wolever, 1992 (42)	Type 2 ($n = 15$)	2	–27 (31)	–3.4 (F)
Wolever, 1992 (43)	Type 2 ($n = 6$)	6	–28 (33)	–11 (F) ²
Brand, 1991 (44)	Type 2 ($n = 16$)	12	–13 (14)	–11 (H) ²
Fontvieille, 1992 (45)	Both 1 and 2 ($n = 18$)	5	–26 (41)	–12 (F)
Frost, 1994 (46)	Type 2 ($n = 25$)	12	–5 (6) ³	–16 (F)
$\bar{x}^4$		7.3	–15 (20)	–10.2

¹ Adapted from reference 5. F, fructosamine; H, glycated hemoglobin.

² $P < 0.05$.

³ With the low-GI diet, carbohydrate intake increased by 5% of energy, and fiber intake increased from 14 to 21 g/d.

⁴ Values represent weighted means.

results of the UK Prospective Diabetes Study suggests that this degree of reduction in glycated hemoglobin would predict an $\approx 10\%$ lower risk of complications (47). In a recent report (48), investigators randomly assigned 63 persons with type 1 diabetes to a low- compared with a high-glycemic-index diet for 4 wk. In addition to reducing integrated daily blood glucose concentrations by 9% ($P < 0.05$), hypoglycemic episodes were reduced by one-half ($P < 0.05$). Until now, neither long-term observational studies nor randomized trials have been conducted to evaluate the effects of high-glycemic-index diets on cardiovascular complications among patients with diabetes.

In summary, both metabolic and epidemiologic evidence suggests that replacing high-glycemic-index forms of carbohydrate with low-glycemic-index carbohydrates will reduce the risk of type 2 diabetes. Among patients with diabetes, the weight of evidence suggests that replacing high-glycemic-index with low-glycemic-index forms of carbohydrate will improve glycemic control and reduce hypoglycemic episodes among those treated with insulin. These dietary changes can be accomplished by replacing products made with white flour and potatoes with whole-grain, minimally refined cereal products. Because this low-risk dietary pattern has also been associated with reduced incidence of coronary heart disease (49–52) and a lower occurrence of diverticular disease (53) and constipation (54), this is an appropriate component of recommendations for an overall healthy diet. 

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