Glycemic response and health—a systematic review and meta-analysis: relations between dietary glycemic properties and health outcomes

Geoffrey Livesey, Richard Taylor, Toine Hulshof, and John Howlett

ABSTRACT

Background: Reduction of dietary glycemic response has been proposed as a means of reducing the risk of diabetes and coronary heart disease. The impact of glycemic response on markers of health remains to be elucidated.

Objective: We assessed the evidence relating the glycemic impact of foods to measures relevant for health maintenance and management of disease.

Design: This was a systematic review and synthesis of intervention evidence from literature reported on glycemic index and markers of health through the use of meta-analyses and meta-regression models.

Results: Data from 45 relevant publications were found to January 2005. Lower glycemic index (GI) diets reduced both fasting blood glucose and glycated proteins independently of variance in available and unavailable carbohydrate intakes. Elevated unavailable carbohydrate added to improvements in both blood glucose and glycated protein control. These effects were greater in persons with poor fasting blood glucose control. No effects were seen on fasting insulin <100 pmol/L; above this, study numbers were few but consistent with prevention of hyperinsulinemia in some but not all overweight persons. Insulin sensitivity according to a variety of measurement methods was improved by lower GI, higher unavailable carbohydrate interventions in persons with type 2 diabetes, in overweight and obese persons, and in all studies combined. Fasting triacylglycerol in addition to body weight reduction related more to glycemic load than to GI. Glycemic load reduction by >17 g glucose equivalents/d was associated with reduced body weight.

Conclusions: Consumption of reduced glycemic response diets are followed by favorable changes in the health markers examined. The case for the use of such diets looks compelling. Unavailable carbohydrate intake is equally important. Am J Clin Nutr 2008; 87(suppl):258S–68S.

KEY WORDS Carbohydrate, glycemic response, glycemic index, glycemic load, meta-analysis, fasting blood glucose, glycated proteins, fasting insulin, insulin sensitivity, fasting triacylglycerols

INTRODUCTION

Foods vary in their ability to provoke a postprandial glycemic response in humans. This response has been quantified in various ways, including the glycemic index (GI) (1), the relative GI (2), the glycemic load (GL) (3), and others such as the glycemic glucose equivalent (4) or the equivalent GL (5). For the present, information about GI and GL is available for a wide variety of foods (6), and such information has formed the basis of 45 relevant intervention studies in humans to ascertain whether foods with a low impact on blood glucose also have a high impact on disease risk reduction (7). Possibly central to all these approaches is GL, which may be indexed to carbohydrate or to food weight or to serving size for the purpose of describing the food and estimating cumulative intakes (8).

Although information from intervention studies has been reviewed previously (7, 9–12), none of those reviews focused on the contribution of GL versus GI and the role of unavailable carbohydrate in studies on reduced GI, or why GI appears not to show dose-dependent effects on health risk factors, issues that are addressed at present. Such information is critical to an understanding of whether interventions to reduce the glycemic impact of the diet might be useful either as a treatment modality or as a public health measure. It is already clear from epidemiologic studies in the United States and Europe that the intake of both unavailable and available carbohydrate of low GI or low GL each may have a role in prevention of metabolic disease. For example, type 2 diabetes (3, 13, 14), coronary heart disease (2), and health risk markers for both diabetes and heart disease (15, 16) each associate statistically with the glycemic impact of foods (GI or GL). Although epidemiology can provide ideas about possible public health strategy and treatment plans, interventional studies are essential to proving whether such ideas work in practice and to uncovering any unforeseen influences limiting utility of the approach.

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A previous article showed that studies that lower GI as a treatment plan may also reduce the intakes of available carbohydrate and metabolizable energy significantly, though without elevating fat intake (7). Low GI diets also may elevate the intake of unavailable carbohydrate and protein to variable extents (7). We therefore implement meta-regression as well as meta-analysis as one of our investigative tools to assess what dietary factors are important in affecting health risk markers.

From a user perspective, meta-analysis and meta-regression call for somewhat different approaches. The latter requires more data, but has the potential to assess the significance of covariates. The former aims for datasets that are homogenous, ie without variation in observations between different studies of the same ‘fixed’ effect (17, 18). However, meta-regression aims for a heterogeneous dataset and attempts to explain the heterogeneity (19, 20), which may otherwise appear to be a ‘random’ effect. Doing so in the present context can provide a broader understanding of the factors influencing health risk. This would seem especially important in nutrition in general where study outcomes can often vary appreciably from one study to another. The heterogeneous data set analyzed at present includes persons who are healthy, glucose intolerant, type 1 or 2 diabetic, at primary (due to family history) or secondary coronary heart disease risk, and hyperlipidemic. Among these subject groups were either normal weight or overweight or obese persons (7). In combining data from such varied healthy types it was convenient to consider health risk markers to represent a continuum from the healthy state to the diseased state, and this seems to represent the situation for both diabetes and coronary heart disease (21, 22). In addition we considered study outcomes by categories: by health type, by different types of food intake control and by different body weight bands; normal, overweight, and obese (7).

MATERIALS AND METHODS

The construction of a database comprising data extracted from 45 controlled dietary intervention trials on GI reported in the literature to January 2005 has been described previously (7). Information is given there also about the literature search, the inclusion and exclusion criteria, data extraction, and the calculation methods.

The database includes observations from 972 participants per treatment arm of all ages (study group mean ages 10 to 63 y) with both males (511) and females (461) represented. Participants were either normal weight (16 studies), overweight (18 studies) or obese (10 studies) or unclassified by weight (1 study). Similar numbers of participants took part per treatment arm (770 on the high and 793 on the low GI treatment). Study participants were either healthy, ie no diagnosis of disease was evident (13 studies) or had impaired glucose tolerance (2 studies, duration of impairment unknown) or had type 1 diabetes (7 studies, mean duration from diagnosis 3 to 16 y, one unknown duration) or had type 2 diabetes (17 studies, mean duration from diagnosis =0 to 12.5 y, 7 unknown duration) or were at risk of primary CHD (4 studies, duration unknown) or secondary CHD (1 study, duration unknown) or had hyperlipidemia (1 study combining Type II a, Type II b, and Type III; mean duration from diagnosis 4.7 y). Studies included participants on medication. Insulin dosage was reported in all 7 studies with persons with type 1 diabetes, 2 of 17 studies with persons with type 2 diabetes, and in one of one study with participants at risk of secondary CHD. In all but one study with persons with type 2 diabetes, subjects received non-insulin medication for glycemic control (hypoglycemic agents).

Categorization of studies according health type was based on what authors stated was the study group condition. The same studies were cross categorized also according to body weight as normal, overweight or obese, again according to what authors stated or according to body mass index (bands cut at BMI > 25 or > 30 kg/m²). Interventions were by diet, with intention to exchange the form of available carbohydrate (high versus low GI). All studies were free-living, ie no subjects were hospitalized, housed in metabolic wards or centers of human nutrition.

Biochemical risk factors extracted were fasting blood glucose, fasting insulin, glycated proteins (HbA₁c and fructosamine and these combined, glycated albumin and glycated protein), insulin sensitivity, retrospectively calculated insulin sensitivity by homeostatic model assessment (HOMA %S), calculated pancreatic B-cell function (HOMA %B), cholesterol (total, LDL and HDL) and fasting plasma triacylglycerols. Risk factors not reported on here were either a) complex (HOMA model) and so receives only brief comment or b) showed evidence of one or more factors confounding results of simple meta-analyses (total and fractions of cholesterol) or c) were too few to analyze separately (glycated albumin and glycated protein combined). At this time these data simply remain to be more fully assessed.

Body weight was the only constitutional risk factor extracted. Dietary risk or nutritional factors extracted were metabolizable energy, fat, available carbohydrate, unavailable carbohydrate, and protein intake, together with potential risk factors GI and the calculated GL. The last was calculated as GI multiplied by available carbohydrate intake and was expressed as g carbohydrate equivalents. Duration of treatment was extracted either as a continuous variable (weeks) or as a categorical variable by treatment duration < or ≥ 12 wk.

Data were subjected to random effects meta-analyses and meta-regressions using meta and metareg the latter using restricted maximum likelihood (REML) in Stata 9.2 SE (Stata Corp, TX) according to Cochrane guidelines (17). Studies are weighted by inverse variance. Analyses are reported as either random effects or when variation between studies was zero they are reported as fixed effects. Computation of the study effect and dependent SE were as described previously (7) for inputting as the mean effect (Ø) and the SEM effect (seØ) study-by-study (in STATA terminology). For comparison of treatments we use methods difference versus methods average (23). Discussion of this and other approaches can be found elsewhere together with developments in multivariate meta-analyses (20). While the behavior of univariate meta-regression allows valid inferences given valid datasets, the validity and behavior of bivariate meta-regression has only recently been investigated and recommended over multiple uses of univariate analyses (19). Bivariate meta-regression is reported to inflate heterogeneity without systematic bias in the coefficients; this tends to widen the CIs and provide conservative estimates of significant effects. It seems reasonable for the present to make a similar assumption about multivariate meta-regression models in general. We assume ‘measurement error’ is not a cause of bias. This appears reasonable when investigating relations with dietary variables that are highly heterogeneous, as in the present dataset (7). However, failure of this assumption would lead to under strength regression coefficients.
and conservative estimates of the statistical significance of results. Abbreviations used in the results are provided in the footnotes to Table 1.

RESULTS

Fasting blood glucose concentrations

Thirty-six studies reported fasting blood glucose concentrations in either venous plasma or capillary blood and achieved reductions in GI ranging from 4 to 32, with accompanying reductions in GL ranging from 6 to 134 g glucose equivalents. Study durations ranged from 2 to 26 wk.

Subjects were reported as normal healthy (8 studies), glucose intolerant (2 studies), type 1 diabetic (4 studies), type 2 diabetic (16 studies), type 1 and type 2 diabetic observations combined (1 study) and at risk of primary (4 studies) or secondary coronary heart disease (1 study). For analysis, fasting venous plasma glucose concentrations were converted to the equivalent capillary

<table>
<thead>
<tr>
<th>TABLE 1</th>
</tr>
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<tbody>
<tr>
<td>Difference in fasting glucose as a function of the average fasting glucose at the end of treatment with lower glycemic index (GI) or glycemic load (GL), variably higher unavailable carbohydrate diets</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Fall in fasting glucose</th>
<th>Mean slope</th>
<th>SE</th>
<th>P</th>
<th>k</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before adjustment</td>
<td>–0.3</td>
<td>0.12</td>
<td>0.026</td>
<td>18</td>
</tr>
<tr>
<td>After adjustment</td>
<td>–0.34</td>
<td>0.13</td>
<td>0.021</td>
<td>16</td>
</tr>
<tr>
<td>Δ Carbohydrate (g/d)</td>
<td>–0.33</td>
<td>0.12</td>
<td>0.027</td>
<td>16</td>
</tr>
<tr>
<td>Δ Energy (kJ/d)</td>
<td>–0.34</td>
<td>0.12</td>
<td>0.017</td>
<td>16</td>
</tr>
<tr>
<td>Δ GL (g eq/d)</td>
<td>–0.32</td>
<td>0.12</td>
<td>0.024</td>
<td>16</td>
</tr>
<tr>
<td>Δ GI (%glucose)</td>
<td>–0.30</td>
<td>0.12</td>
<td>0.029</td>
<td>16</td>
</tr>
<tr>
<td>Δ Protein (g/d)</td>
<td>–0.32</td>
<td>0.13</td>
<td>0.030</td>
<td>15</td>
</tr>
<tr>
<td>Δ Unavailable carbohydrate (g/d)</td>
<td>–0.26</td>
<td>0.14</td>
<td>0.085</td>
<td>15</td>
</tr>
</tbody>
</table>

1 Results for high minus low GI or GL diet treatments before and after adjustment for treatment differences in potential covariates. All study groups were at near maintenance and had fasting blood glucose > 5 mmol/L. FBG, fasting blood glucose; Δ, difference, here in treatment means; ×, bar indicating a mean or average, here the average of treatment means; Mean slope, refer to the regression coefficients, and SE slope, the corresponding Knapp & Hartung’s estimates of the SE; SE residual, residual SE (ie, the SE of the fitted values also known as the within-study SE); Tau, the between-study SE; P > |x|, the level of statistical significance of Tau based on the likelihood-ratio test of Tau² = 0; P > |x|, level of statistical significance based on the test by using Knapp & Hartung’s estimate of SE; k, number of studies; df, error degrees of freedom.

2 REML random effects model weighted by inverse variance (df = k − 3): ΔFBG (mmol/L) = constant + slope × FBG (mmol/L) + slope × covariate shown (units shown) ± Tau (mmol/L) ± SE residual (mmol/L). The univariate model (before adjustment) was the same as the bivariate model, except for constraining slope to zero and df = k − 2.

3 The univariate model before adjustment was heterogeneous, with a between-studies error (Tau) of 0.63 mmol/L and remained in the range of from 0.58 to 0.61 after invoking one of the possible covariates listed in the bivariate model. Tau was significant in all analyses (P > |x| < 0.001).

4 None of the covariates were statistically significant (P > |x| > 0.2), because of either an absence of effect or too narrow a range of values.

Blood glucose concentrations (fasting capillary blood glucose = – 0.61 + 0.94 x fasting venous plasma glucose (24)).

The totality of evidence on fasting blood glucose (Figure 1) includes intermediate observations made at timed intervals up to the end of the treatment period in addition to the end of treatment observations. The figure is plotted according to the convention for methods comparison (difference plotted against average). Visual inspection shows no overall treatment difference in fasting blood glucose concentration to be evident when the study population mean is approx. 5 mmol/L. When above 5 mmol/L (22 studies) the lower glycemic treatment outcome departed increasingly from that on the higher glycemic treatment, with the difference being greatest for the highest average of treatment means. After omitting the intermediate observations to obtain independent information, meta-regression revealed a significant relation (slope = −0.30 SE 0.10 Δmmol/L per mmol/L; P < |x| = 0.010, df 20, Tau 0.6 mmol/L). Further omission of observations so that all studies had fasting blood glucose > 5 mmol/L and all study participants were fed diets intended at energy maintenance resulted in 18 studies remaining for which meta-regression again indicates a significant relation (Figure 2; slope = −0.3 SE 0.12 Δmmol/L per mmol/L, P < |x| = 0.026, df 16, Tau 0.5 mmol/L).

It has been reported previously (7) that among these studies differences occur between treatments with respect to intakes of energy, protein, and available and unavailable carbohydrate, although not fat. When these dietary components, together with GI and GL, are used as covariates (Table 1), the regression slope remains essentially unaltered at around −0.3 Δmmol/L per mmol/L (range −0.26 to −0.34). Such similar slopes suggest that none of these dietary factors were sufficiently determinant, either uniquely by themselves or collinearly, to displace fasting blood glucose as an over-riding determinant of the effect size in simple meta-regressions; that is regressions not including interactive terms.

It was found that many interventions that intended to lower the GI of a diet also resulted in increased intakes of unavailable carbohydrates and varied intake of available carbohydrate causing usually a decreased GL. It is important to try to disentangle...
the effects of each of these. To understand the separate roles of reduced GL of foods and increased unavailable carbohydrates intake on fasting blood glucose, the interaction between these 2 variables and the severity (or impairment) of glycemic control were studied. Severity (S) is quantified here by excessive fasting blood glucose (S = FBG – 5 mmol/L). In this more complex model both interactions were significant (Table 2). Therefore GL clearly has an effect independently of the unavailable carbohydrate content of the diet. Likewise unavailable carbohydrates appear to act independently of GL. Both act to control fasting blood glucose as can be seen in Figure 3 (upper). This helps to explain a reported variability in the effectiveness of the reduced GI diets and illustrates that the GL is as effective as the unavailable carbohydrate in lowering fasting blood glucose. Of the 15 studies in Figure 3 upper, no more than 3 reached 12 wk treatment duration.

An assessment was made of whether, after accounting for unavailable carbohydrate intake, the variation remaining in fasting blood glucose reduction attributable to GL could be partitioned between change in GI and change in available carbohydrate intake. Changes in GI in the range from −4 to −32 in these studies were accompanied by a range for change in available carbohydrates intake from +53 g/d to −35 g/d with a low correlation between the 2 dietary measures (adjusted $r^2 = 0.02$); this allowed a potentially good distinction between them. The bivariate analysis of change in fasting blood glucose due to change in GL showed no significant association for available carbohydrate ($P > |k-h-t| = 0.54$) while a strong association was evident for GI ($P > |k-h-t| = 0.004$). Thus it appears that GL is better reduced by reduction in GI than by reduction in available carbohydrate.

Further, observations (Table 2) indicate that the size of the effects of GL or GI and unavailable carbohydrate is dependent on the persons consuming the diet, that is their level of blood glucose control (S, the severity of impairment); this is all important in enabling any understanding of these studies.

Maximum control of fasting blood glucose was achieved by elevation of unavailable carbohydrate intake together with a lowering of GI. Unavailable carbohydrate had stronger impact than GL on a per g weight basis but remained approximately equally important when taken together with the range of intakes (Figure 4 upper).

**Glycated proteins**

Twenty-eight studies reported on glycated protein concentrations. Measures include glycated albumin, glycated plasma protein, fructosamine, and HbA$_{1c}$. Subjects were categorized as

![FIGURE 2. Difference in fasting blood glucose after treatment versus the average fasting blood glucose concentration after treatment with lower glycemic, variably higher unavailable carbohydrate diets ($k = 18$, univariate model Table 1). Bubbles are weights by inverse variance and lines are the meta-regression line, its SE (—), and 95% CI (— —).](image-url)

**TABLE 2**

<table>
<thead>
<tr>
<th></th>
<th>$\Delta$Glycemic load or $\Delta$Glycemic index × severity interaction</th>
<th>$\Delta$Glycemic load or $\Delta$Glycemic index × severity interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$[S \cdot \Delta GL; U$ per (mmol/L · g/d)] or $[S \cdot \Delta GI; U$ per (mmol/L · %)]</td>
<td>$[S \cdot \Delta GL; U$ per (mmol/L · g/d)] or $[S \cdot \Delta GI; U$ per (mmol/L · %)]</td>
</tr>
<tr>
<td>$k$</td>
<td>Mean$_{slope}$</td>
<td>SE$_{slope}$</td>
</tr>
<tr>
<td>$\Delta$Fasting blood glucose (mmol/L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unavailable carbohydrate and glycemic load</td>
<td>15</td>
<td>$-0.013$</td>
</tr>
<tr>
<td>Unavailable carbohydrate and glycemic index</td>
<td>15</td>
<td>$-0.012$</td>
</tr>
<tr>
<td>$\Delta$Fructosamine (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unavailable carbohydrate and glycemic load</td>
<td>12</td>
<td>$-0.169$</td>
</tr>
<tr>
<td>Unavailable carbohydrate and glycemic index</td>
<td>12</td>
<td>$-0.136$</td>
</tr>
</tbody>
</table>

$^1$ All studies (food intake categories) combined. REML random effects regression weighted by inverse variance (df = $k - 2$): $\Delta$Fasting blood glucose (mmol/L) or $\Delta$Fructosamine (%) = no constant + slope $\beta_1 \times S \cdot \Delta$UC (mmol/L · g/d) + slope $\beta_2 \times S \cdot \Delta$GL (mmol/L · g/d) or + slope $\beta_3 \times S \cdot \Delta$UC (mmol/L · g/d) + slope $\beta_4 \times S \cdot \Delta$GI (mmol/L · %) ± Tau (mmol/L or %) ± SE$_{within}$ (mmol/L or %). The same model was used for $\Delta$fructosamine (% difference) in place of $\Delta$fasting blood glucose (mmol/L). The model was constrained to have no effect (no constant) at a fasting blood glucose concentration of 5 mmol/L for fasting blood glucose (see Figure 2) and 3.5 mmol/L for fructosamine concentration (see Figure 5) to facilitate convergence consistent with a consideration that little or no treatment effect is expected at or below this concentration. U, units for the analyte concentration (for change in glucose this was mmol/L, for change in fructosamine this was % of treatment average). Other abbreviations are as in Table 1.
healthy (2 studies), at risk of primary coronary heart disease (1 study), impaired glucose tolerance (1 study), type 1 diabetic (7 studies), type 2 diabetic (16 studies) and hyperlipidemic (1 study). Among these studies, some offered observations at intermediate time points providing a combined total of 38 effect estimates.

The totality of evidence shows treatment diets to lower the blood glycated protein concentrations (Figure 5). The effect is greater for some persons than others dependent on their level of glycemic control. This figure combines information on fructosamine and glycated hemoglobin, observations from the end of studies, and observations from intermediate time points. Choosing only the independent observations (discarding intermediate time points), statistical significance of this trend toward greater effect in persons with poor blood glucose control is achieved both

FIGURE 3. Upper: Implications of the effect of unavailable carbohydrate intake and glycemic load for fasting blood glucose concentrations. A REML meta-regression model (Equation 1) result was obtained interrelating the change (Δ) in fasting blood glucose to change in both unavailable carbohydrate intake (UC, g/d) and glycemic load [GL, g (glucose equivalents)/d] at the different levels of severity of diabetes (Equation 1). This was recast to assess the potential implications of unavailable carbohydrate intake and glycemic load on the fasting blood glucose values (Equation 2). The relative fasting blood glucose concentrations were estimated independently of severity S (Equation 3). Thus, estimates (Equation 2) were calculated for all 9 (a) combinations of GL and UC shown in the figure. All 9 estimates were expressed as a fraction of the central values at 15 g UC/d and 150 g (glucose equivalents)/d GL.

ΔFasting plasma glucose = S × ΔUC × β₁ + S × ΔGL × β₂  
Fasting plasma glucose = S × [UC × β₁ + GL × β₂]  
Relative fasting plasma glucose
= [(UC × β₁ + GL × β₂)UC=15, GL=150]/[(UC × β₁ + GL × β₂)UC=15, GL=150]  

FIGURE 4. Upper: Implications of the effect of unavailable carbohydrate intake and glycemic index for fasting blood glucose concentrations. Lower: Implications of the effect of unavailable carbohydrate intake and glycemic index for plasma fructosamine concentrations. In both the upper and lower figures, the observations and models are the same as in Figure 3, with the use of glycemic index in place of glycemic load, eq. glucose equivalents.

The totality of evidence shows treatment diets to lower the blood glycated protein concentrations (Figure 5). The effect is greater for some persons than others dependent on their level of glycemic control. This figure combines information on fructosamine and glycated hemoglobin, observations from the end of studies, and observations from intermediate time points. Choosing only the independent observations (discarding intermediate time points), statistical significance of this trend toward greater effect in persons with poor blood glucose control is achieved both

FIGURE 5. Difference in glycated protein after treatment (ΔT) as a percentage of the mean fasting blood glucose after treatment (MT) with lower glycemic index or glycemic load, higher unavailable carbohydrate diets. Bubble sizes are relative √/n weights for 28 studies and 10 repeats (totaling 38 bubbles). As the result of variation in measurement methods, the treatment average fasting blood glucose was used in place of average fasting glycated protein concentrations, and treatment difference is expressed as a percentage of the treatment average.
TABLE 3
Difference in glycated proteins as a function of average fasting blood glucose at the end of the treatment with lower glycemic index or glycemic load, variably higher unavailable carbohydrate diets.

<table>
<thead>
<tr>
<th>Measurement</th>
<th>ΔFructosamine (%)</th>
<th>ΔHbA1c (%)</th>
<th>Combined</th>
<th>Adjusted for half-lives</th>
<th>ΔFructosamine (%)</th>
<th>ΔHbA1c (%)</th>
<th>Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fall in glycated protein (% per mmol/L)</td>
<td>Mean_{slope}</td>
<td>SE_{slope}</td>
<td>P &gt;</td>
<td>kh-t</td>
<td></td>
<td>Mean_{slope}</td>
<td>SE_{slope}</td>
</tr>
<tr>
<td>Unadjusted</td>
<td>-2.03</td>
<td>0.37</td>
<td>0.001</td>
<td>12</td>
<td>-2.85</td>
<td>0.56</td>
<td>0.001</td>
</tr>
<tr>
<td>Adjusted for half-lives</td>
<td>-1.43</td>
<td>0.23</td>
<td>0.001</td>
<td>24</td>
<td>-1.55</td>
<td>0.94</td>
<td>0.12</td>
</tr>
<tr>
<td>Combined</td>
<td>-2.21</td>
<td>0.44</td>
<td>0.001</td>
<td>24</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1 All studies (food intake categories) combined. REML random effects model weighted by inverse variance (df = k - 1); ΔGlycated protein (%) = noconstant + slope × [FBG - 3.5] (mmol/L) ± Tau (mmol/L) ± SE_{residual} (mmol/L). The model was constrained to have no effect (noconstant) at a fasting blood glucose concentration of 3.5 mmol/L to facilitate convergence consistent with a consideration that little or no treatment effect is expected at or below this concentration (see Figure 5). Tau minimized at a fasting glucose concentration of 3.5 mmol/L when the SE between studies was 45% of the prevailing glycated protein concentration (P > |X| = 0.001). HbA1c, glycated hemoglobin. Other abbreviations are as in Table 1.

for the 2 glycated protein types combined and for fructosamine alone; for HbA1c alone, the effect is more probable than not (Table 3). The effect appears greater after adjustment for the half-life of fructosamine (2.5 wk) and HbA1c (4.5 wk). This is because many of the studies are shorter in duration than the 3 half-lives necessary to avoid dilution of effect by the subjects pretreatment diets (ie <12 wk for HbA1c).

Variability in the effect of the lower GI/GL higher unavailable carbohydrate diets on fructosamine, as with fasting blood glucose, depended on the extent to which both the GI (and so GL) and the unavailable carbohydrate intake varied (Table 2, Figure 4).

Again attempts were made to assess whether after accounting for unavailable carbohydrate intake, the remaining variation attributable to change in GL could be partitioned between GI and available carbohydrate intake. For these studies, the change in GI was in the range from -5 to -31 while the range of change in available carbohydrates intakes (g/d) was from +43 to -40. Although correlation between the 2 dietary measures was high (r²-adjusted, 0.78) bivariate analysis resolved that any effect of available carbohydrate intake was non-significant (P < |kh-t| = 0.54) while GI has significant effect (P < |kh-t| >0.03), a result consistent with observations on fasting blood glucose. Hence variation in fructosamine concentrations is contributed to in the greater part by variations in unavailable carbohydrate intake and GI (Figure 3 and 4 lower).

Altogether, the observations made imply optimum reduction in fasting blood glucose and fructosamine occur with intakes of unavailable carbohydrate at or above 25g/d (Figure 3 and 4), GL at or below 100g (glucose equivalents) per d (Figure 3) or GI < 45 (Figure 4). Of the 15 studies in Figure 3 and 4 on fasting blood glucose and the 12 studies in Figure 3 and 4 concerning fructosamine, no more than 3 reached 12 wk treatment duration.

Fasting insulin

Eighteen relevant studies reported on fasting insulin concentrations. No treatment effects or meta-regression trends were observed for concentrations < 100 pmol/L in the totality of evidence (Figure 6) or in end of study results whether for all studies combined or by health type or body weight band (Table 4). Fasting insulin concentrations are difficult to interpret without reference to corresponding fasting blood glucose concentrations (25) and so the absence of change in insulin concentration does not necessarily mean an absence of effect on insulin production or effectiveness. Treatment effects on the insulin concentration may depend on hyperinsulinemia > 100 pmol/L (Figure 6, Table 4) which developed on the high GI/GL diets in a small number of studies in some overweight or obese persons but not all.

TABLE 4
Summary of fixed and random effects meta-analyses for differences in fasting insulin on treatment with lower glycemic, variably higher unavailable carbohydrate diets.

| Studies combined | Combined effect Δinsulin (pmol/L) | \( \bar{x} \) | SE | P > |z| | k |
|------------------|----------------------------------|---------|----|----|----|-----|
| All with insulin < 100 pmol/L | 2.7 | 3 | 0.32 | 12 |
| All with insulin > 100 pmol/L | -12 | 18 | 0.49 | 6 |
| All nondiabetes with insulin > 100 pmol/L | -73 | 23 | 0.001 | 2 |
| All type 2 diabetes | 5.9 | 6.8 | 0.38 | 5 |
| All overweight or obese nondiabetes with insulin < 100 pmol/L | 4.6 | 3.9 | 0.24 | 5 |
| All overweight or obese nondiabetes with insulin > 100 pmol/L | -73 | 23 | 0.001 | 2 |

1 All meta-analyses converged on fixed effects except for insulin > 100 pmol/L, which was marginally heterogeneous (Q-test P > |X| > 0.40). k, number of studies.

2 Below the minimum of 3 studies normally required for meta-analysis.
Insulin sensitivity

Eighteen relevant studies either reported on insulin sensitivity using a range of different methods, or provided postprandial information from which this could be assessed. Among these studies, observations were from healthy subjects (5 studies), glucose intolerant subjects (2 studies), persons with type 1 diabetes (1 study), persons with type 2 diabetes (5 studies), and subjects at risk of primary or secondary coronary heart disease (5 studies). The methods used included the euglycemic hyperinsulinemic clamp technique, the insulin tolerance test, the frequent sampling intravenous glucose tolerance test, erythrocyte insulin binding, and the inverse postprandial homeostatic model assessment method (inverse HOMA PP). Some studies reported assessments using more than one method. Some provided additional information from which the inverse HOMA PP was calculable and others describe the sensitivity to insulin of glucose consumption by human adipocytes in vitro. Fixed and random effects meta-analyses for differences in insulin sensitivity achieved by intervention expressed as a percentage of average insulin sensitivity are summarized by health type, by body weight band, by method of assessment, and by study duration (Table 5). For all 18 studies combined, the lower glycemic, variably higher unavailable carbohydrate intervention results in a 20% improvement in insulin sensitivity (P > |z| = 0.004).

By subjects’ health type, improved insulin sensitivity was statistically significant for 12 studies of nondiabetics combined and for 5 studies on persons with type 2 diabetes combined. Results for other health types were consistently increased although did not reach statistical significance.

By body weight band, statistically significant increases in insulin sensitivity are apparent for overweight subjects combined (11 studies), obese subjects combined (3 studies) and both these groups combined (14 studies). The mean increase for all normal weight subjects combined (4 studies) suggests a potentially sensitive response but it does not achieve statistical significance.

All methods of assessing insulin sensitivity yield combined means that are positive toward improved sensitivity, and statistically significant in some though not in others (Table 5). Comparison between methods is hampered by the occurrence of heterogeneity and the small number of studies. Most observations were available for HOMA PP (8 studies) the combined mean for which indicates a 30% improvement in insulin sensitivity of glucose disposal in the postprandial state.

For all studies and methods combined (Table 5) the mean improvement in studies of < and ≥ 12 wk treatment duration was similar at 20% and 16% respectively for a total of 14 and 4 studies respectively, and with similar 95% CIs (−0.35 to 35% each). The larger number of studies in the short term indicate a significant effect while over the longer term the effect appears more probal than not.

Fasting plasma triacylglycerols

Thirty-two studies reported on fasting plasma triacylglycerol concentrations. The observations were for healthy subjects (7 studies), persons with type 1 diabetes (4 studies), persons with type 2 diabetes (13 studies), subjects at risk of primary CHD (4 studies), glucose intolerant subjects (1 study), and hyperlipidemic groups (1 study with 4 types). Six of the studies provide repeated observations at various time points. The total evidence included 45 effect estimates (Figure 7). There was no clear evidence for a difference in fasting triacylglycerols following treatment with the lower GI/GL intervention, although triacylglycerols concentrations were reduced among groups with the highest concentrations.

Meta-regression was used to search for an explanatory factor confounding a possible effect of GL, examining treatment differences in the intake of protein, energy, available and unavailable carbohydrate, fat and GL as covariates in bivariate meta-regression (Table 6). Statistically significant effects lowering
fasting triacylglycerols were evident for lower GL (dependent on GI) and higher fat intake (independent of GI).

After adjustment for variation in fat intake the effect of GL was significant \( P < 0.014 \) among the 30 studies that informed about both variables (fat and GL). This effect of GL was significant in all studies combined and in all studies with subjects in the normal range of body weight (Figure 8). Each health type (healthy, type 1 and 2 diabetic and CHD risk) and body weight band (normal, overweight, obese) contributed to varying extents to the statistical significance found for all studies combined, although each category alone was without statistically significant effect. Over all a 10% fall in fasting triacylglycerols requires achievement of a drop in GL by 30 to 100 g eq./d for those categories showing large or significant effects (Figure 8).

Body weight

Twenty-three relevant studies reported on body weight and change from high to low GI diets; of these 19 informed about GI. Among these studies, observations were on healthy subjects (4 studies), glucose intolerant subjects (1 study), persons with type 1 diabetes (1 study), persons with type 2 diabetes (9 studies), and

subjects at risk of primary or secondary coronary heart disease (4 studies).

Meta-regression indicates body weight to fall with reduction in GL and vice versa (Table 7). The trend was statistically significant for all studies combined and occurred in 2 of the 3 food intake control categories: ad libitum and limited controlled intake but not in the controlled food intake category. Combining the ad libitum and limited controlled food intake categories, reductions in body weight occur when GL is reduced by at least 17 g eq./d (intercept on x-axis for y = 0) and most consistently when the reduction is by 42 g. eq./d (95% CI) (Figure 9).

Among a number of dietary variables, differences in body weight associates univariately most closely with treatment differences in GL, though body weight differences also associate

TABLE 6

| Covariate | Units for covariate effect | Mean \( \text{slope}_1 \) | SE | \( P > |\text{kh-t}| \) | \( k \) |
|-----------|---------------------------|----------------|---|----------------|---|
| \( \Delta \) Protein (g/d) | (% per g/d) | -0.19 | 0.36 | 0.61 | 29 |
| \( \Delta \) Energy (kJ/d) | (% per kJ/d) | -0.002 | 0.007 | 0.87 | 30 |
| \( \Delta \) Unavailable carbohydrate (g/d) | (% per g/d) | -0.1 | 0.48 | 0.84 | 30 |
| \( \Delta \) Available carbohydrate (g/d) | (% per g/d) | 0.21 | 0.13 | 0.13 | 30 |
| \( \Delta \) Fat (g/d) | (% per g/d) | -1.08 | 0.43 | 0.019 | 30 |
| \( \Delta \) Glycemic load (g eq/d) | (% per g eq/d) | 0.34 | 0.10 | 0.003 | 30 |

1 REML random effects model weighted by inverse variance (df = \( k - 3 \)): \( \Delta \text{FTG} \) (% treatment average) = constant + \( \text{slope}_1 \times \text{covariate} \) (units shown) + \( \text{slope}_2 \times \text{treatment average FTG (mmol/L)} \) + Tau (% treatment average FTG) \( \pm \text{SE}_{\text{within}} \) (% treatment average FTG). Between-studies errors (Tau) were in the range of from 16% to 20% of the treatment average triacylglycerol (TG) concentration; all were significant \( P > |X| < 0.001 \). Other abbreviations are as in Table 1.
with treatment differences in available carbohydrate intake, GI and metabolizable energy intake (Table 8).

**DISCUSSION**

Low glycemic response diets are proposed as a means to favorably influence physiologic parameters implicated as markers for conditions including overweight and obesity, diabetes mellitus and risk of coronary heart disease. The present meta-analyses provide evidence that supports the view that intervention to reduce the diets glycemic impact will favorably affect several health risk markers.

For individuals with fasting blood glucose concentrations in excess of 5 mmol/L, there is evidence that fasting blood glucose is reduced by the consumption of lower GI or GL. Higher unavailable carbohydrate has an effect that is additive to that of lower GI (and resulting GL), ie both together have optimum effect. Further, the evidence indicates that the effect of consuming lower GI and higher UC diets is greater in absolute units in persons with poorer control of blood glucose, including persons with both type 1 and type 2 diabetes.

Similarly, for individuals with fasting blood glucose concentrations in excess of 5 mmol/L, there is evidence that both lower GI (and so lower GL) and higher UC in diets reduce the levels of glycated proteins. The evidence is stronger for fructosamine than for glycated hemoglobin. Again, the size of the effect is greater in persons with poorer control over blood glucose.

Although the data suggest that the consumption of lower GI/GL, higher unavailable carbohydrate diets lead to a reduction in fasting insulin concentrations in overweight or obese individuals who had fasting concentrations > 100 pmol/L, the evidence is weak due to few studies. In individuals with fasting insulin levels < 100 pmol/L, meta-analysis provides evidence of no significant effect.

Overall, this review provides evidence that insulin sensitivity is improved by consumption of lower GI/GL, higher unavailable carbohydrate diets. Although the increase is evident in all body weight bands combined, and in nondiabetics, the increase is not shown to be statistically significant in subjects in the normal body weight range.

While a simple meta-analysis of interventions with low GI/GL, variably higher unavailable carbohydrate diets did not provide a combined mean effect on fasting triacylglycerol concentrations, a more sophisticated analysis suggests an apparent absence of effect is due to a confounding factor. After adjustment for fat intake unrelated to GI or load (7), the evidence shows reductions in GI to reduce fasting triacylglycerols.

Overall, all studies relevant for the purpose taken together, it is evident that intervention with low GI/GL, high unavailable carbohydrate diets do associate significantly with reductions in body weight. Such evidence is consistent with evidence on reductions in food energy intake (7). The present analysis suggests a minimal reduction in GL or index is necessary for this effect to occur (Figure 9 and Table 8 in ref. 7). This could arise either because a threshold needs to be surpassed to achieve an effect or

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**TABLE 7**

<table>
<thead>
<tr>
<th>Food intake category</th>
<th>Combined effect (g/wk per g eq/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controlled intake</td>
<td>Mean$_{\text{slope1}}$ 1.7, SE 0.7, P &gt;</td>
</tr>
<tr>
<td>Limited controlled intake</td>
<td>1.9, 0.9, 0.052, 14$^2$</td>
</tr>
<tr>
<td>Ad libitum intake</td>
<td>2.8, 1.3, 0.11, 5$^3$</td>
</tr>
<tr>
<td>Ad libitum + limited controlled intakes</td>
<td>2.1, 0.7, 0.011, 19$^3$</td>
</tr>
<tr>
<td>All categories combined</td>
<td>1.7, 0.7, 0.017, 31$^3$</td>
</tr>
</tbody>
</table>

$^1$ REML random effects model weighted by inverse variance (df = k − 2); $\Delta$Body weight (g/wk) = constant + slope$_{\text{within studies}}$ $\times$ $\Delta$ glycemic load (g eq/d) + Tau (g/wk) ± SE$_{\text{within studies}}$ (g/wk). Abbreviations are as in Table 1.

$^2$ The model yielded fixed effects results because the between-studies error was zero.

$^3$ The between-studies error (Tau) ranged from 52 to 71 g/wk.

**TABLE 8**

<table>
<thead>
<tr>
<th>Dietary attribute (units)</th>
<th>Combined effect (g/wk per unit)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycemic load (g eq/d)</td>
<td>Mean$_{\text{slope1}}$ 2.1, SE 0.7, P &gt;</td>
</tr>
<tr>
<td>Available carbohydrate (g/d)</td>
<td>2.4, 1.0, 0.04, 20</td>
</tr>
<tr>
<td>Glycemic index (% glucose)</td>
<td>6.9, 3.2, 0.05, 19</td>
</tr>
<tr>
<td>Metabolizable energy (kJ/d)</td>
<td>0.8, 0.4, 0.05, 20</td>
</tr>
<tr>
<td>Protein (g/d)</td>
<td>4.3, 4.4, 0.36, 20</td>
</tr>
</tbody>
</table>

$^1$ All studies were combined from the ad libitum and limited controlled food intake categories (ie, studies with controlled food intake were excluded). REML random effects model weighted by inverse variance (df = k − 2); $\Delta$Body weight (g/wk) = constant + slope$_{\text{within studies}}$ $\times$ $\Delta$ dietary attribute (units shown) ± Tau (g/wk) ± SE$_{\text{within studies}}$ (g/wk). Abbreviations are as in Table 1. The between-studies error (Tau) ranged from 71 to 110 g/wk.

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**FIGURE 9.** Difference in the average rate of change in body weight during treatment as a function of the difference in glycemic load during the treatment with low glycemic, variably higher unavailable carbohydrate diets. Data are combined from the ad libitum and limited controlled food intake groups. Lines are the regression coefficient and 95% CIs. Labels are first author and year of publication. eq. glucose equivalents. (For citations and table of study characteristics, see reference 7.)
because dietary advice is imprecisely implemented by the researchers, health professionals, and consumers involved.

Although the evidence generally supports the view that intervention with a low GI/GL and higher unavailable carbohydrate diet is associated with favorable changes in a number of health risk markers relevant to persons who are overweight, obese, diabetic or at risk of coronary heart disease, the evidence also indicates for some markers that not all subjects respond equally. For reductions in fasting blood glucose concentrations and glycated proteins, there is evidence that the effects are greatest among those with poorest glycemic control. For reduction in fasting blood glucose, the threshold for this effect is at about 5 mmol/L. For glycated proteins the threshold is at about 3.5 glucose mmol/L. Unpublished meta-analysis of the effect of the low GI sugar fructose indicates a threshold of effect on glycated hemoglobin at about 4% HbA1c (Livesey and Taylor, unpublished observations, 2007). Hence absence of effect in those with good glycemic control is not evident. Also, when fasting glucose is low (<5 mmol/L) and study precision is accounted for, then below median normal fasting blood glucose is elevated to a small but statistically significant extent by such diets (in which case the ‘threshold’ mentioned above is a pivot point). The evidence for a small rise in fasting glucose below 5mmol/L comes with evidence of publication bias consistent with hesitance to report such normalization. While the present data taken together with influence on insulin sensitivity points toward improved control among non-diabetics (in addition to persons with diabetes), a role in disease prevention remains to be established.

The studies reviewed had the intention to treat by reducing the GI of available carbohydrate ingested. Compliant treatments show variable elevations in unavailable carbohydrate and protein intake and reductions in available carbohydrate, metabolizable energy, and GL when food intake was not firmly controlled (7). Even when intake was controlled the reductions in GI were accompanied by significant reductions in available carbohydrate intake and so in GL (7). However, among the health markers examined 3 factors were clearly important, glycemic index, available carbohydrate intake and unavailable carbohydrate intake. Altogether, improvement in the control of health markers cannot be said to be clearly due to GI alone.

Overall, considering all the markers of health examined here together, it is difficult to establish whether GI is stronger than GL, in part due to their co-linearity (7) and in part because some markers appear affected by available carbohydrate intake while others are not. While there is no affirmative evidence that variation in available carbohydrate intake (± 50g/d) influences fasting blood glucose or glycated proteins in these studies, there is evidence that reductions in available carbohydrate intake do accompany or play a role alongside GI in the beneficial effects of lower GL on fasting triacylglycerols (herein), body weight (herein) and food intake (7). On the other hand, it must also be considered that limiting harm due to glycaemic load by attempts to lower available carbohydrate intake will risk elevating harm from higher total or saturated fat intake. Benefits of reduction in available carbohydrate intake would be expected only in a context of no increase in total or saturated fat intake. It is evident in the studies reviewed here that lower available carbohydrate intake following marked reductions in glycaemic index were not accompanied by elevation in fat intake (7). In this context, the balance favors reduced harm.

The meta-analyses confirm that GI or load has a significantly stronger relation with glycaemic control than does available carbohydrate in the present context in which change in fat intake is minimal. Attaining an optimum diet for health therefore requires consideration of glycaemic impact of foods eaten in preference to consideration of carbohydrate content alone, each in the context of a balanced diet meeting nutrient requirements. The extent to which reduction in GL using ingredient carbohydrates has similar effects to those in the studies reviewed requires to be more fully evaluated. Fructose appears at least equally effective for HbA1c control (Livesey and Taylor, unpublished observations, 2007) and added unavailable carbohydrate can be effective in glycaemic control (8, 26, 27).

The evidence shows also that, independently of increasing unavailable carbohydrate intake, reductions in GI (and so GL) do improve glycaemic control. For optimal control over fasting blood glucose concentrations in persons with diabetes, the evidence points toward the need for foods that are of low impact on glycaemia (independently of fat intake) and foods that are high in unavailable carbohydrate. Diets that achieve one without the other would be suboptimal for diabetes control.

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The contributions of the authors were as follows—GL and RT: data collection; GI: analysis; JH and GI: writing; and TH: comment. GL and RT had no financial or personal conflicts of interest. 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. TH works for Kellogg.

REFERENCES