



## The glycemic index issue

Jennie Brand-Miller<sup>a</sup> and Anette E. Buyken<sup>b</sup>

### Purpose of review

In recent years, many of the concerns surrounding the glycemic index have been addressed by methodological studies and clinical trials comparing diets carefully matched for other nutrients. These findings are reviewed together with new observational evidence for the role of the dietary glycemic index in the etiology of cardiovascular disease.

### Recent findings

The determination and classification of the glycemic index of a food product is now standardized by the International Standards Organization. Systematic studies using isoenergetic single and mixed meals have shown that glycemic index and/or glycemic load are stronger predictors of postprandial glycemia and insulinemia than carbohydrate content alone. In overweight individuals, a diet that combined modestly higher protein and lower glycemic index carbohydrates was the most effective diet for prevention of weight regain. New observational studies have reported increased risks of coronary heart disease associated with higher intakes of carbohydrates from high glycemic index foods. Epidemiological evidence has emerged linking dietary glycemic index to visceral fat and inflammatory disease mortality.

### Summary

There is growing recognition that replacing saturated fat with refined, high glycemic index carbohydrates increases postprandial glycemia and may be detrimental for weight control and predisposition to cardiovascular and inflammatory disease. In contrast, low glycemic index carbohydrates reduce risk.

### Keywords

cardiovascular disease, glycemic index, glycemic load, postprandial glycemia, weight

## INTRODUCTION

In the past 2 years, macronutrient advice for the prevention of cardiovascular disease has undergone a remarkable transition [1,2]. This follows the realization that the efficacy of reducing saturated fat intake largely depends on which foods are substituted [3]. Replacing saturated fat with carbohydrates (the conventional low-fat diet) is not effective, unless the quality of the carbohydrate as defined by markers such as the glycemic index is also specified [4<sup>\*\*\*</sup>]. The glycemic index compares the glycemic nature of the carbohydrates in different foods with that of a reference food. Although postprandial glycemia is tightly controlled in healthy individuals, the rapid digestion and absorption of high glycemic index foods or meals challenges homeostatic mechanisms, particularly  $\beta$ -cell function. Recent prospective observational studies and clinical trials suggest that diets with a high glycemic index or high glycemic load (glycemic load = glycemic index  $\times$  carbohydrate content) compromise weight control and cause oxidative stress and inflammatory responses in susceptible individuals. In contrast, low glycemic index carbohydrates appear to reduce risk.

## VALIDITY OF THE GLYCEMIC INDEX AS A PREDICTOR OF POSTPRANDIAL GLYCEMIA OR INSULINEMIA

Despite three decades of research, the glycemic index is still contentious, primarily because of concerns relating to methodology and extrapolation to mixed meals. However, the determination of the glycemic index *in vivo* is now the subject of an international standard [5<sup>\*\*</sup>] which member countries are obliged to adopt. Bao *et al.* [6<sup>\*\*</sup>] systematically studied postprandial glycemia and insulinemia after consumption of 121 single foods in 1000 kJ portions

<sup>a</sup>School of Molecular Bioscience and Boden Institute of Obesity, Nutrition and Exercise, University of Sydney, Sydney, New South Wales, Australia and <sup>b</sup>Research Institute of Child Nutrition, Rheinische Friedrich-Wilhelms-Universität Bonn, Dortmund, Germany

Correspondence to Professor Jennie C. Brand-Miller, Boden Institute of Obesity, Nutrition & Exercise, Biochemistry Building, G08, The University of Sydney, New South Wales, 2006, Australia. Tel: +61 2 9351 3759; fax: +61 2 9351 6022; e-mail: jennie.brandmiller@sydney.edu.au

**Curr Opin Lipidol** 2012, 23:62–67

DOI:10.1097/MOL.0b013e32834ec705

## KEY POINTS

- Dietary strategies to lower postprandial levels of glycemia and insulinemia may offer substantial benefits without risk of the adverse effects associated with pharmacological therapy.
- Replacing saturated fat with carbohydrate appears to have detrimental effects on risk of cardiovascular disease. High glycemic index carbohydrates increase risk, whereas low glycemic index carbohydrates may reduce risk.
- A new large-scale systematic study provides robust physiological validation of the twin concepts of dietary glycemic index and glycemic load as measures of postprandial glycemia and insulinemia.
- Five of six new observational studies demonstrated that glycemic index and glycemic load were independent predictors of the risk of cardiovascular disease in one or more subgroups, for example, women and overweight men.
- A recent large randomized controlled trial in eight European countries found that low glycemic index carbohydrates facilitate weight loss maintenance to the same extent as higher protein intake. A diet combining low glycemic index carbohydrates with modestly higher protein showed the best outcome including lowest drop rate.
- Emerging evidence suggests that low glycemic index diets improve inflammatory markers and reduce the risk of noncardiovascular, noncancer diseases of inflammation.

and 13 mixed meals in 2000 kJ portions by lean young healthy individuals. Glycemic responses were more strongly correlated with glycemic load and glycemic index than with carbohydrate content, explaining 85, 76 and 66% of the variation, respectively. Among the mixed meals, glycemic load was also the strongest predictor, whereas carbohydrate was not directly correlated with either glycemia or insulinemia. Lan-Pidhainy and Wolever [7] showed that glycemic index is valid property of a food because its value is similar in healthy controls and in patients with type 2 diabetes, and independent of their metabolic status. Among free-living individuals with type 2 diabetes fitted with continuous glucose monitors, Fabricatore *et al.* [8<sup>9</sup>] demonstrated that glycemic index and/or glycemic load, but not other macronutrients or fiber, were significantly associated with area under the glucose curve, mean glucose, percentage of values in euglycemic and hyperglycemic ranges and the mean amplitude of the glycemic excursion. The low glycemic index of fructose has also complicated the glycemic index

issue, although Stanhope *et al.* [9] showed that the adverse metabolic responses to fructose are independent of the low postprandial glucose and insulin responses that characterize fructose-sweetened products.

Taken together, these studies provide evidence for the physiologic validity and use of glycemic index and glycemic load in epidemiologic and clinical trials.

## POSTPRANDIAL GLYCEMIA AND CARDIOVASCULAR DISEASE RISK

A recent meta-analysis of five large epidemiological studies confirmed that risk for cardiovascular events and cardiovascular mortality progressively increases with higher glycated hemoglobin 1c (HbA1c) levels, with a higher risk already evident for minimally elevated HbA1c levels [10<sup>10</sup>]. Because HbA1c primarily captures postprandial spikes and persistently elevated postprandial glucose concentrations in nondiabetic individuals, this finding strongly suggests a link between postmeal glycemic responses and cardiovascular disease (CVD).

On the contrary, recent clinical trials among persons with existing diabetes mellitus have failed to confirm a benefit of intensified glycemic control for cardiovascular events. Nonetheless, post-hoc analyses of the Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS) suggest that good glycemic control initiated during the early stages of type 1 and type 2 diabetes mellitus may yield a legacy benefit for later cardiovascular events [11]. It has been argued that these inconsistencies do not provide support for treatments specifically targeting postprandial hyperglycemia [12]. However, these clinical trials addressed the effect of optimizing glycemia by means of drugs, which entail side-effects and potentially problematic interactions with other drugs. By contrast, dietary strategies to lower postprandial levels of glycemia and insulinemia may offer substantial benefit at no risk of adverse effects.

## GLYCEMIC INDEX, GLYCEMIC LOAD AND CARDIOVASCULAR DISEASE RISK

Direct evidence for a role of postprandial glucose excursions in the etiology of cardiovascular diseases stems from observational studies investigating the relation between glycemic index/glycemic load and the risk of CVD. Two meta-analyses considering data from earlier studies both reported significantly increased risks in the upper quantiles of glycemic index/glycemic load. Out of the six studies published

in 2010 and 2011, five found associations with glycemic index or glycemic load in one or more subgroups [4<sup>13</sup>,13,14,15<sup>16</sup>,16,17], for example, among women [13], overweight men [14,16] or among Afro-Americans [15<sup>17</sup>]. Furthermore, two out of three studies, reported a higher risk of experiencing a stroke [18<sup>19</sup>] or dying from stroke [19] among those with a higher dietary glycemic index.

Two of these large recent studies in European populations also addressed the relevance of carbohydrates from foods with a low or high glycemic index. Among the female participants of the EPICOR study, increasing carbohydrate intake from high-glycemic index foods (glycemic index >57) was significantly associated with greater risk of experiencing coronary heart disease during 8 years of follow-up (relative risk (RR), 1.68; 95% confidence intervals (CI): 1.02–2.75), whereas increasing the intake of low-glycemic index carbohydrates (glycemic index ≤57) was not [13]. Several recent studies suggest that replacement is an important issue when dealing with the effects of macronutrients on CVD risk. For example, Jakobsen *et al.* [4<sup>20</sup>] investigated the risks associated with substituting carbohydrates from low or high glycemic index foods for saturated fatty acids. Risk was increased only when substituting carbohydrates with high-glycemic index values (i.e. highest tertile) for saturated fatty acids (hazard ratio for myocardial infarction per 5% increment of energy intake from carbohydrates 1.33; 95% CI: 1.08–1.64).

In large-scale epidemiological studies, the only feasible approach to determining the overall dietary glycemic index or glycemic load is from a food frequency questionnaire (FFQ). Nonetheless, this is linked to several methodological limitations because none of the employed FFQ have been specifically developed to assess the dietary glycemic index. Many foods with low and high glycemic index are commonly entered into the same food grouping (e.g. whole-kernel and wholemeal breads, respectively). Furthermore, assignment of glycemic index values to the foods in the FFQ is often based on glycemic index values available for similar foods, and may vary from researcher to researcher. In view of these problems, some studies may not be able to validly discriminate consumers of diets with a high dietary glycemic index from those consuming a lower glycemic index diet. Although it is likely that these general methodological problems of determining dietary glycemic index in epidemiological studies will never be fully resolved, the international tables of glycemic index values measured according to standardized protocols are increasing constantly. In particular, data on locally available foods has become available, allowing more precise assignments of glycemic index.

## GLYCEMIC INDEX, GLYCEMIC LOAD AND CARDIOVASCULAR RISK FACTORS

As intervention studies comparing diets with high and low dietary glycemic index/glycemic load for the prevention of CVD are neither feasible nor affordable, appreciation of the evidence for a role of glycemic index/glycemic load in CVD etiology needs to encompass studies on their associations with CVD risk factors.

### Epidemiological studies

In the past 10 years, many cross-sectional studies among European and US populations have reported lower levels of HDL-cholesterol and higher levels of triglycerides among participants in the upper quantiles of dietary glycemic index or glycemic load [17,20,21]. By contrast, epidemiological studies do not provide consistent evidence of an association with LDL-cholesterol levels. Recent observational studies in South Indian, Korean and Japanese [22<sup>23</sup>] populations have confirmed this pattern. This is of interest because in these populations overall carbohydrate intake amounts to 50–60% of total energy with rice as the main carbohydrate food. The fact that similar associations are seen in populations with diverse sources of dietary carbohydrate supports the proposition that postprandial glycemia is the unifying mechanism, and refutes the concern that dietary glycemic index/glycemic load may be a marker of a specific dietary pattern.

Two recent analyses from the EPIC cohort suggest that dietary glycemic index may be specifically linked to visceral fat. Among 89 432 individuals from five European countries, a higher baseline dietary glycemic index was associated with subsequent gains in waist circumference, but not in body weight during the 6 years of follow-up [23]. In a further analysis among 48 631 participants aged 60 years or younger at baseline, glycemic index was related to waist circumference for a given BMI ( $WC_{BMI}$ ), that is a proxy measure of visceral adiposity [24<sup>25</sup>]. In longitudinal studies involving over 120 877 men and women, Mozaffarian *et al.* [25<sup>26</sup>] found that diets that contained higher consumption of potato products (which are often high glycemic index) had the strongest association of all foods with future weight gain.

Interestingly, the majority of epidemiological studies suggest that a higher dietary glycemic index and/or glycemic load is related to higher levels of C-reactive protein, a marker of chronic low-grade systemic inflammation, or lower levels of adiponectin, an adipose-secreted anti-inflammatory cytokine [26]. In addition, one recent epidemiological study directly links dietary glycemic index to mortality

from non-CVD noncancer inflammatory diseases, a new categorization recently introduced by Jacobs *et al.* [27], which explicitly focuses on diseases for which inflammation or oxidative stress is the predominant pathophysiological factor. For 1490 women in the Blue Mountains Mountain Eye study, there was an almost three-fold higher risk of inflammatory mortality during 13-year follow-up among women in the highest glycemic index tertile compared with those in the lowest glycemic index tertile [28].

### Intervention studies

In patients with type 2 diabetes ( $n=210$ ), 6-month treatment with a low-glycemic index diet resulted in lower HbA1c, lower LDL-cholesterol and higher HDL-cholesterol levels compared with a high-cereal fiber diet [29]. In the Reading, Imperial, Surrey, Cambridge, and Kings (RISCK) trial ( $n=548$ ), substituting either monounsaturated fat or carbohydrates for saturated fat, lowered total and LDL cholesterol, but improvements were significantly enhanced among those who substituted low glycemic index carbohydrates for saturated fat [30]. Insulin sensitivity, however, was similar on all four diets.

In obese, prediabetic individuals, a high-glycemic index diet, but not a low glycemic index diet, was found to impair pancreatic  $\beta$ -cell and intestinal K-cell function, despite significant weight loss through dietary restriction and vigorous physical activity [31]. Only the low glycemic index diet was associated with improvements in compensatory hyperinsulinemia. In contrast, Vrolix and Mensink [32] found no differences in cardiovascular risk factors after 14 weeks on low vs. high glycemic load diets among 15 overweight Dutch individuals.

In obese Americans with type 2 diabetes ( $n=79$ ), a 40-week low glycemic load diet produced larger reductions in HbA1c ( $-0.8\%$  points) than those on the conventional low fat diet ( $-0.1\%$  points) [33], but groups were similar in other biochemical outcomes. In Asian individuals with type 2 diabetes ( $n=102$ ), a 12-week low glycemic index diet produced similar changes in HbA1c as a carbohydrate exchange diet [34].

There is conflicting evidence that low glycemic index diets enhance weight loss. However, the findings of the Diogenes Study [35] in 773 overweight and obese individuals from eight European nations provide robust evidence that modest changes in glycemic index and glycemic load are related to weight-loss maintenance. In this study, participants were randomly assigned to one of five ad-libitum diets to prevent weight regain over a 26-week period.

Two levels of protein and two levels of glycemic index, as well as a control diet, were studied. Weight maintenance was enhanced by both lower glycemic index and higher protein interventions, with lower drop-out rate in participants who were randomized to the low glycemic index higher protein diet. Among completers, the lower protein high glycemic index diet (i.e. a conventional low fat diet) was associated with significant weight regain. Among the 465 children in the study, the lower protein/high glycemic index diet increased body fat percentage significantly more than the other diets, whereas the percentage of overweight/obese children in the high protein low glycemic index group decreased significantly during the intervention [36].

In addition, recent intervention studies conducted in diverse populations, including pregnant women [37], support the potential relevance of dietary glycemic index or glycemic load for inflammation, independent of potential effects on body weight. However, one cross-over study conducted in overweight or obese men found similar decreases in inflammatory markers in both high and low glycemic index groups [38,39]. Marsh *et al.* [40] found greater improvements in insulin sensitivity, menstrual pattern and serum fibrinogen concentration after 12 months among women with polycystic ovary syndrome ( $n=96$ ) randomized to either a high carbohydrate low glycemic index vs. high glycemic index diet.

### Mechanistic studies

Studies in obesity-prone mice fed high vs. low glycemic index starch diets provide mechanistic insights that help to explain the effects of high glycemic index diets in humans. Elegant studies by Isken *et al.* [41] demonstrated that high glycemic index feeding caused rapid-onset marked increase in body fat mass and liver fat, a gene expression profile in the liver consistent with elevated lipogenesis, and after long-term exposure, significantly reduced glucose clearance following a glucose load. Fatty acid oxidation was significantly blunted as early as 3 weeks at a time when body fat mass was still comparable between groups. The long-term high glycemic index diet also led to a delayed switch in both carbohydrate and fat oxidation in the postprandial state, indicating reduced metabolic flexibility. van Schothorst *et al.* [42] demonstrated that mice fed a low glycemic index diet had enhanced whole body insulin sensitivity and lower body fat even in the context of high fat feeding. In the low glycemic index group, they found increased expression of PPAR- $\gamma$  and lower serum levels of total and LDL-cholesterol.

## CONCLUSION

Recent research has addressed some of the long-standing concerns about the glycemic index. First, that glycemic index values only apply to individual foods and not to realistic meals; second, that the effects seen in clinical trials arise from confounding by macronutrients or fiber; and third, that the concept is confusing and impractical for the general public. Indeed, the higher completion rate in the low glycemic index groups of the Diogenes Study provides compelling evidence of the practicality of low glycemic index diets. Recent observational studies with both hard cardiovascular and risk factor outcomes as well as randomized controlled trials with cardiovascular risk factor outcomes provide consistent evidence for the benefits of low glycemic index diets.

In our view, the replacement of saturated fat with 'inadvertent' consumption of high glycemic index carbohydrates has likely contributed to the global rise in the burden of obesity and diabetes. Replacement with healthy sources of low glycemic index, carbohydrate should, therefore, be a practical component of intensive lifestyle interventions. Although there is growing support for the use of the glycemic index as a concept, there is also a simultaneous and worrisome trend for health authorities to equate low glycemic index with 'wholegrain' or 'unrefined' cereals [1,25<sup>\*\*\*</sup>]. Unfortunately, many foods labeled as 'wholegrain' contain finely milled endosperm, and are consequently just as easily digested and absorbed (and high in glycemic index) as the low fiber counterpart. Presently, the glycemic index is not readily identifiable by the appearance of the food or ingredient list on the food label. Because the glycemic index testing procedure is now internationally standardized, we believe that now is a good time to have a serious debate about whether the glycemic index ought to appear on food labels, particularly of foods identified as 'wholegrain'.

## Acknowledgements

*J.B.M. receives funding from the National Health and Medical Research Council (Australia). J.B.M. is co-author of books about the glycemic index (The New Glucose Revolution Hodder and Stoughton, London; Marlowe and Co., NY; The Low GI Diet, Hachette Livre, Sydney; and elsewhere), director of a not-for-profit GI food endorsement program (<http://www.gisymbol.com>), and manages the University of Sydney GI Research Service (SUGiRS).*

## Conflicts of interest

*There are no conflicts of interest.*

## REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 70).

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