Glycemic index and metabolic risks: how strong is the evidence?1–3
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An intense debate has been going on for decades about the role of the glycemic index (GI) in relation to type 2 diabetes (T2D), cardiovascular disease (CVD), and body weight management. Considering the increased need for measures to prevent further escalation of these lifestyle-related conditions, the topic remains very relevant but is also still controversial.

The GI was introduced >30 y ago and is a method for ranking carbohydrates according to their effect on blood glucose responses (1). Its usefulness is obvious when evaluating the glucose response of single foods. This can be done under very standardized conditions by using the recommended 50 g of available carbohydrate from the food in question, which produces fairly reproducible values. However, it is less obvious when combinations of carbohydrate-rich foods, mixed meals, or even whole diets are evaluated. To adjust for this, the glycemic load (GL) and the weighted GI have been introduced. The GL takes the actual amount of carbohydrate consumed into account, and the weighted GI takes all relevant food items consumed in a meal into account. However, a number of other factors may influence GI such as dietary fiber, fat, and protein content; food processing; meal preparation; and serving temperature. These can have a great impact on the results and should ideally be kept constant when evaluating the effect of GI per se. However, keeping all factors fixed but one is a huge challenge in food and nutrition research. If one uses real foods as they are normally eaten, many factors beyond the one studied (eg, GI) will normally differ. If one wants to study one specific characteristic of meals or diets (eg, GI) and keep all other factors identical, this will normally mean that you have to use less natural or adapted foods that would not normally be eaten in real life. Both have a purpose, depending on whether the focus is on mechanisms or on real-life situations. For the clinical staff dealing with real patients and real foods, the latter is probably of greater relevance.

In this issue of the Journal, 3 studies have been published that all relate to the health effects of carbohydrates and/or GI in real-life situations (2–4). In all 3 articles, longer-term exposure to diets differing in GI/GL or source of carbohydrates (rice) is studied, but by using different approaches. Two articles (2, 3) used data from population-based studies focusing on the development of T2D or cardiovascular morbidity/mortality in adults. The third is a randomized controlled clinical trial focusing on body weight, appetite, and metabolic risk factors (4).

In the article by Eshak et al (2), the associations between rice consumption and CVD is explored in a prospective study in 91,223 Japanese men and women aged 40–69 y for up to 18 y. Self-administered food-frequency questionnaires (FFQs) were used 5 y apart. Rice constitutes one-quarter to one-third of total caloric intake in Japanese (mainly refined white rice), so the topic is highly relevant in this population. At follow-up, there were no associations between rice consumption and stroke, ischemic heart disease, or risk of mortality from CVD. Furthermore, there were no sex differences or influence of BMI. In the same cohort, a high intake of rice was previously reported to be associated with increased risk of T2D. The lack of association with CVD in this cohort can perhaps be explained by the fact that the refining process of white rice induces loss of nutrients (eg, insoluble fiber, magnesium, phytoestrogens) more related to T2D than to CVD (5). Also, rice was associated with a decreased risk of hypertension in a Chinese study, which is supportive of the lack of association with CVD risk seen here (6).

The other population-based study derives from the Harvard group by Bhupathiraju et al (3) and the, by now, very-well-known large US cohorts (Nurses’ Health Study, Health Professionals Follow-Up Study). It also includes an updated meta-analysis on GI, GL, and risk of T2D from the 3 US and other cohort studies. In the 3 cohort studies, >200,000 women and men were followed up biannually for up to 24 y by using different validated questionnaires for diet (FFQs), medical history, lifestyle factors, and chronic diseases. Not only baseline data for food intake were used but the FFQ was administered every 4 y and updates were done if needed, including analyses of GI in foods if not in the database. Extensive statistics including sensitivity analyses were performed, and the joint effects of GI, GL, and cereal fiber were assessed.

The data showed that individuals with a high-GI (HGI) or high-GL diet and low cereal fiber intake had an almost 40% increased risk of T2D, although GI appeared to be more strongly associated with T2D than GL. In addition, a high BMI increased the risk 10-fold, underlining the risk of the obese state itself. Those individuals consuming a higher-GI diet were younger and less physically active and had a higher-GL diet, higher intakes of cereal fiber and trans fatty acids, and lower intakes of alcohol, total protein, mag-

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4 Abbreviations used: CVD, cardiovascular disease; FFQ, food-frequency questionnaire; GI, glycemic index; GL, glycemic load; HGI, high glycemic index; LGI, low glycemic index; T2D, type 2 diabetes.

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nesium, and coffee. Adjustment for most of these factors did not substantially change the picture. Interestingly, however, when adjusting for total protein intake, the association with T2D became stronger. Thus, protein seems to be associated with T2D in these cohorts. In the meta-analyses (including 10–14 studies covering most parts of the world), the risk estimate of GL and T2D was similar to the cohort studies, although the risk was less in magnitude than in previous meta-analyses.

Causality cannot be established, however, from population studies, and reverse causality may be present, even if trying to adjust for explanatory factors and confounders. Therefore, as concluded in the article by Bhupathiraju et al (3), a large randomized controlled trial should be considered to evaluate the role of low-GI (LGI) and low-GL diets in preventing T2D.

The mechanisms that are likely involved in the potential role of an HGI/GL diet in developing T2D are related to the high blood glucose followed by a high insulin concentration, and then to a high demand on the pancreatic β cells, eventually leading to β cell exhaustion and failure.

Support for the suggested mechanisms was, among other variables, studied in the article by Juanola-Falgarona et al (4). In the GLYNDIET study, 122 overweight or obese adults were randomly assigned to 1 of 3 isocaloric, energy-restricted diets for 6 mo. The diets consisted of a moderate-carbohydrate and HGI diet, a moderate-carbohydrate and LGI diet, and a high-carbohydrate and HGI, low-fat diet. After 6 mo, BMI was reduced in all 3 groups, and more so in the LGI compared with the low-fat diet. But there was no significant difference between the HGI and LGI diets. Fasting insulin, HOMA-IR, and HOMA-β cell function followed a similar pattern, but no other differences were observed in fasting or postprandial appetite sensations, blood lipids, or inflammatory markers after 6 mo. This study does not support that dietary GI per se has a role in body weight regulation and risk factors for metabolic diseases. The GLYNDIET study was of a reasonably long duration and conducted in large groups of subjects. However, the energy restriction and isocaloric design could have blurred possible differences between diets of high and low GIs.

In real life, people normally eat ad libitum until pleasantly satisfied, even if trying to follow certain dietary principles. Thus, the ad libitum design is in many ways more relevant. Furthermore, it is relatively easy for most people to lose weight on a specified diet. The huge challenge is to keep body weight down after weight loss. Therefore, it is of more interest to study body weight maintenance after weight loss than weight loss per se.

In a previous ad libitum study, in which macronutrients, dietary fiber, and energy density were well matched and only GI was manipulated, there was also no significant difference in 10-wk body weight or fat mass in the overweight study subjects (7). However, after 10 wk of consumption of the LGI diet, fasting LDL cholesterol as well as postprandial plasma glucose, serum insulin, and glucagon-like peptide 1 were significantly reduced, supporting the role of the LGI concept for these risk factors (8).

In the DioGenes Study, a design including both the ad libitum principle and weight maintenance after weight loss was used. Here, it was shown that a combination of an ad libitum LGI, high-protein diet maintained body weight loss better and had a favorable effect on glycemic control and insulin sensitivity than did other protein and GI combinations after 6 mo (9, 10). Still, in a 12-mo follow-up study in a subgroup of subjects, the opposite pattern for GI and body weight maintenance was seen, making interpretation of the role of GI in long-term weight maintenance difficult (11).

With regard to prevention of T2D, it was previously shown in large diabetes prevention programs that a healthy dietary pattern together with lifestyle modification was more efficient than pharmacologic treatment in preventing T2D in prediabetic individuals (12, 13). In neither of these studies, however, was GI in focus. Thus, long-term intervention studies that focus on GI and T2D are clearly needed.

Recently, we received a European Union grant to study the combined effects of GI, protein, and other lifestyle factors on the development of T2D in prediabetic subjects. The project PREVIEW (PREVention of diabetes through lifestyle Intervention and population studies in Europe and around the World) involves both a 3-y randomized controlled trial and cohort studies (www.previewstudy.com) and is currently ongoing (14). It will hopefully be able to answer some of the open questions and thus provide more evidence on the role of GI for body weight maintenance, metabolic risk factors, and incidence of T2D.

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REFERENCES

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