

## Postprandial glycemia, glycemic index, and the prevention of type 2 diabetes<sup>1,2</sup>

Jennie C Brand-Miller

Prevention of type 2 diabetes is one of the biggest challenges facing public health in the 21st century. Studies such as the Diabetes Prevention Program have shown that intensive diet and exercise programs are not only highly effective in delaying or preventing the disease but are more cost-effective than even the cheapest drug (1). Can we do better still? Are there superior dietary approaches that can prevent most cases of type 2 diabetes? Specifically, would it be helpful—even in the absence of weight loss—to modify the amount and kind of carbohydrate consumed in a way that helps preserve  $\beta$  cell function? Results of the STOP-NIDDM Study, which assessed the effectiveness of acarbose (an  $\alpha$ -glucosidase inhibitor that acts within the gut) in preventing type 2 diabetes, provide direct evidence that reducing the rate of carbohydrate absorption per se delays or prevents the conversion of impaired glucose tolerance to diabetes (2). In addition, acarbose halved the risk of cardiovascular events and hypertension, which highlights the diverse pathologic nature of postprandial hyperglycemia. Unfortunately, the use of naturally occurring slow-release carbohydrates or carbohydrates with a low glycemic index (GI) to achieve the same end is steeped in controversy.

Some confusion is not surprising when we consider the mechanisms of diabetes development. Worsening insulin resistance over time with compensatory hyperinsulinemia and declining  $\beta$  cell function is critical to the pathogenic process. Dietary strategies that preserve  $\beta$  cell function by improving insulin sensitivity and reducing the degree of postprandial glycemia, or insulinemia (insulin demand), are likely to be beneficial. In this context, replacing saturated fat with carbohydrate could be a 2-edged sword; it would improve insulin sensitivity and glucose tolerance on the one hand but would increase postprandial hyperglycemia and insulin demand on the other, particularly in persons with insulin resistance. The level of postprandial glycemia, however, is dictated by both the quality and quantity of carbohydrate, and it makes sense to consider them both simultaneously—enter the concept of glycemic load (GL).

GL is defined as the product of the carbohydrate content per serving of food and its GI. This concept was introduced by Harvard researchers to derive a “global” estimate of postprandial glycemia and insulin demand (3). The results of recent studies have validated the concept in a physiologic sense. In one study, servings of food with the same GL produced similar levels of postprandial glycemia, and stepwise increases in GL resulted in predictable increases in glycemia and insulinemia (4). Moreover, when 4 isoenergetic diets with different GLs were compared in

mixed meals over 10 h, they produced the expected rank order of responses (FS Atkinson, JMR McMillan-Price, P Petocz, JC Brand-Miller, unpublished observations, 2003).

What evidence do we have that a diet with a high GI or GL might lead to diabetes? In the Nurses’ Health Study, a positive association between the GI and the risk of diabetes was observed over a 6-y period; the relative risk (RR) was 1.37 in a comparison of the highest with the lowest quintiles of GI (3). Use of the GL rather than the GI strengthened the relation with diabetes risk (RR = 1.47). These findings were confirmed in a 16-y follow-up study. The GI was also found to correlate with the risk of diabetes in men; the RR was 1.37 in a comparison of extreme quintiles of GI (5). The correlation with GL, although positive, was not statistically significant. In this issue of the Journal, the study by Schulze et al (6) provides the strongest evidence yet in a large cohort of younger women. The women in the highest quintile of GI had an approximate 60% increased risk of diabetes in a multivariate analysis. The GL was also positively correlated with incident diabetes but was significant only in those women with low physical activity (RR = 2.01) or a family history of diabetes (RR = 2.04). The findings of Schulze et al suggest that the quality of carbohydrate (ie, the GI) is important irrespective of its amount. However, the results also imply that a high GL is of little consequence in insulin-sensitive persons. Thus, a diet based on large amounts of carbohydrate from high-GI sources might be tolerated by insulin-sensitive persons but is excessively challenging to the  $\beta$  cells of persons who are more insulin-resistant or predisposed to diabetes.

The findings of 2 studies, one large and one small, do not support the hypothesis that a high-GI diet leads to diabetes. In the Iowa Women’s Health Study (7) and the Atherosclerosis Risk in Communities Study (8), neither GI nor GL showed any relation to diabetes risk. However, particular strengths of the Harvard work (3) suggest that it may provide a more accurate picture. One strength of this study was that the diagnosis of diabetes was confirmed by medical records. In contrast, diabetes was self-reported in the Iowa Women’s Health Study, despite the finding that a diagnosis of diabetes was confirmed by a physician in only 28 of 44 women who reported having diabetes at baseline (7).

<sup>1</sup> From the Human Nutrition Unit, School of Molecular and Microbial Biosciences, The University of Sydney, Australia.


<sup>2</sup> Reprints not available. Address correspondence to JC Brand-Miller, Human Nutrition Unit, G 08, The University of Sydney, NSW 2006, Australia. E-mail: j.brandmiller@mmb.usyd.edu.au.

The quality of the GI database is also critical. David Jenkins of the University of Toronto, who first proposed a GI of foods, coded the Harvard database and tested some of the key foods. Because many breads and cereal products have unknown GI values, extrapolation may be a significant source of error. In the Iowa Women's Health Study, the 2 lowest quintiles of GI had surprisingly low median values in comparison with those of other studies, which implies improbably that 40% of the population derived most of their carbohydrates from low-GI sources. Misclassification would bias results toward the null hypothesis. The Harvard database is also validated in the sense that the GI and the GL were shown to predict blood markers of carbohydrate metabolism, including HDL, triacylglycerol, and C-reactive protein concentrations, in a subgroup of women.

Despite the limitations of current food databases, other groups around the world are also reporting relations between disease risk or markers of risk and GI, GL, or both. In studies in 5 different countries and population groups, including Australia (where the GI database is more extensive), the GI and the GL have been shown to be inversely associated with HDL-cholesterol concentrations (9). In healthy children, fasting insulin concentrations were predicted by the GI of the overall diet (10). In healthy pregnant women (11) and adults with type 1 diabetes (12), the GI was an independent predictor of glycated hemoglobin. In large case-control and observational studies, cancer risk in various parts of the body was predicted by the GI, the GL, or both (13).

A diet with a low GL can be achieved in several ways: by replacing energy from carbohydrate with energy from protein, replacing energy from carbohydrate with energy from fat, replacing a high-GI source of carbohydrate with a low-GI source, or a combination of all 3 approaches. Whether each of these strategies equally prevents the development of diabetes is unknown. A high carbohydrate intake from low-GI sources may well be superior in terms of increasing fat oxidation and improving overall glucose disposition (14). If this is the case, it might explain why the quality of carbohydrate (ie, GI) more often shows a significant association with disease risk (diabetes, heart disease, and cancer) than does the carbohydrate content or GL of the diet.

Last, ample evidence in the form of laboratory, animal, clinical, and observational research supports the view that postprandial glycemia should be minimized, even when fasting glucose concentrations are normal (15, 16). Although only randomized controlled trials can prove that low-GI diets prevent diabetes (or conversely that high-GI diets increase the risk), the robust findings of

prospective observational studies, such as the one conducted by Schulze et al, together with those of the STOP-NIDDM Study (2), suggest that costly intervention studies may not only be unnecessary but perhaps unethical. 

## REFERENCES

1. Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 2002;346:393–403.
2. Chiasson J, Josse RG, Hanefeld M, et al. Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomised trial. *Lancet* 2002; 359:2072–7.
3. Salmeron J, Manson J, Stampfer M, Colditz G, Wing A, Willett W. Dietary fiber, glycemic load, and risk of non-insulin-dependent diabetes mellitus in women. *JAMA* 1997;277:472–7.
4. Brand-Miller J, Thomas M, Swan V, Ahmad Z, Petocz P, Colagiuri S. Physiological validation of the concept of glycemic load in lean young adults. *J Nutr* 2003;133:2728–32.
5. Salmeron J, Ascherio A, Rimm E, et al. Dietary fiber, glycemic load, and risk of NIDDM in men. *Diabetes Care* 1997;20:545–50.
6. Schulze MB, Liu S, Rimm EB, Manson JE, Willett WC, Hu FB. Glycemic index, glycemic load, and dietary fiber intake and incidence of type 2 diabetes in younger and middle-aged women. *Am J Clin Nutr* 2004;80:348–56.
7. Meyer K, Kushi L, Jacobs D, Slavin J, Sellers T, Folsom A. Carbohydrates, dietary fiber, and incident type 2 diabetes in older women. *Am J Clin Nutr* 2000;71:921–30.
8. Stevens J, Kyungmi A, Juhaeri, Houston D, Steffan L, Couper D. Dietary fiber intake and glycemic index and the incidence of diabetes in African-American and white adults. *Diabetes Care* 2002;25:1715–21.
9. Brand-Miller J. Glycemic load and chronic disease. *Nutr Rev* 2003;61: S49–55.
10. Scaglioni S, Stival G, Giovannini M. Dietary glycemic load, overall glycemic index, and serum insulin concentrations in healthy schoolchildren. *Am J Clin Nutr* 2004;79:339–40.
11. Scholl T, Chen X, Khoo C, Lenders C. The dietary glycemic index during pregnancy: influence on infant birth weight, fetal growth and biomarkers of carbohydrate metabolism. *Am J Epidemiol* 2004;159:467–74.
12. Buyken A, Toeller M, Heitkamp G, et al. Glycemic index in the diet of European outpatients with type 1 diabetes: relations to glycated hemoglobin and serum lipids. *Am J Clin Nutr* 2001;73:574–81.
13. Franceschi S, Dal ML, Augustin L, et al. Dietary glycemic load and colorectal cancer risk. *Ann Oncol* 2001;12:173–8.
14. Wolever T, Mehling C. Long-term effect of varying the source or amount of dietary carbohydrate on postprandial plasma glucose, insulin, triacylglycerol, and free fatty acid concentrations in subjects with impaired glucose tolerance. *Am J Clin Nutr* 2003;77:612–21.
15. Heine R, Balkau B, Ceriello A, Del Prato S, Horton E, Taskinen M-R. What does postprandial hyperglycaemia mean? *Diabet Med* 2004;21: 208–13.
16. The DECODE group, European Diabetes Epidemiology Group. Glucose tolerance and mortality: comparison of WHO and American Diabetes Association diagnostic criteria. *Lancet* 1999;354:617–21.

