Proceedings of the Nutrition Society (2005), **64**, 105–113 DOI:10.1079/PNS2004400

A Satellite Symposium sponsored by Palatinit was held at Trinity College, Dublin, Republic of Ireland on 6 July 2004

Satellite Symposium on 'The role of low-glycaemic diets in obesity and health'*

Low-glycaemic diets and health: implications for obesity

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The present review considers the background to terminology that relates foods, glycaemia and health, including 'available carbohydrate', 'glycaemic index' (GI), 'glycaemic glucose equivalent', 'glycaemic response index' and 'net carbohydrate', and concludes that central to each of these terms is 'glycaemic load' (GL). GL represents the acute increase in exposure of tissue to glucose determined by foods; it is expressed in ingested glucose equivalents (per 100 g fresh weight or per serving), and is regarded as independent of the state of glucose metabolism from normal to type 2 diabetes mellitus (T2DM). *Ad libitum* studies in overweight or obese adults and children show that low-GL diets are associated with marked weight benefits, loss of adiposity and reduced food intake. Weight benefits appear on low-glycaemic *v*. high-glycaemic available carbohydrates, unavailable *v*. available carbohydrates and protein *v*. available carbohydrate. Energy intake immediately after lowering of meal GL via carbohydrate exchanges is apparent only after a threshold cumulative intake of >2000 MJ. Various epidemiological and interventional studies are discussed. A relationship between GL and the development of T2DM and CHD is evident. Studies that at first seem conflicting are actually consistent when data are overlaid, such that diets with a GL of >120 glucose equivalents/d would appear to be inadvisable. Whereas certain studies might place GI as being slightly stronger than GL in relation to T2DM risk, this situation appears to be associated with observations in a lower range of GL or when the range of GI is too narrow for accuracy; nevertheless, authors emphasise the importance of GL. Among the studies reviewed, GL offers a better or stronger explanation than GI in various observations including body weight, T2DM in nurses, CHD, plasma triacylglycerols, HDL-cholesterol, high-sensitivity C-reactive protein and protein glycation. Where information is available, the associations between risk factors and GL are either similar or stronger in the overweight or obese, as judged by BMI, and apply to both body weight and blood risk factors. The implications tend to favour a long-term benefit of reducing GL, for which further study is necessary to eliminate any possibility of publication bias and to establish results in clinical trials with overweight and obese patients.

Obesity: Diabetes: CHD: Health markers: Glycaemic load

The blood glucose (glycaemic) response to foods has been of concern for many years, especially in the management of diabetes mellitus (McCance & Lawrence, 1929). Concern now extends to conditions that may precede type 2 diabetes mellitus (T2DM), such as obesity (Brand-Miller *et al*. 2002; Ludwig, 2003), glucose intolerance (Wolever & Mehling, 2002) and the metabolic syndrome (McKeown *et al*. 2004). Further, there is concern for initially-healthy individuals who may develop related life-threatening conditions such as T2DM (Salmeron *et al*. 1997*a*,*b*) and CHD (Liu *et al*. 2000). Not surprisingly, such concern impacts on the approach to the analysis and description of foods. Terms (described later, pp. 106–107) such as available carbohydrate (McCance & Lawrence, 1929),

*This symposium was not part of the main programme of the Summer Meeting of the Nutrition Society jointly with the Association for the Study of Obesity held at Trinity College, Dublin, Republic of Ireland on 5–8 July 2004.

Abbreviations: GI, glycaemic index; GL, glycaemic load; T2DM, type 2 diabetes mellitus.
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glycaemic index (GI; Jenkins *et al*. 1981), glycaemic load (GL; Salmeron *et al*. 1997*a*,*b*; Liu *et al*. 2001, 2002), glycaemic glucose equivalent (Monro, 2002, 2003; Liu *et al*. 2003) and glycaemic response index (Anfinsen *et al*. 2004) each aim to relate foods, postprandial glycaemia and health. Such a variety of terms reflects disquiet over the limitations and adequacy of 'available carbohydrate', and more recently 'GI', and impacts on clarity in scientific communications. Another related term is 'net carbohydrate', which was introduced ostensibly for the related purpose of 'carbohydrate-controlled' weight reduction (Atkins, 2003), and has attracted interest from regulatory authorities in communication with the consumer (Food and Drug Administration, 2004). Understanding these terms, their origin and the strength of their relationship to health and health risk factors will probably prove important in future discussions of nutrition and health, the design of related intervention studies and the eventual implementation (if appropriate) in public health measures (population needs) or for informing individual consumer choice (individual patients or non-patients). It would seem appropriate, therefore, to begin with the terminology.

Terminology

Interrelationship between the different terms communicating glycaemic potential

Fig. 1 shows the interrelationship between the various terms used to communicate the potential of 'foods' to impact on glycaemia and health. These terms will be considered individually. GL is evidently the central concept related to each of the other terms. Its determination may be via direct methods such as the glycaemic glucose equivalent (Monro, 2002) or an ostensibly identical glycaemic response index (Anfinsen *et al*. 2004). GL is also calculated as the product of available carbohydrate and fractional GI. Direct approaches have arisen because of certain inherent difficulties in the determination and application of both available carbohydrate and GI.

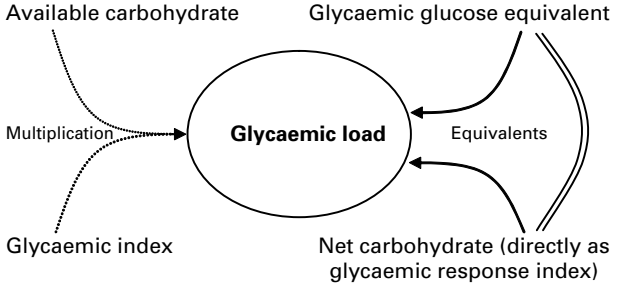

Fig. 1. Terminology surrounding the concept of food, glycaemia and health. Glycaemic load is the central or common concept. One approach to its derivation is indirectly as the product of available carbohydrate (McCance & Lawrence, 1929) and glycaemic index (Jenkins *et al*. 1981). When available carbohydrate is expressed in g/100 g fresh weight food, glycaemic load (Salmeron *et al*. 1997*a*,*b*) has similar units because glycaemic index is dimensionless. Two other approaches that have originated independently are the glycaemic glucose equivalent (Monro, 2002) and net carbohydrate now measureable directly as a glycaemic response index (Anfinsen *et al*. 2004). The latter two approaches are ostensibly identical (symbolised by the curved parallel line of equality) and derive from similar direct method(s) of determination (see p. 107). The direct approach avoids many inherent pitfalls in the indirect approach that uses calculation (see p. 107).

'Available carbohydrate'. By definition, available carbohydrate is that 'absorbed via the small intestine and used in metabolism' and it was originally seen as challenging blood glucose control and the tolerance of diabetics (McCance & Lawrence, 1929). All other carbohydrate is 'unavailable' and suitable for diabetics, as it cannot challenge blood glucose (unless excreted in urine), and some carbohydrates, e.g. pectins, have been recognised as sources of energy. It is now proposed that available carbohydrates should be graduated or subdivided. Those carbohydrates that are low or moderately glycaemic would also be suitable for diabetes management (Jenkins *et al*. 1981; Brand-Miller *et al*. 2003). Hence, unavailable and low- to moderate-glycaemic carbohydrates might be considered together as suitable, while available-carbohydrate foods with a high glycaemic response could be considered less suitable or even unsuitable. This approach renders the original purpose of classifying carbohydrates as available or unavailable somewhat meaningless in terms of glycaemic control, as recognised by the Food and Agriculture Organization (1998). The reason for maintaining the available–unavailable distinction now rests mainly with gut function and food energy evaluation. Available carbohydrate has gross energy that is used fully to fuel metabolism; by comparison unavailable carbohydrate contributes $\leq 50\%$ of its gross energy to fuel metabolism, and non-fermentable carbohydrate not surprisingly contributes none (Livesey, 2001, 2002*b*). Certain analytical issues and errors implicated in relation to available carbohydrate will be described.

'Glycaemic index'. GI was introduced (Jenkins *et al*. 1981) to describe the impact of a food containing 50 g available carbohydrate on the glycaemic response expressed as the incremental area under the blood glucose curve and expressed as a percentage (indexed) to 50 g oral glucose. In practice the term GI is not well understood. For example, it is often described simplistically in lay terms as 'the rate at which carbohydrate is digested and enters blood' or 'how quickly blood glucose is raised'. These descriptions are obvious scientific inaccuracies, and the variation in the area under the curve may also depend on variations in the rate of blood glucose disposal into the tissues (Schenk *et al*. 2003), which may itself depend on the glucose-dependent insulinogenic effect of co-ingested fats (Livesey, 2003; Flint *et al*. 2004). Interestingly, in relation to food intake and obesity, an important quality of GI has been described as 'how quickly blood glucose concentration falls (declines) after eating' (Melanson *et al*. 1999*a*,*b*; J Brand-Miller, unpublished results). Of relevance to nutrition and health, the quantity and the source of carbohydrate are important. Many foods of high GI have proved unchallenging to blood glucose, and vice versa (Foster-Powell & Miller, 1995; Monro, 2002). As a consequence, the more recent concept of 'GL' has evolved.

'Glycaemic load'. GL is the product of GI (as a proportion) and 'available carbohydrate'. GL was introduced

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to assess the relationship between the average glycaemic response of foods consumed and the health outcome in epidemiological studies (Salmeron *et al*. 1997*a*,*b*; Liu *et al*. 2000, 2001). Many epidemiological data are adjusted to a common level of food energy intake, so that GL may actually be given in scientific publications as a load (glucose equivalent; g) per 8·4 MJ (2000 kcal) intake (or per average energy intake in the study population per d). Such modes of expression are not compatible with those used to describe foods, which express amounts on a per 100 g fresh weight basis or per serving size (compare with food tables and labels). Thus, the term 'glycaemic glucose equivalent' has been conceived.

'Glycaemic glucose equivalent'. Glycaemic glucose equivalent is the GL per 100 g fresh weight or per serving (Monro, 2002, 2003; Liu *et al*. 2003). Among its many advantages, the glycaemic glucose equivalent can be determined directly and without the need to analyse the available carbohydrate (or other component) in the food, which is still more problematic than is generally realised. The glycaemic glucose equivalent overcomes problems of assessing foods of low energy density (high bulk) for which the analytical requirement to ingest 25–50 g available carbohydrate can lead to large non-physiological masses of food being eaten, and which depresses the glycaemic response; this situation is particularly relevant to small individuals.

There are several problems arising from the use of available carbohydrate in the assessment of the glycaemic response, as discussed for GI. Such carbohydrate may be determined and expressed differently by various authorities, and it would be impractical to have GI determinations for each of these variations. Authorities use total carbohydrate, total carbohydrate less dietary fibre and directly available carbohydrate. Among these representations of available carbohydrate, several methods are available for the dietary fibre analysis required, and analysts may or may not include non-digestible oligosaccharides with dietary fibre. Direct determinations of available carbohydrate may or may not capture digestible oligosaccharides. The mode of expression of available carbohydrate is a source of variation between authors; some authors use available carbohydrate by difference (the actual weight of the available carbohydrate plus the sum of errors in all other components), some authors use the sum weight of sugars, dextrins and starches determined directly and some authors use adjustment or more direct determination as 'monosaccharide equivalents'. There can also be a 20% difference in the levels (mol/g carbohydrate) of waters of hydration and condensation (excluding moisture). When available carbohydrate is calculated by difference the errors in protein (particularly when derived as N multiplied by an appropriate factor), fat, ash and moisture determination affect the GI value for the available carbohydrate. Thus, the *in vitro* analytical value is of uncertain reliability *in vivo* during determination of GI, particularly in many high-fibre or exotic or bush foods (Thorburn *et al*. 1987). Indeed, this problem has been discussed (Ramdath *et al*. 2004), and can be difficult to overcome. Furthermore, attempts to modify the GI of starchy foods (Bjorck *et al*. 2000) or of sugars (Livesey, 2003) often result in an elevation of the resistant carbohydrate fraction, such that estimates of reduced GI (and GL calculated from GI) are accounted for in part by the replacement of available carbohydrate with unavailable carbohydrate. Direct determination of GL avoids these problems (Fig. 1).

'Net carbohydrate'. In human nutrition this term originally defined the carbohydrate content of food and was conceptually identical with 'available carbohydrate by difference' (Atkins, 2003); consequently, it has many of the pitfalls that have been described for available carbohydrate. A more recent definition is 'total carbohydrate less dietary fibre and polyols'. Dietary fibre is deducted because it is non-glycaemic (McCance & Lawrence, 1929; Atkins, 2003; Atkins-Nutritional, 2004). Similarly, the purpose of deducting polyols is because they are also generally very-low glycaemic or non-glycaemic carbohydrates (Livesey, 2003; Atkins-Nutritional, 2004). In keeping with this approach, after an initial diet low in carbohydrates (20–40 g) the Atkins (2003) weight reduction plan now includes a staged and limited re-introduction of carbohydrate, accepting those sources with a low-glycaemic response. Perhaps mistakenly, Atkins (2003) applied the concept of GI, forgetting, or not realising, that some low-GI foods have a marked impact on blood glucose because of the quantity normally eaten or served. The short-term success of maintained (or higher)-protein low-carbohydrate diets on weight control is now evident (Westman *et al*. 2002; Brehm *et al*. 2003; Foster *et al*. 2003; Samaha *et al*. 2003; Sondike *et al*. 2003; Price *et al*. 2004; Yancy *et al*. 2004). The purpose here is not to extol the potential virtues of such diets, but to note that these observations fall within the overall low-glycaemia–health concept, with importance falling more on GL than on GI (Livesey, 2002*a*; Price *et al*. 2004). If there were really a mistake in the adoption of GI by Atkins (2003; see Mendosa, 2004), it is ameliorated by more recent intentions for direct determination of GL as a 'glycaemic response index' (Anfinsen *et al*. 2004).

As noted earlier, all these modes of expression, determination or representation of the glycaemic response to foods come together conceptually via the GL (Fig. 1), the direct determination of which avoids the pitfalls mentioned.

Obesity

Whether or not the use of certain low-glycaemic diets can be advised in the control of obesity depends on there being an affirmative answer to one of two important questions. The first question concerns whether weight (adipose) gain or reduction can be usefully modified by such diets. The second question is whether health outcome can be usefully influenced by such diets, even if there is no influence on body weight (or adiposity). Observations to date provide an interesting and helpful illumination of the current state of the evidence.

Body weight

Whether the glycaemic response to foods is a determinant of body weight is currently controversial. The scope for controversy has been great and the debate inevitably inconclusive because of the limited amount of

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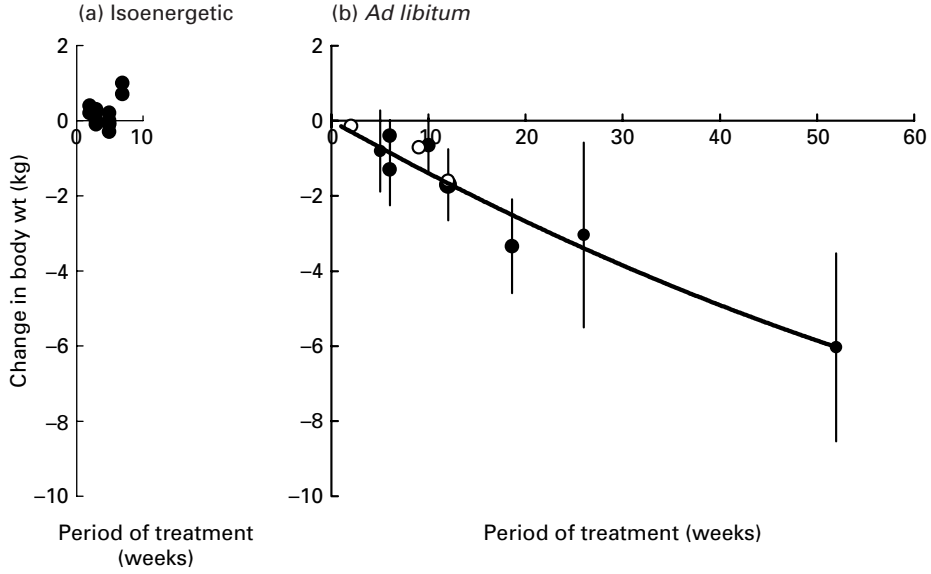

Fig. 2. Glycaemic load and body weight: (a) isoenergetic studies; (b) *ad libitum* studies. The isoenergetic comparisons comprise fourteen studies and 171 difference measurements, and dietary treatment was provided completely or partly to participants (for brevity, references are not given). The *ad libitum* comparison comprised five studies with 111 difference measurements plus forty-nine repeated difference measurements (Spieth *et al*. 2000; Bouche *et al*. 2002; Ebbeling *et al*. 2003; Price *et al*. 2004; Sloth *et al*. 2004) and was verified by duplicate extraction of data from publications by different readers. One other *ad libitum* study was excluded because of inconsistency in the reported diets, and another study was excluded because the authors had made unjustified suppositions about their diets or for statistical reasons (compare with Fig. 4). The curve is derived from an interim analysis fitted by equal-effects regression ($P < 0{\cdot}05$), in which individual coefficients have no particular meaning ($y = c + bx + bx^2$). The standard errors, represented by vertical bars, are estimates for individual studies. The relative sensitivity of individual studies ($\sqrt{n}$) is indicated by the size of data points (●). Too few data limited the scope for identifying satisfactory fixed or random-effects regression models because of excessive leverage. Overlaid are data (o) calculated from (Spengler & Boehme, 1984), in which the glycaemic load was reduced using isomalt in place of sucrose at increasing doses of 12, 24 and 48 g/d consecutively for 2, 7 and 3 weeks respectively.

relevant data (Pawlak *et al*. 2002; Raben, 2002). Slightly more data are now available and interim meta-analysis shows, unsurprisingly, that high-quality intervention studies of isoenergetic low-glycaemic-carbohydrate *v*. high-glycaemic-carbohydrate diets have practically no impact on body weight (Fig. 2(a)); this outcome is in agreement with the findings of Raben (2002), who noted the need for *ad libitum* studies. Data available by verified extraction from reliable studies with mostly adequate dietary information clearly indicate that low-glycaemic-carbohydrate *v*. high-glycaemic-carbohydrate diets eaten *ad libitum* result in a lower body weight (Fig. 2(b)); this finding is in agreement with that of Pawlak *et al*. (2002), who had already been involved in such a study. It is noteworthy that *ad libitum* low-fat low-glycaemic-carbohydrate diets are better than conventional low-fat diets whether the latter is fed *ad libitum* (Price *et al*. 2004) or in restricted amounts with limited energy-dense foods (Spieth *et al*. 2000). Also, low-glycaemic carbohydrate appears better than higher-glycaemic carbohydrate when fed in isoenergetic restricted amounts (Slabber *et al*. 1994), suggesting better compliance.

Although Fig. 2(b) shows a consistent fall (or success in not gaining) body weight, most researchers would agree that more information is needed to establish applicability to all or most *ad libitum* circumstances and to establish whether the effect is maintained beyond 1 year. Moreover, while the data at present favour the use of lower-glycaemic-carbohydrate or non-glycaemic-carbohydrate foods, there are insufficient numbers of studies of various sizes to be reasonably sure, on the basis of an Egger's test (Egger *et al*. 1997), that the benefit is reliably free of publication bias, although likely it is.

In relation to the body-weight reduction shown in Fig. 2(b), a question of importance is whether it derives from diets of lower GL or lower GI. Recent randomised parallel intervention studies of Price *et al*. (2004) have compared the exchange of low-GL carbohydrates for high-GL carbohydrates and the exchange of protein for high-GL carbohydrate; each of these exchanges would decrease the GL. They found that body-weight reduction is associated with reduced GL. A study (Spengler & Boehme, 1984) in which dietary GL was reduced by replacing sucrose with a mostly unavailable carbohydrate, 'isomalt', has also been

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reported. Data calculated from this study are superimposed on Fig. 2(b). Again, more body weight is lost than expected, based on energy intake, and the energy intake does not compensate to maintain body weight. Once more, reduced GL rather than GI appears to be the stronger explanation.

Few life-long studies of GL reduction have appeared, even in animals. However, two such *ad libitum*-feeding studies have been carried out, one in mice and another in rats (Smits-Van Prooije *et al*. 1990). In these cases 50 g starch/kg diet was replaced by isomalt (equivalent to 30 g daily in human subjects). In both species it was found that there is life-long reduction in both energy intake and body weight, with improved survival in old age in those animals consuming isomalt (Smits-Van Prooije *et al*. 1990). Data for the rat study are shown in Fig. 3. Again, this result is more in keeping with a response to reduced GL than a response to reduced GI when applied to available carbohydrate. There are no similar longevity studies in human subjects, although there is two-step evidence. Both isomalt- (Livesey, 2003) and low-GI-based foods (Brand-Miller *et al*. 2003) have been shown to reduce the glycated

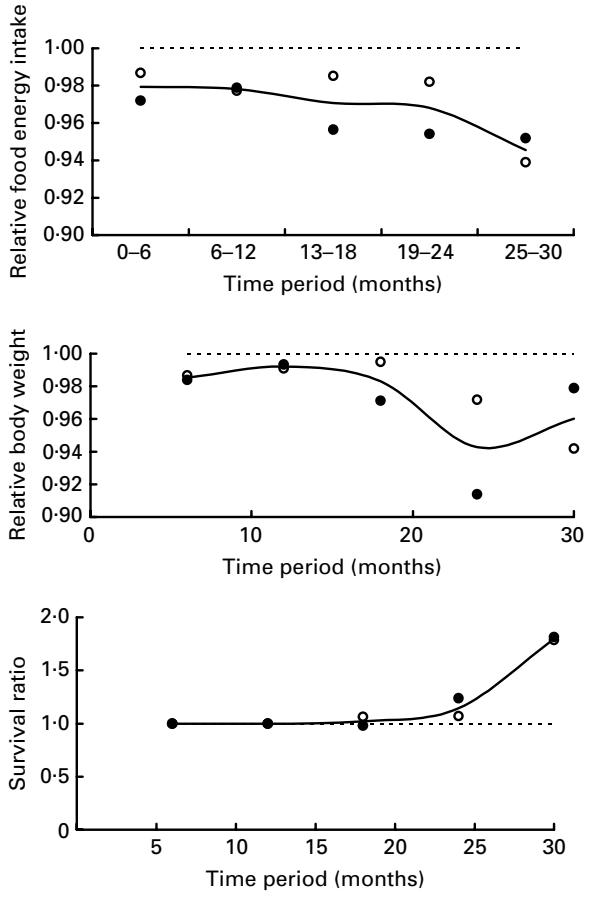

Fig. 3. Energy intake, body weight and survival in animals consuming a diet of reduced glycaemic load. Data points are calculated as values for the treatment divided by values for the control (isomalt/maize starch), with maize starch replaced by isomalt at a rate of 50 g/kg diet fed *ad libitum* to male (●) and female (○) rats. (Calculated from Smits-Van Prooije *et al.* 1990.)

Hb concentrations from previously raised values, and large prospective cohort studies in men >45 years of age have shown raised glycated Hb to be a risk factor for all-cause mortality (Khaw *et al*. 2001).

As with isoenergetic high-glycaemic to low-glycaemic available-carbohydrate exchanges (Fig. 2(a)), a controlled *isoenergetic* exchange of isomalt (mostly unavailable, sugar-free, 8·4 kJ (2 kcal)/g and very-low-glycaemic carbohydrate) and sucrose (available, sugar, 16·8 (4 kcal)/g and higher- or moderately-glycaemic carbohydrate) has no impact on body weight in human subjects (Spengler *et al*. 1987). Consequently, the body-weight reduction seen on reducing the GL using isomalt as an unavailable carbohydrate (Fig. 2(b)) must be brought about by a reduction in food intake, just as in animals (Fig. 3) and as inferred for available carbohydrate exchanges in *ad libitum*-fed human subjects (Fig. 2(b)) as long as energy expenditure is unaffected.

BMI, adiposity and energy intake

All else being equal, reduced body mass is inevitably accompanied by reduced BMI (kg/m^2). Among overweight and obese paediatric patients the reduction associated with low-GL-carbohydrate diets appears to be either independent of initial BMI (<28– >35 kg/m^2) or potentially is slightly greater at higher BMI (Spieth *et al*. 2000). BMI is used as a surrogate for body fat content. After treatment of obese adolescents for 6 months the proportion of body weight associated with body fat appears to be more strongly related to the GL of the diet than to its fat content (Ebbeling *et al*. 2003). A reduction in body fat content as a result of the lowering of GL by carbohydrate exchanges has been observed by other researchers (Slabber *et al*. 1994; Price *et al*. 2004).

Lower body fat has been linked to a greater scope for fat oxidation (lower RQ) when the GL is reduced by exchange of available carbohydrate with either available carbohydrate of lower GL (Pawlak *et al*. 2003, unpublished results) or unavailable carbohydrate (isomalt; Thiebaud *et al*. 1984). Once again, the explanation must relate to the change in GL rather than GI. In the case of isomalt the additional body fat loss is equal to the energy that would be expended by 30 min walking, i.e. not an insignificant amount.

Greater feelings of fullness after low-GL-carbohydrate *v*. higher-GL-carbohydrate meals are also suggested to contribute towards body fat reduction (Brand-Miller *et al*. 2002), but whether energy intake is responsive to such dietary change is controversial (Pawlak *et al*. 2002; Raben, 2002). The following discussion throws some light on this issue. Feelings of greater fullness can be unrelated to the initial glycaemic and insulinaemic response because both glucose (25 g in 250 ml water, high GL and insulinaemic) and isomalt (25 g in 250 ml water, very-low GL and insulinaemic) intake by human subjects elevate feelings of fullness to a similar extent (SUGiRS, 2002). However, a subsequent fall in fullness (returning to feelings of emptiness) occurs quicker after oral glucose than after isomalt; this effect is more marked after accounting for the full power of the study ($P < 0{\cdot}05$; G Livesey, unpublished results) and in association with the more stable blood

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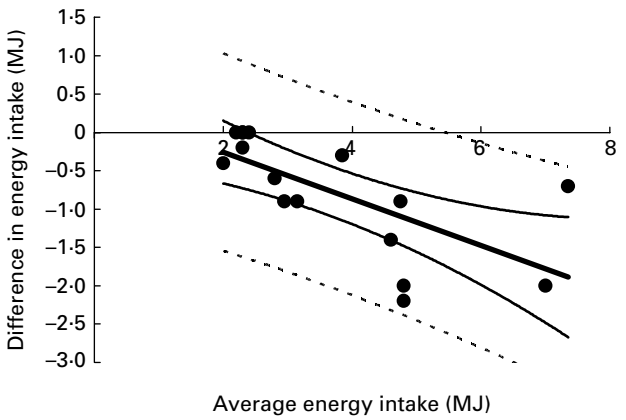

Fig. 4. Energy intake in human subjects on reducing the glycaemic load (GL) of a previous meal. The 'difference' and 'average' intakes for the two treatments (low-GL *v.* high-GL carbohydrate) within each study are calculated from information tabulated by Raben (2002) plus data from Agus *et al.* (2000) and Warren *et al.* (2003) less one outlying point (standardised residual deviation >3) from a study in which a GL difference was presumed rather than determined. Curves show an interim analysis fitted by equal-effects regression (y = 0·35 (SE 0·3) − 0·30 (SE 0·08); $P < 0·04$). (●), Study means; (▬▬), regression line; (——), 95% CI for regression line; (- - - -), 95% CI for population of study means.

glucose concentrations after oral isomalt. This finding is consistent with meal initiation being related to transient or dynamic declines in blood glucose following previous glycaemic loading (Melanson *et al*. 1999*a*,*b*).

In human subjects the subsequent intake of food is possibly diminished only for higher energy intakes, as seen when comparing results from different studies (Fig. 4). There appears to be little effect on cumulative energy intake up to about 2000 MJ, but at higher cumulative intakes during the day there appears to be a substantial and significant reduction in energy intake (slope $P < 0·05$) over the duration of these data (range 2 h–2 d). The data have not yet been assessed for possible publication bias, and direct measurements of intake in the long term are not currently available. The outcome is, however, consistent with the 1-year record (to date) on reduced body weight in *ad libitum*-fed human subjects (Fig. 2(b)) and similar life-long records in animals (Fig. 3). These issues deserve further study in human subjects to establish their reliability, durability and underlying mechanism(s).

Health and health markers

This area of investigation has gained considerable impetus with a publication (Liu *et al*. 2000) showing that the risk of CHD in a large cohort study (10 years follow up in 75 000 women) is related to dietary GL. This finding has widened the scope of relevance beyond previous observations on the development of T2DM (Salmeron *et al*. 1997*a*,*b*; Meyer *et al*. 2000), and has markedly raised awareness of the importance of GL because of the far greater prevalence of CHD. Of relevance in the present context is the observation that the relationship is stronger among individuals who are overweight or obese. Moreover, the association is stronger with GL than with GI, and is stronger still after adjustment for the intake of fats. Likewise, the relationship between fasting plasma triacylglycerol, another marker of CHD risk, and GL is stronger in individuals with higher BMI and stronger for GL than for GI in cross-sectional data (Liu *et al*. 2001). More recently, an inflammatory protein marker of CHD risk (high-sensitivity C-reactive protein) has also been found to be strongly related to GL. Again, the association is stronger with GL than with GI, and is stronger in individuals with higher BMI (Liu *et al*. 2002).

Low serum HDL-cholesterol is also a marker of CHD risk, but there appears to be conflicting evidence for an inverse relationship with GL or GI. An association is evident according to a cross-sectional investigation in both a sample of 6825 men and a sample of 7082 women in the National Health and Nutrition Examination Survey (1988–1994; Ford & Liu, 2001) and 280 women in cross-sectional data from the Nurses' Health Study (Liu *et al*. 2001). These data confirm earlier findings from small cross-sectional samples, both for men and for women sampled in the UK (Frost *et al*. 1999). Other epidemiological data have been reportedly unable to confirm this finding in small samples of 280 women (Ford & Liu, 2001) or 394 men (van Dam *et al*. 2000). However, preliminary examination of all these data together in an equal-effects model shows a relationship is evident that is of similar strength in men and women (G Livesey, unpublished results). Failure to confirm the finding in certain individual studies can be attributed to: (a) one quintile being deviant while other quintiles fit the general relationship well; (b) ranges of diet-induced glycaemia that are too narrow and low; (c) small sample sizes; (d) other reasons already noted in the literature by various authors commentating on the subject. The association with HDL-cholesterol is reported to be as strong with GL as with GI, and is evident at both lower and higher BMI (Ford & Liu, 2001; Liu *et al*. 2001). However, comparison of the highest quintiles with the lowest quintiles in these studies would suggest a possible 14–20% stronger association overall with GL than with GI. Moreover, a potentially stronger association with GL might be confounded by adjustments to equal intakes of protein and fat or carbohydrate in these studies.

Overweight and obese individuals are at increased risk of developing T2DM. This risk may be less amongst those individuals who consume diets of limited GL or GI. GL appears similar or slightly stronger than GI as a determinant of T2DM development in a study of female nurses (Salmeron *et al*. 1997*b*). A similar finding has been reported in a study of professional men (Salmeron *et al*. 1997*a*), while a weaker association has been found in a study that included younger women (Schulze *et al*. 2004). A weak association between T2DM development and dietary glycaemia has been observed in a further study (Meyer *et al*. 2000). A possible explanation for the finding that the stronger association is with GL, albeit provocative, is that the nurses were, on the whole, more likely to have followed nutritional advice to lower their fat intake by excessively elevating (high-glycaemic) carbohydrate intake. In general, better models are needed. A model that includes 'carbohydrate + GI + GL' may be more helpful,

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where the last term (GL) is an interactive term (carbohydrate × GI). This general model illustrates that if the range of GI is very small, as in a very recent study in which it is just 5 GI units (with respect to glucose; Schulze *et al*. 2004), GL alone tends to behave more like carbohydrate, so having a minimal effect, and the relationship with GI is open to leverage by uncontrolled (error causing) factors, which may, by chance, increase or decrease the apparent strength of any relationship with GI. However, despite difficulties in the interpretation of these studies, authors generally emphasise the importance of GL. The clearest information is evident at low cereal-fibre intake when risk associated with high GL is elevated 2·17 times across tertiles in men (Salmeron *et al*. 1997*a*) compared with 1·88 times for high-GI tertiles in women (Schulze *et al*. 2004) and in individuals with a family history of T2DM (relative risks of 2·04 *v*. 1·50 respectively; Schulze *et al*. 2004). GL and GI appear to have similar effects in those individuals with high BMI as in those with low BMI, although neither GL nor GI appears to be influential in the physically fit (Schulze *et al*. 2004).

When combining the previously described epidemiology on diabetes development with that on CHD development (Liu *et al*. 2000) it appears that all studies are consistent, and there is an increase in the risk of each condition whenever GL is >120 g/d (or per 8·4 MJ (2000 kcal) at the prevailing levels of physical activity in these populations). Further consideration of these data is warranted.

It now seems that the glycated Hb concentration is a risk factor for CHD, T2DM and all-cause mortality among both patient and non-patient groups; in addition to an increased risk from diabetic complications, especially retinopathy and perivascular disease (Stratton *et al*. 2000; Khaw *et al*. 2001). Risk increases across all glycated Hb concentrations, at least in men >45 years of age. Based on intervention studies that are not usually >3 months duration a reduction in glycated Hb (or fructosamine, a more-rapidly-responding marker of glycation) is achievable in a number of ways, as demonstrated in subjects with diabetes. For example, a reduction in glycated Hb has been achieved with inhibitors of carbohydrate digestion (increasing the unavailable carbohydrate as well as slowing digestion; Brooks *et al*. 1998), replacement of high-glycaemic-carbohydrate diets with low-glycaemic-carbohydrate diets (Brand-Miller *et al*. 2003) or with protein (Gannon *et al*. 2003) and with the polyol isomalt (Livesey, 2003). These effects seem to reflect a return towards normal rather than an effect of similar magnitude at all glycated protein concentrations (G Livesey, unpublished results). Once again it would appear that GL provides a more satisfactory explanation of these effects than GI.

Paradoxical as it may seem, reducing GL acutely by replacing high-glycaemic carbohydrate with fats (including monounsaturated fats) does not seem to reduce the glycated protein concentration (Harding *et al*. 2001; Anderson *et al*. 2004). A likely reason is that fats have an 'effective GL' operating indirectly over the longer term and numerically similar to that for high-glycaemic available carbohydrates. Possibilities that deserve further consideration include excessive demand for insulin secretion and changes in insulin-sensitive tissues.

Concluding remarks

The use of GL *v*. GI has been discussed. The most central and currently the most useful concept is GL, which can be determined directly, while indirect methods implicate measures of available carbohydrate that are still inherently subject to appreciable error, varied expression and unnecessarily limit application to certain foods. Unlike the current epidemiological data on health and health markers, the current interventional data do not readily allow an assessment of whether groups of individuals with high BMI *v*. low BMI differ in their response to low-GL carbohydrate *v*. high-GL carbohydrate. Nevertheless, the majority of diabetics are overweight and obese individuals are prone to T2DM. Until sufficient clinical data is available, therefore, it would be prudent to consider high-GL-carbohydrate diets as being not advisable for either overweight or obese individuals.

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