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July 2, 2007

Glycemic response and health: summary of a workshop[1–3]

John Howlett and Margaret Ashwell

ABSTRACT

Interest in the glycemic effect of diet on health and well-being is growing among health care professionals and consumers. Diets with high glycemic impact have been postulated to increase risk of obesity, insulin resistance, diabetes, and cardiovascular disease. A reduction in the glycemic effect of the diet has been proposed as a means of assisting body weight management, improving blood glucose control, and reducing diabetic, cardiovascular, and related risks. Foods are increasingly carrying labels that describe their glycemic properties. Yet, a scientific debate exists about whether a relation between the glycemic response to diet and health truly exists, and, if so, which descriptor of a food's glycemic properties best predicts its effect on health outcomes. This article reports the proceedings of a workshop at which a meta-analysis of the relation between the glycemic response to foods and health was presented and the merits of glycemic index (GI), glycemic load (GL), and glycemic glucose equivalent as predictors of health outcomes were discussed. The conclusions include the findings that many studies purporting to investigate lower GI interventions actually studied lower GL interventions; that unavailable carbohydrate (eg, dietary fiber), independent of GI, seems to have at least as big an effect on health outcome as GI itself; that lower GI and GL diets are beneficial for health in persons with impaired glucose metabolism, but that it is as yet unclear what they mean for healthy persons; and that the larger the divergence of glucose metabolism from the norm, the larger the effect of lower GI and GL interventions. *Am J Clin Nutr* 2008; 87(suppl):000S–000S.

KEY WORDS Glycemic response, health, blood glucose control, glycemic index, glycemic load, carbohydrate, diet, food labeling, meta-analysis

INTRODUCTION

Interest in the glycemic properties of foods and the possible contribution of glycemic properties to nutrition and health is growing. The use of descriptors of glycemic properties on food labels is increasing, and articles and publications on the subject appear frequently in the media and in the popular press, bringing the subject increasingly to the awareness of consumers. Meanwhile, within the scientific community, debate exists about the importance of the glycemic response to diet for areas of public health concern, such as its influence on risk of type 2 diabetes and cardiovascular disease, and on the most appropriate descriptor of glycemic properties to use in communicating any benefits to health care professionals and consumers. If the maximum benefit to public and consumer health is to be obtained, it is important that any parameter used in food labeling and in advice to consumers be consistently and reliably measured to reflect the nature of the foods it describes, be a valid indicator of the food's benefits, and be easily applied by consumers in making daily choices of the foods they eat.

AQ: 1

The European branch of the International Life Sciences Institute (ILSI Europe) convened a workshop in Nice, France, from 6–8 December 2006 to debate the scientific evidence relating the glycemic response to the diet to health and disease. In preparation for the workshop, the Dietary Carbohydrates Task Force of ILSI Europe commissioned a systematic review of the scientific literature on the subject. The review by Livesey et al (1, 2) provided the main points for debate in the workshop, and its discussion was preceded by presentations from invited speakers on related topics to provide context. This article summarizes the proceedings of the workshop, the main points of discussion, and the conclusions. The contributions of the invited speakers and the meta-analysis itself are presented in detail in subsequent articles.

The workshop was co-chaired by Martijn Katan of the Free University of Amsterdam, Netherlands, and by Toine Hulshof, Kellogg's Europe, Dublin, Ireland. More than 60 experts from academia, government, and industry in Europe, North America, New Zealand, and South Africa participated.

PRESENTATIONS BY INVITED SPEAKERS

Julie Miller Jones (College of St Catherine, St Paul, MN) presented the conclusions of the ad hoc Committee on Glycemic Carbohydrates of the American Association of Carbohydrate Chemists (3). The committee had been convened in 2004 and had met over a 2-y period to formulate definitions relating to glycemic carbohydrate and its measurement. The terms so defined were to provide a basis for communicating to consumers an understanding of how the carbohydrate content of different foods affects blood glucose concentrations. The committee concluded its work by agreeing on definitions for the following terms: *available carbohydrate*, *glycemic response*, *glycemic carbohydrate*, and *glycemic impact*. Professor Miller Jones described the discussions leading to the adoption of the definitions and the committee's conclusions as to how they should be applied.

[1] From Wembley, United Kingdom (JH) and Ashwell Associates (Europe) Ltd, Ashwell, Hertfordshire, United Kingdom (MA).

[2] This report was commissioned by the Dietary Carbohydrates Task Force of the European Branch of the International Life Sciences Institute (ILSI Europe) and was funded by industry members Cerestar, Coca-Cola, Danisco, Groupe Danone, Kellogg, Kraft Foods, National Starch, Nestlé, RHM Technology, Royal Cosun, Südzucker, and Unilever.

[3] Address reprint requests to ILSI Europe. E-mail: info@ilsieurope.be.

Dario Giugliano (University of Naples SUN, Italy) described the physiologic mechanisms involved in glucose metabolism, the pathways leading to hyperglycemia, and its time course in relation to dietary influences (4). He also described the relation between hyperglycemia and disease states such as type 2 diabetes and cardiovascular disease and discussed the impact and significance of glycemic stress for public health.

In the first of 2 presentations, Geoff Livesey (Independent Nutrition Logic, Wymondham, United Kingdom) described the scope, design, and methodology of the systematic and quantitative review of the scientific literature on the relation between glycemic response and health (1). The review had taken as its baseline the scientific literature up to the year 2005 reporting intervention studies of diets with different glycemic characteristics. Starting with >2700 reported studies, a systematic appraisal against rigorous inclusion criteria yielded 40 studies suitable for meta-analysis. Livesey explained that care had been taken in the review of individual studies to critically examine the relation between glycemic index (GI) and glycemic load (GL) in the reported characteristics of the foods and diets consumed. It was important to do this because scientific debate exists about which of these 2 variables is the better indicator of outcomes for glycemic control. Livesey described how the meta-analysis explored the relations between GI, GL, available and unavailable carbohydrate, energy intake, and markers of health. In a second presentation, Livesey (2) presented the findings of the review in relation to the relative importance of GI and GL as predictors of health outcomes. Inferences were drawn from an examination of 26 epidemiologic studies published before 2005.

John Monro (New Zealand Institute for Crop and Food Research, Palmerston North, New Zealand) described the relations between GI, GL, and glycemic glucose equivalent as measures characterizing the glycemic impact of foods relative to a standard carbohydrate (5). He discussed the merits of the glycemic glucose equivalent, which is independent of measures of the available carbohydrate content of food, as an alternative to GI and also showed how the glycemic glucose equivalent can be used within food tables.

Current uses of the glycemic concept in labeling and an assessment of consumers' use of the information presented were discussed by Helen Mitchell (Danisco, Redhill, UK) (6). Mitchell described consumer response to glycemic labeling in different regions and countries and examples of food products that carry such information, noting that glycemic index is the most commonly used parameter. She described some of the opportunities available to the food industry to modify the glycemic effect of foods through the substitution of high-glycemic carbohydrates by low-glycemic and nonavailable carbohydrate alternatives in product formulations. In concluding, she highlighted some of the barriers to effective communication of the glycemic concept and its potential benefits to consumers.

In 2 consecutive presentations, Tom Wolever (University of Toronto, Toronto, Canada) first described the history of the development of the glycemic index and its relation to health and then presented the results of an interlaboratory study on the measurement of glycemic index involving 2 standardized foods in 28 laboratories worldwide (7). Wolever explained that although all the laboratories had used the same methodology, some aspects of study design, such as restrictions on subjects' dietary regimen before measurement and data analysis after measurement, had been left to local discretion. He concluded that the observed variability in the measurement of GI could be reduced by improved standardization of study design and that controlled studies and cost-benefit analyses were needed to identify those factors that should be controlled and those that could remain optional.

Jeya Henry (Oxford Brookes University, Oxford, UK) described studies in which favorable modulation of 24-h blood glucose concentrations has been shown in response to simple modifications of the diet. He explained that the changes could be related to structural properties of foods that affected the susceptibility of starch to digestion and to other components of the diet that affect its absorption. He proposed that increased knowledge of the relation between the structure of starchy foods and the physiologic responses they induce would provide opportunities for further improving the glycemic properties of the diet.

Simin Liu (University of California, Los Angeles, CA) presented an analysis of the role of glucose homeostasis in body weight maintenance and its relation to type 2 diabetes and coronary heart disease. Liu concluded that glycemic index and glycemic load, which serve as direct measures of the blood glucose-raising potential of carbohydrate-containing foods, have more value as descriptors of carbohydrates than do terms such as *simple* and *complex*. It is important, however, that they be used in conjunction with other concepts, such as energy density and nutrient composition. He also highlighted the need to consider body weight, sex, age and genetic factors when assessing the relation between diet and disease.

Gabriele Riccardi (Frederico II University, Naples, Italy) discussed the value of glycemic index and glycemic load as dietary descriptors in relation to the healthy state, the prediabetic state, and in frank diabetes (9). He presented some examples of the influence of the carbohydrate and the dietary fiber contents of foods on postprandial blood glucose concentrations. He also described the mechanisms by which high dietary glycemic load and its interrelation with body weight, low physical activity, and genetic factors may lead to impaired glucose regulation and increased diabetes and cardiovascular disease risk. In discussing the scientific evidence for the existence of relations between GI and health, he noted that most studies have been of short duration. He concluded that GI and GL are useful parameters to consider in the choice of foods for individuals with diabetes or impaired glucose regulation, and that they may also be relevant for normoglycemic individuals with insulin resistance or metabolic syndrome.

Fred Brouns (Cerestar, Vilvoorde, Belgium) described the conclusions and comprehensive recommendations of a review of the methodologic considerations surrounding the measurement of glycemic index (10). The authors had considered aspects of the measurement of GI including choice and number of subjects, choice of reference food, conduct and timing of the measurement, number of replications, and methods of calculation.

DISCUSSION OF THE META-ANALYSIS

Workshop participants were divided into 4 working groups to undertake a detailed consideration of the review and meta-analysis carried out by Livesey et al. The focus topics for the 4 working groups were

- health aspects,
- relative importance of GI and GL and other parameters,
- GI methodology, and

- applications and implications of the findings of the review.

Each working group was asked to structure its discussions around

- those findings that could be considered to reflect a scientific consensus,
- those findings of the review with which they could not agree,
- additional issues that could be addressed or explored by using the database assembled for the review, and
- questions that could not be resolved during the course of discussion in the working groups and that might be taken forward in future work.

Health aspects

This working group agreed that the meta-analysis was an important state-of-the-art analysis. The findings were statistically significant despite the methodologic and biological diversity among the studies reviewed. Although the markers chosen require further validation with respect to their predictive value, they are relevant for the purposes of the analysis. Limitations of the review included the fact that markers for some aspects (eg, lipoproteins and body composition) were not measured or reported and it had been difficult to separate the influence on health outcomes of GI and GL from that of unavailable carbohydrate. The value of the review, although already significant, could be enhanced by updating it with recently published studies and by giving consideration to the representativeness of the study groups with respect to subjects' health status.

Does changing the glycemic effect of a person's diet affect their health?

Although there was agreement that the meta-analysis provided evidence of positive health effects of a reduction in dietary glycemic effect for diabetic persons, there was only weak evidence that there was any effect on general well-being in healthy persons. Although it is plausible that diet-induced glycemic changes affect cognitive performance, more research is needed to allow a full evaluation of the direction and magnitude of the possible effects. For effects on satiety, studies with relevant markers are required, and the effect of low- versus high-GI foods on sports performance remains the subject of ongoing research.

If yes, which disorders (eg, diabetes, cardiovascular disease, obesity) are involved positively or negatively by changing the glycemic response and what is the order of priority in health gain for the different disorders?

There was agreement that low-GI diets improve glycemic control in individuals with impaired glucose tolerance and diabetes. There is a need to explore the effects of different low-GI diets in more detail, for example, with respect to their effect on insulin secretion rates and in the presence or absence of fiber. Livesey, as the principle author of the review, emphasized that although the meta-analysis had shown a statistically significant association between glycemic control and GI, glycemic control was correlated more strongly with unavailable carbohydrate than with GI.

Although there is some evidence of beneficial effects of low-GI diets on risk factors for cardiovascular disease in short-term studies, the evidence for positive long-term effects is limited. The association between glycated hemoglobin (a marker of glycemic control commonly used in patients with diabetes) and long-term cardiovascular disease risk in healthy persons requires further evaluation.

There is evidence for a positive effect of low-GI, high-fiber diets on body weight maintenance and reduction, but an effect specific to low GI remains to be substantiated. It is probable that the correlation with a low-GL diet derives mainly from a reduction in energy intake.

Should an effort be made to inform consumers about the GI or GL of a food by food labeling or other means?

Are the beneficial effects of low-GI foods the result of a low GI or other properties of the food?

No evidence exists to support a change in the current advice to consumers to maintain ≥40% of their total energy intake as carbohydrate. Therefore, in any advocacy for the beneficial effects of a low-GI or low-GL diet, care should be taken to avoid confusing consumers, lest they equate it with a lowering of carbohydrate intake. Consideration should be given to the use of GI because it relates to the quality of the carbohydrate and it reflects, for example, the nature of the carbohydrate within the structure of the food matrix and its interaction with other food components.

Relative importance of GI and GL and other parameters

The working group agreed that the meta-analysis had provided evidence that reductions in the GL and the GI of the diet are associated with reductions in fasting blood glucose and glycated proteins in diabetic persons. There was consensus that insulin sensitivity tended to improve with lower-GL diets and higher unavailable carbohydrate intake; the more severe the dysglycemia, the greater the positive effect of reducing glycemic load and increasing unavailable carbohydrate intake. The group noted the counterintuitive finding that moderate reductions in the GL or GI of the diet were associated with elevated carbohydrate and energy intakes and higher fasting blood triacylglycerol concentrations. However, an assessment of the relevance of this association requires further consideration of the data. Responses to the specific questions addressed were as follows.

Is the health effect of changing the glycemic effect of a food determined better by its GI or by its GL?

On the basis of the evidence of the meta-analysis, the participants agreed that GL is the better predictor of health outcomes in the context of foods high in unavailable carbohydrate. However, both GI and GL are important in informing consumer choice in relation to carbohydrate and fiber-based foods, provided that protein and fat intakes are maintained within dietary guidelines. It was suggested that if GI alone were used, there would be a risk that the positive contribution of unavailable carbohydrates, which have a role in reducing glycemic response, would be overlooked.

Is the relation between low glycemic response and health due to low glycemic response to a food per se or to other properties of the food?

Given that the meta-analysis was unable to distinguish the separate roles of available and unavailable carbohydrate, it is not possible to conclude whether improvement in glycemic response alone mediates health outcomes. Further research is needed into

the role of other minor food constituents in influencing glycemic response.

Are the GI and GL relevant to healthy persons?

The concept of the GL, taken together with unavailable carbohydrate, is relevant to healthy populations. When considering at-risk populations, both GI and GL are even more relevant. There are indications that GI and GL or unavailable carbohydrate may have relevance for body weight maintenance, but the evidence for a role in body weight reduction is limited.

GI methodology

This group agreed with Livesey's conclusion that the positive health effects of low-GI diets identified in the review may, in part, be due to an increase in the intake of unavailable carbohydrate. The group also agreed with the finding that the positive effect of a low-GI diet was greater in subjects with impaired glucose control. They concluded that the quality of the available carbohydrate in the diet influences markers of health outcome independently of the total amount.

Uncertainties, however, were raised in relation to how the sizes of different studies had been accounted for in the meta-analysis. Furthermore, the possibilities for discriminating between the influence of GI and that of GL on different health outcomes were felt to be limited by the small range in GI compared with the large range in GL and its consequences for differences in the discriminating power of the studies. This group also noted that a moderate reduction in the GI of the diet was associated with an increase in energy intake and suggested that the role of energy intake should be further explored. Responses to the specific questions addressed were as follows:

Are the GI values from the interventions studies, as used in the Livesey meta-analysis valid? If not, what is the expected impact?

It was noted that GI values reported in different studies were derived by different methods. In some cases, they were obtained by measurements made on foods in human subjects; in other cases, they were derived from GI tables and from in vitro measurements. As a result, it was not certain that the values are directly comparable. The effect of this uncertainty on the outcome of the meta-analysis is not known.

Can the GI of a meal be calculated from the GIs of the individual components?

There was agreement that the GI of a meal can be calculated from the GI values of its individual components. However, the extent to which the observed response can be ascribed to the GI of the meal will depend on several factors: *1*) the accuracy of the GI values ascribed to the individual components, *2*) the magnitude of the difference in GI expected from the intervention, and *3*) whether the difference in GI value is the only variable introduced in terms of meal composition.

Because of the variability in GI measurements, should we recommend the use of GI categories (low, medium, high) and not exact values for GI for consumer communication?

The use of categories carries risks of misclassification and the use of values is more precise, but categorization is simpler for consumers to understand. The use of 3 categories (low, medium, and high) was judged to be reasonable. However, the dose-response relation between GI and health outcomes has not been quantified, and setting boundary values might require subjective judgement. Finally, GL and glycemic glucose equivalents are usually expressed numerically and these too might benefit from a categorization approach.

Applications and implications of the findings of the review

This working group agreed that the review had identified a significant role for unavailable carbohydrate. This is important in assessing the effect of substituting available carbohydrates in the diet in attempting to modulate the GI or GL. The group further agreed that the GL appeared to be more relevant than the GI as a predictor of health outcomes and that exploration of the GI-GL concept provided a useful means of assessing the effects of carbohydrate quality on health.

The group expressed reservations concerning some of the findings on GI and GL and body weight management, particularly with respect to categorizing these effects as potentially adverse. Care would have to be taken in communicating the findings on body weight management lest it lead to misunderstandings on the part of consumers. Additionally, care must be taken in using the term *GI* in relation to total carbohydrate to avoid undermining the use of GI in its traditional sense (ie, relating it only to available carbohydrate and not including unavailable carbohydrate). Responses to the specific questions addressed were as follows.

Is knowledge of the GI or GL of a food useful for healthy persons or patients?

For healthy persons, the meta-analysis had not shown clinical relevance for the GI or GL of foods in relation to insulin sensitivity. The investigation of relevance for disease risk reduction or prevention in this area would require the development of appropriate markers and their use in appropriately designed studies. However, the review provided indications that other clinically relevant effects may exist, for example, on blood lipids and blood pressure. For persons with impaired insulin sensitivity, it was agreed that relevant effects had been shown.

If yes, should glycemic effect labeling be used on packaging?

In light of the above, the evidence is insufficient to support glycemic labeling of food products on the grounds of benefit for healthy individuals. There is, however, sufficient evidence to support labeling on the grounds of benefit for diabetic persons. There is, of course, debate about the need for special foods for diabetic persons, but, in this context, it was also noted that current estimates suggest that diabetic persons and those in a prediabetic state constitute a significant ($\approx$20%) and growing proportion of the populations of developed and developing countries. Any benefits to be obtained from glycemic labeling for this section of the population, therefore, have the potential to make a major impact on public health. In relation to the total population, there is at least the possibility that glycemic labeling would provide guidance leading to healthy dietary choices.

If labeling is to be effective, it would require existing food tables to be supplemented with comprehensive glycemic data for currently available foods in a form accessible both by nutrition and health professionals and by diabetic consumers. Support

would be needed for the creation of such data on the basis of valid in vivo measurements and for their inclusion in food tables.

If yes, should it be GI or GL?

GI has the advantage of providing an indication of the glycemic quality of carbohydrates present in food, whereas GL has the advantage of providing information about the glycemic quantity, albeit information that is open to misinterpretation unless carefully related to portion size. The glycemic glucose equivalent was seen as an alternative to the GL with the possible advantage that it can be inserted directly into the conventional labeling panel for nutrient declarations because of the way it is measured and expressed. Overall, there was no clear consensus that one parameter has more merit over another.

In discussing the merits of categorization and banding against those of numerical values, it was again noted that banding could lead to misclassification between broad groupings. However, it was also recognized that, because of the variability inherent in measurement, numerical values themselves in fact represent ranges.

Do you think that low-GI food labeling is open to abuse? If so, how?

The GI concept carries a high risk of misinterpretation by consumers. In particular, care is needed to ensure that consumers are not misled into overly simplistic associations. They must not equate low-GI foods with low-energy foods, and they must not assume that consumption of low-GI foods will lead to weight reduction. Moreover, they must not be led to assume that high GI equates to high sugar. It is most important that consumers are provided with sufficient information to enable them to interpret the GI in the context of the nutrition profile of the overall diet to benefit from an improved glycemic response.

FINAL DISCUSSION AND CLOSURE OF THE WORKSHOP

During the final discussion, it was stressed that any glycemic labeling of foods must be based on sound evidence of a relation between the glycemic properties of foods and positive health outcomes. The value of the glycemic index or glycemic load as descriptors for the characterization of the glycemic properties of foods would be enhanced by the availability of standardized and validated food tables listing GI values or glycemic loads for a comprehensive and relevant range of foods. This would enable healthcare professionals and consumers to make optimal use of the glycemic concept in exercising dietary choice.

In relation to the meta-analysis, the following key conclusions were reached:

- Many studies purporting to investigate lower GI interventions actually used lower GL interventions.
- Unavailable carbohydrate (eg, dietary fiber), independent of GI, seems to have at least as big an effect on health outcome as GI itself.
- Lower GI and GL diets are beneficial for health in persons with impaired glucose metabolism, but it is as yet unclear what their benefit is for healthy persons. AQ: 2
- The larger the divergence of glucose metabolism from the norm, the larger the impact of lower GI and GL interventions.

Overall, there was consensus among the workshop participants that the review by Livesey et al represented a significant contribution to the discussion of the effect of glycemic response on health.

JH and MA acted as rapporteurs for the workshop and jointly wrote this account of the proceedings of the meeting. JH is currently advising an industry group comprising food manufacturers and retailers who are preparing a submission to the authorities in Europe supporting the case for the use of glycemic index in the labeling of food products. MA is Director of Ashwell Associates (Europe) Ltd, who are currently advising various food manufacturers who are interested in the relation between carbohydrate quality and health.

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AQ1—Is the revised sentence (beginning "If the maximum benefit") as meant? If not, please suggest additional edits.

AQ2—Is the revised point (beginning "Lower GI and GL diets" as meant?