High-carbohydrate–low-glycaemic index dietary advice improves glucose disposition index in subjects with impaired glucose tolerance

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Controversy exists about the optimal amount and source of dietary carbohydrate for managing insulin resistance. Therefore, we compared the effects on insulin sensitivity ($S_I$), pancreatic responsivity ($AIR_{glu}$) and glucose disposition index ($DI = S_I \times AIR_{glu}$) of dietary advice aimed at reducing the amount or altering the source of dietary carbohydrate in subjects with impaired glucose tolerance (IGT). Subjects were randomized to high-carbohydrate–high-glycaemic index (GI) (high-GI, $n = 11$), high-carbohydrate–low-GI (low-GI, $n = 13$), or low-carbohydrate–high-monounsaturated fat (MUFA, $n = 11$) dietary advice, with $S_I$, $AIR_{glu}$ and $DI$ measured using a frequently sampled, intravenous glucose tolerance test before and after 4 months treatment. Carbohydrate and fat intakes and diet GI, respectively, were: high-GI, 53 %, 28 %, 83; low-GI, 55 %, 25 %, 76; MUFA, 47 %, 35 %, 82. Weight changes on each diet differed significantly from each other: high-GI, $20.49 \text{ kg (SEM 0.29 kg)}$; low-GI, $20.19 \text{ kg (SEM 0.40 kg)}$; MUFA +0.27 (SEM 0.45) kg. Blood lipids did not change, but glycated haemoglobin increased significantly on MUFA, 0.02 (SEM 0.11) %, relative to low-GI, $20.19 \text{ (SEM 0.08) %}$, and high-GI, $20.13 \text{ (SEM 0.14) %}$. Diastolic blood pressure fell by 8 mmHg on low-GI relative to MUFA ($P = 0.038$). Although $S_I$ and $AIR_{glu}$ did not change significantly, $DI$, a measure of the ability of $\beta$-cells to overcome insulin resistance by increasing insulin secretion, increased on low-GI by $20.50 \%$ ($P = 0.02$). After adjusting for baseline values, the increase in $DI$ on low-GI, 0.17 (SEM 0.07), was significantly greater than those on MUFA, $-0.09 \text{ (SEM 0.08)}$ and high-GI, $-0.03 \text{ (SEM 0.02)}$ ($P = 0.019$). Thus, the long-term effects of altering the source of dietary carbohydrate differ from those of altering the amount. High-carbohydrate–low-GI dietary advice improved $\beta$-cell function in subjects with IGT, and may, therefore, be useful in the management of IGT.

Dietary carbohydrates: Insulin sensitivity: Insulin secretion: Clinical trial

Over the past 20–25 years, high-carbohydrate, low-fat diets have been recommended for the general public (US Department of Agriculture, 1990; Food and Agricultural Organization of the United Nations, 1998). This advice is challenged by recent data showing that, compared with diets high in monounsaturated fat, high-carbohydrate diets raise plasma glucose, insulin and triacylglycerol and reduce HDL-cholesterol (Garg et al. 1994; Jeppesen et al. 1997), factors associated with atherosclerosis (Stout, 1990) and CHD (Balkau et al. 1998; Gordon & Rifkind, 1989; Hokanson & Austin, 1996). Furthermore, a high-carbohydrate diet raised plasma insulin to the greatest extent in people with insulin resistance (Jeppesen et al. 1997), which itself is associated with increased risk of obesity, cardiovascular disease, diabetes, and hypertension (Reaven, 1995). Thus it has been suggested that, since high-carbohydrate diets exacerbate the metabolic abnormalities of insulin resistance, they are deleterious for treating insulin resistance (Reaven, 1997).

However, not only are there few data on the effect of high-carbohydrate v. high-monounsaturated fat diets in insulin-resistant, non-diabetic subjects, but also few studies comparing the effects of low- and high-carbohydrate diets have taken into account the source of dietary carbohydrate.

Abbreviations: $AIR_{glu}$, pancreatic responsivity; $DI$, glucose disposition index; FSIGTT, frequently sampled intravenous glucose tolerance test; FSD, fractional standard deviation; GI, glycaemic index; $HbA_1c$, glycated haemoglobin; high-GI, high-carbohydrate–high glycaemic index diet; IGT, impaired glucose tolerance; low-GI, high-carbohydrate–low-glycaemic index diet; MUFA, low-carbohydrate–high monounsaturated fat diet; NEFA, non-esterified fatty acids; $S_I$, insulin sensitivity.

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Different carbohydrate foods are digested \textit{in vitro} at different rates (Jenkins et al. 1982), which, in turn, are directly related to the blood glucose and insulin responses they elicit (Wolever et al. 1988). The glycaemic responses of foods are classified using the glycaemic index (GI) (Wolever et al. 1991). The incorporation of low-GI foods into mixed meals reduces glucose and insulin responses in normal (Chew et al. 1988) and diabetic subjects (Indar-Brown et al. 1992). Also, low-GI and high carbohydrate meals reduce postprandial non-esterified fatty acid (NEFA) concentrations (Wolever et al. 1995), which, in turn, may improve insulin secretion (Zhou & Grill, 1994; Carpentier et al. 1999) and insulin action (Boden et al. 1994). Since the pathogenesis of type 2 diabetes involves defects in insulin action and insulin secretion (Ferrannini, 1998; Gerich, 1998), consideration of both insulin secretion and insulin sensitivity is important for those at risk of type 2 diabetes.

Since there is controversy about the optimal source and amount of carbohydrate for the management of insulin resistance, we compared the effects of altering the source of dietary carbohydrate with those of altering the amount of carbohydrate on insulin secretion and insulin sensitivity in subjects with impaired glucose tolerance (IGT). Reducing diet GI and reducing carbohydrate intake can have similar acute effects on reducing postprandial glucose and insulin responses. However, we hypothesized that these dietary manoeuvres would have different effects on insulin sensitivity and secretion in subjects with IGT.

**Methods**

A total of 257 subjects with at least one risk factor for diabetes (obesity, family history of diabetes, previous gestational diabetes, previous high blood glucose or triacylglycerol) were screened with a 75 g oral glucose tolerance test. Male and non-pregnant females with IGT, aged 30–65 years, with BMI $< 40$ kg/m$^2$ and serum triacylglycerol $< 10$ mmol/l were eligible. Thiadze diets were used by one MUFA and one high-GI subject and a beta-blocker by one low-GI subject at stable doses throughout the study. IGT was defined as fasting plasma glucose $< 7-8$ mmol/l and plasma glucose 2 h after 75 g oral glucose $\approx 7-8$ mmol/l and $< 11-1$ mmol/l (World Health Organization, 1980). Diagnostic criteria for diabetes changed after recruitment started (American Diabetes Association, 1997). Of the forty-four subjects identified as having IGT, thirty-seven (84%) had normal fasting plasma glucose (<6-1 mmol/l), six had impaired fasting glucose (6-1–6-9 mmol/l) and one, with fasting plasma glucose of 7-0 mmol/l, would now be considered to have diabetes.

After baseline data were collected, subjects were randomized to one of three diets for 4 months: high-carbohydrate–high-GI (high-GI), high-carbohydrate–low-GI (low-GI), or low-carbohydrate–high-MUFA (MUFA). During the baseline period two 3-d food records were used as a basis for individualized dietary advice. Diets were prescribed on an \textit{ad-libitum} basis. The aim was for the diets to be weight-maintaining, with the high-carbohydrate diets containing 55% of energy from carbohydrate and 30% from fat, and the MUFA diet 45% carbohydrate and 40% fat of which half was monounsaturated fat. Subjects on the high- or low-GI diets, respectively, were asked to have at least one serving of a high- or low-GI food at each meal. Lists of high- or low-GI foods were provided to subjects, along with specific food products to be used in the diet. Examples of high-GI foods provided included breakfast cereal, polished rice, instant potato and instant soups. Low-GI foods included breakfast cereal, bread, pasta, barley, parboiled rice, legumes and instant soups. Subjects on the MUFA diet were given supplements of olive oil and margarine made from non-hydrogenated rape-seed oil. Subjects were seen monthly for fasting blood samples, weight measurement, consultation with the dietitian and to hand in 3-d diet records and pick up study foods.

Insulin sensitivity ($S_I$), glucose effectiveness, pancreatic responsiveness (calculated as the area under the insulin response curve for 10 min after intravenous glucose; $AIR_{glu}$) and glucose disposition index (DI = $S_I \times AIR_{glu}$) were assessed by the frequently sampled intravenous glucose tolerance test (FSIGTT) (Finegood et al. 1990) at baseline and 4 months. After fasting blood samples at $-20$, $-10$ and $-5$ min, 50% glucose solution (25·1 ml/m$^2$ of body surface area) was rapidly injected at time 0 min and further blood samples taken at 2, 3, 4, 6, 8, 10, 12, 14, 16 and 19 min. At 20 min, insulin (1·6 U/m$^2$) was injected and blood samples obtained at 22, 23, 24, 25, 27, 30, 40, 50, 60, 70, 80, 100, 120, 140, 160, 180, 200, 220 and 240 min. Plasma glucose and insulin results were analysed using the MINMOD computer program (Pacini & Bergman, 1986).

Fasting total cholesterol and triacylglycerol were measured using a Vitros Analyser 950 (Johnson & Johnson Clinical Diagnostics, Rochester, NY) with HDL-cholesterol measured after precipitation of other lipoproteins with dextran sulfate and magnesium chloride. LDL-cholesterol was calculated as total cholesterol – (HDL + triacylglycerols/2) (only for triacylglycerol $< 4·51$ mmol/l). Glycated haemoglobin (HbA$_{1c}$) was measured by Diamat HPLC (Bio-Rad Laboratories (Canada) Ltd., Mississauga, Ontario, Canada). Fasting lipids and HbA$_{1c}$ were measured at monthly intervals. Fasting plasma NEFA were measured at baseline and 4 months using a commercial kit (NEFA C, ACS-ACOD Method; WAKO Chemicals USA, Richmond, VA).

Of forty-four eligible subjects, seven declined, and thirty-seven were randomized by coin toss, with stratification for age, gender and BMI, to receive one of the three test diets. Two high-GI and one MUFA subjects dropped out before the study ended. One subject participated in two arms of the study (MUFA and high-GI). For comparison with baseline data from IGT subjects, eight lean and seven obese normal controls underwent the FSIGTT.

The number of subjects studied was based on two considerations. The intra-individual variation of $S_I$ in healthy young subjects has been reported to have a CV of 14-4% (Ferrari et al. 1991). Using this CV, with twelve subjects in each group, there would be 90% power to detect a difference in $S_I$ of 20% (StatMate version 1.01; Graph Pad software, San Diego, CA). Using a different method to measure insulin sensitivity, we found that acarbose...
significantly improved insulin sensitivity by 17% in a parallel design study involving a total of only eighteen subjects with IGT (Chiaisson et al. 1996).

Data are presented as means and standard errors of the mean. Baseline data for outcome variables were subjected to one-way ANOVA to determine if differences between groups existed. When no significant main effects were found, changes from baseline were subjected to one-way ANOVA. For post-hoc comparisons of individual means, the Newman–Keuls method was used to adjust for multiple comparisons. Adjustment for baseline values was performed by adding the residuals of the linear regression of change on baseline value to the mean change. Dietary intake data were subjected to ANOVA examining for main effects of diet and time and diet × time interaction. Values for glycaemic load were calculated by multiplying the diet GI by carbohydrate (g) and adjusting the resulting values for recorded energy intake (Salmerón et al. 1997b)

Results

Characteristics of IGT and control subjects are shown in Table 1. IGT and obese control subjects were of similar age and BMI, but were significantly older and more obese than lean controls. Generally, metabolic parameters were significantly impaired in IGT subjects relative to lean controls, with obese control values being intermediate. There was no difference between IGT and control subjects for serum lipids and NEFA. S1 and AIRglu were significantly lower in IGT subjects than lean controls, with values for obese controls being intermediate (Table 1, Fig. 1(a)). DI was the only variable for which IGT, lean and obese control subjects differed significantly from each other. There was no significant difference in any parameter at baseline among the groups of IGT subjects randomized to the high-GI, low-GI or MUFA diets (Table 2, serum lipids and NEFA not shown).

Recorded energy intake during the study fell by about 690kJ on low-GI, increased by about 880kJ on MUFA and did not change on high-GI (diet × time interaction, P=0·03, Table 3). Subjects on MUFA recorded about 11% less energy than those on low- and high-GI, respectively (P<0·05). The differences in total fat were accounted for by differences in monounsaturated fat. Subjects on low-GI recorded about 13 g/d more dietary fibre and lower diet GI than those on the other two diets. Glycaemic load was significantly lower on MUFA than high-GI, with the value on low-GI being intermediate. The percentage of total energy contributed by various food groups before and during the dietary treatments is shown in Fig. 2. On high-GI, subjects increased their intake of high-GI starchy foods by 8% of energy, with about a 4% reduction in low-GI starchy foods and smaller reductions in fats, oils, nuts and mixed dishes. On the low-GI diet, there were small (<2% energy) changes in intake of foods from several food groups; the main changes were an increased intake of low-GI starch (11%) and low-GI soups (3%) and a reduced intake of high-GI starch (8%). On the MUFA diet, subjects increased intake of fats, oils and nuts by about 9% of energy and reduced intake of dairy foods by 4%, with smaller reductions in high-GI starch, meats, and fruits and vegetables.

Mean body weight changes were very small, but there was a significant main effect of diet (Fig. 3(a)). Body weight tended to decrease on high-GI and low-GI and to increase on MUFA. The mean fall in body weight over weeks 4–16 on high-GI, −0·49 (SEM 0·29) kg, was significantly greater than that on low-GI, −0·19 (SEM 0·40) kg, which, in turn, was significantly different from the small

<table>
<thead>
<tr>
<th>Table 1. Comparison of control and impaired glucose tolerance (IGT) subjects at baseline</th>
<th>Mean</th>
<th>SEM</th>
<th>Mean</th>
<th>SEM</th>
<th>Mean</th>
<th>SEM</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>n: Total</td>
<td>34</td>
<td>7:27</td>
<td>7</td>
<td>3:4</td>
<td>8</td>
<td>3:5</td>
<td>NS</td>
</tr>
<tr>
<td>Men:women</td>
<td>2:1</td>
<td></td>
<td>2:0</td>
<td></td>
<td>2:0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>55·6a</td>
<td>2:1</td>
<td>58·7a</td>
<td>5·8</td>
<td>32·4b</td>
<td>4·1</td>
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<tr>
<td>BMI (kg/m²)</td>
<td>30·9a</td>
<td>1·0</td>
<td>29·3a</td>
<td>0·8</td>
<td>22·9b</td>
<td>0·9</td>
<td>0·003</td>
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<tr>
<td>Fasting glucose (mmol/l)</td>
<td>5·20a</td>
<td>0·15</td>
<td>4·89a</td>
<td>0·29</td>
<td>4·04b</td>
<td>0·12</td>
<td>0·003</td>
</tr>
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<td>Glycated haemoglobin (%)</td>
<td>5·67a</td>
<td>0·12</td>
<td>5·20ab</td>
<td>0·18</td>
<td>4·74ab</td>
<td>0·16</td>
<td>0·002</td>
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<td>NEFA (mEq/l)</td>
<td>0·54a</td>
<td>0·04</td>
<td>0·45a</td>
<td>0·04</td>
<td>0·41a</td>
<td>0·09</td>
<td>NS</td>
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<td>Cholesterol (mmol/l)</td>
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<td>5·33a</td>
<td>0·35</td>
<td>4·51a</td>
<td>0·25</td>
<td>NS</td>
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<td>Triacylglycerol (mmol/l)</td>
<td>1·87a</td>
<td>0·14</td>
<td>2·04a</td>
<td>0·42</td>
<td>1·10a</td>
<td>0·27</td>
<td>NS</td>
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<td>HDL-cholesterol (mmol/l)</td>
<td>1·21a</td>
<td>0·06</td>
<td>1·33a</td>
<td>0·16</td>
<td>1·56a</td>
<td>0·21</td>
<td>NS</td>
</tr>
<tr>
<td>LDL-cholesterol (mmol/l)</td>
<td>3·18a</td>
<td>0·13</td>
<td>3·08a</td>
<td>0·29</td>
<td>2·45a</td>
<td>0·27</td>
<td>NS</td>
</tr>
<tr>
<td>S1 (10⁻²/µmol x 10 min)</td>
<td>5·17a</td>
<td>0·51</td>
<td>7·39a</td>
<td>1·36</td>
<td>13·20b</td>
<td>2·55</td>
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</tr>
<tr>
<td>S0 (10⁻⁷/µmol)</td>
<td>1·7</td>
<td>0·1</td>
<td>4·2</td>
<td>2·7</td>
<td>2·5</td>
<td>0·4</td>
<td>NS</td>
</tr>
<tr>
<td>AIRglu (10⁶µmol/l x 10 min)</td>
<td>6·89a</td>
<td>1·18</td>
<td>9·79ab</td>
<td>2·64</td>
<td>14·14b</td>
<td>1·74</td>
<td>0·026</td>
</tr>
<tr>
<td>DI (µl)</td>
<td>0·32a</td>
<td>0·06</td>
<td>0·84a</td>
<td>0·39</td>
<td>1·70b</td>
<td>0·30</td>
<td>&lt;0·001</td>
</tr>
</tbody>
</table>

NEFA, non-esterified fatty acids; S1, Insulin sensitivity index; S0, glucose effectiveness; AIRglu, pancreatic responsivity (area under the insulin response curve for 10 min after intravenous glucose); DI, glucose disposition index.

*Significance of F value from one-way ANOVA.
Fig. 1. Plasma glucose and insulin concentrations during the frequently sampled intravenous glucose tolerance test. (a), Values in thirty-four subjects with impaired glucose tolerance (○), seven obese controls (●) and eight lean controls (△); (b), values before (■) and after (□) 4-months treatment with the high-carbohydrate–high-glycaemic index diet; (c), values before (▲) and after (△) 4-months treatment with the low-carbohydrate–high-monounsaturated fat diet; (d), values before (●) and after (□) 4-months treatment with the high-carbohydrate–low-glycaemic index diet. Values are means with their standard errors represented by vertical bars.

Table 2. Comparison of subjects in the three diet groups at baseline*†
(Mean values and standard errors of the mean)

<table>
<thead>
<tr>
<th>Diet...</th>
<th>High-GI</th>
<th>Low-GI</th>
<th>MUFA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SEM</td>
<td>Mean</td>
</tr>
<tr>
<td>Total</td>
<td>11</td>
<td>2.9</td>
<td>13</td>
</tr>
<tr>
<td>Men:women</td>
<td>2:9</td>
<td></td>
<td>3:10</td>
</tr>
<tr>
<td>Age (years)</td>
<td>58-8</td>
<td>4.0</td>
<td>55-2</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>29-3</td>
<td>2.2</td>
<td>29-7</td>
</tr>
<tr>
<td>Fasting glucose (mmol/l)</td>
<td>5-35</td>
<td>0.28</td>
<td>5-22</td>
</tr>
<tr>
<td>Glycated haemoglobin (%)</td>
<td>5-95</td>
<td>0.18</td>
<td>5-67</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>126</td>
<td>6</td>
<td>129</td>
</tr>
<tr>
<td>Blood pressure (mmHg)</td>
<td>78</td>
<td>3</td>
<td>80</td>
</tr>
<tr>
<td>Sf (10⁻³ /min x pmol/l)</td>
<td>5-61</td>
<td>0-89</td>
<td>4-47</td>
</tr>
<tr>
<td>So (10⁻² /min)</td>
<td>1-7</td>
<td>0-2</td>
<td>1-7</td>
</tr>
<tr>
<td>AIRglu (10² x pmol/l x 10 min)</td>
<td>6-02</td>
<td>2-07</td>
<td>5-13</td>
</tr>
<tr>
<td>DI (/10)</td>
<td>0-29</td>
<td>0-12</td>
<td>0-22</td>
</tr>
</tbody>
</table>

High-Gl, high-carbohydrate–high-glycaemic index diet; low-Gl, high-carbohydrate–low-glycaemic index diet; MUFA, low-carbohydrate–high-monounsaturated fat diet; Sf, insulin sensitivity index; So, glucose effectiveness; AIRglu, pancreatic responsivity area under the insulin response curve for 10 min after intravenous glucose; DI, glucose disposition index.

* For details of diets see p. 478.
† None of the differences was statistically significant.
The plasma glucose and insulin during the FSIGTT for the three treatment groups are shown on Fig. 1. For each FSI GTT test, a fractional SD (FSD) was derived for the estimate of $S_I$ as a measure of the goodness of fit of the data points to the kinetic model (FSD = SD of estimate expressed as a % of the value for $S_I$). The median value of FSD for the seventy FSIGTT tests in the IGT subjects was 3·15 %, with 71 % of the values being ≤5 %. In the control subjects, the median FSD was 2·3 %. $S_I$ and AIR$_{glu}$ tended to improve from baseline on the low-GI diet and to deteriorate on high-GI and MUFA (Figs. 5 and 6), but the differences were not significant. Relative to baseline, mean DI increased by 56 % on low-GI and decreased by 16 % on MUFA, with no change on high-GI. After adjusting for baseline values, the increase in DI on low-GI was significantly different from the changes on both MUFA and high-GI (Figs. 5 and 6). Changes in DI were not significantly related to individual changes in body weight, nor to recorded energy, carbohydrate or monounsaturated fat intakes, or glycaemic load. The correlation between change in DI and diet GI during treatment was not quite significant ($r$ $-$0·31; $P$ $=$0·070) but became significant when adjusted for carbohydrate intake as % of energy ($r$ $-$0·34; $P$ $<$0·044).

### Discussion

A low dietary glycaemic load is associated with a reduced risk of developing type 2 diabetes (Salmerón et al. 1997a,b) and is considered desirable in the dietary management of insulin resistance because it reduces postprandial
plasma insulin (Jeppesen et al. 1997; Reaven, 1997). Reducing postprandial insulin may be beneficial because a vicious cycle may exist in which insulin resistance and high plasma insulin exacerbate each other (Kahn et al. 1993; Del Prato et al. 1994). However, there are two different ways of reducing dietary glycemic load: reducing carbohydrate intake, or reducing diet GI. Our results show that these two manoeuvres do not have the same effects in subjects with IGT: reducing diet GI improved HbA1c, diastolic blood pressure and glucose DI compared with reducing carbohydrate intake.

DI can be considered an index of the ability of the β-cell to compensate for changes in insulin sensitivity by increasing insulin secretion, with a low value indicating reduced β-cell responsiveness (Chen et al. 1988). Although there is a wide range of S1 and AIRglu in the normal population, the product of S1 × AIRglu (i.e. DI) tends to be constant (Kahn et al. 1993; Clausen et al. 1996). We found that DI improved significantly by over 50% on low-GI relative to both the MUFA and high-GI. Since defects in both insulin sensitivity and β-cell responsiveness are required for type 2 diabetes to develop (Ferrannini, 1998; Gerich, 1998), a treatment associated with sustained improvement in β-cell responsiveness would be expected to reduce conversion from IGT to diabetes. Indeed, in Pima Indians who converted from IGT to diabetes, DI fell by 48% (Weyer et al. 1999). Thus, improved DI could explain why a low diet GI was associated with reduced risk of developing type 2 diabetes in both the Nurses’ Health (Salmerón et al. 1997b) and Health Professionals Follow-up Studies (Salmerón et al. 1997a).

The low-GI diet was associated with increased β-cell responsiveness in the absence of a change in insulin resistance. Since hyperinsulinaemia may promote the atherosclerotic process (Stout, 1990), it can be asked whether increased β-cell responsiveness may have a deleterious long-term effect on cardiovascular disease risk by increasing plasma insulin. The answer is not known, but we do not believe this to be a strong possibility. Increased β-cell responsiveness means that more insulin is secreted for a given change in plasma glucose concentration; it does not necessarily imply an increase in plasma insulin. Indeed, Swinburn et al. (1991) showed that a high-carbohydrate diet improved β-cell responsiveness with no change in insulin sensitivity and that this was associated with a reduction in mean plasma insulin, presumably due to a simultaneously reduced plasma glucose. The results of the UK Prospective Diabetes Study provide evidence that raising plasma insulin does not promote cardiovascular disease, at least in subjects with diabetes. Treatment of type 2 diabetes with insulin or sulfonylurea had similar effects on glycaemic control, but increased plasma insulin significantly compared with the use of metformin. Despite an increase in plasma insulin, the reduction in the risk of developing cardiovascular complications in subjects treated with insulin or sulfonylurea was virtually identical to that in subjects treated with metformin (UK Prospective Diabetes Study Group, 1998).

The high-GI diet contained typical North American foods and is similar to diets used in studies that failed to show any effect of high carbohydrate intake on insulin sensitivity (Borkman et al. 1991; Swinburn et al. 1991; Garg et al. 1992; Hughs et al. 1995). The present results are consistent with this in that high-GI had no effect on insulin sensitivity, pancreatic responsiveness or DI compared with MUFA.

One of the main arguments against a high-carbohydrate diet for insulin-resistant subjects is that it enhances cardiovascular disease risk because of increased serum triacylglycerol and reduced HDL (Garg et al. 1994; Jeppesen et al. 1997). Studies showing these effects are typically 3–6 weeks long and employ metabolically controlled diets with carbohydrate intake increased from 40 to 60% of energy. Several features of our study design could explain why we saw no effect on triacylglycerol and a trend toward increased HDL on high-GI relative to MUFA. The 16-week study period may have missed transient changes in lipids (Parks & Hellerstein, 2000). Schaefer et al. (1995) have suggested that high-carbohydrate diets may not adversely affect blood lipids in ad-libitum situations because the small amount of weight lost may offset the deleterious effects on blood lipids seen when the diets are given on...
an iso-energetic basis. This is consistent with our results in which there was about 0.75 kg weight loss on high-GI relative to MUFA. Furthermore, the 5–7% increase in carbohydrate intake may have been too small to have an effect on triacylglycerol and HDL (Parks & Hellerstein, 2000).

The small, but statistically significant, differences in body weight change between the three dietary treatment groups may have confounded some of the effects observed, but we do not believe they can account for the changes in DI. Despite the significant difference in weight change between the high-GI and MUFA diets, there was no difference in low-carbohydrate–high monounsaturated fat (Δ) diets. Mean represents the mean of the changes at 1, 2, 3 and 4 months. Values are means with their standard errors represented by vertical bars. a,b,c Mean values with unlike superscript letters were significantly different (P<0.05).

Fig. 3. Changes in body weight (a); diastolic blood pressure (DBP) (b); fasting plasma glucose (c); and glycated haemoglobin (HbA1c) (d) during the 4-month treatment with the high-carbohydrate–high-glycaemic index (●), high-carbohydrate–low-glycaemic index, low-carbohydrate–high monounsaturated fat (△) diets. Mean represents the mean of the changes at 1, 2, 3 and 4 months. Values are means with their standard errors represented by vertical bars. a,b,c Mean values with unlike superscript letters were significantly different (P<0.05).

It is well-known that self-reported energy intake is inaccurate, especially among obese subjects who underestimate their true intakes (Heymsfield et al. 1995). However, there is evidence that reported percentage nutrient intakes are fairly reliable (Lissner & Lindroos, 1994). The significant diet × time interaction for recorded energy intake probably represents reporting error rather than a true difference. If 1570 kJ/d more energy really was consumed on MUFA than low-GI, >5 kg weight would have been gained; however, the observed weight difference was only 0.4 kg. Daily walking for 1 h would be required to expend 1570 kJ/d with no change in weight, an amount of activity that would probably improve insulin sensitivity (Despres & Lamarche, 1994), and is not consistent with the effects we observed on MUFA. Lack of correlation between changes in recorded energy intake and changes in weight, and lack of difference in blood lipids also argue against any significant difference in energy intake in the three diet groups.

Slowing carbohydrate absorption by pharmacological inhibition of carbohydrate digestive enzymes reduces postprandial insulin and improves insulin sensitivity in subjects with IGT (Chiasson et al. 1996). Also, a low-GI diet has been shown to improve insulin sensitivity measured in vitro in adipocytes and in vivo using a short insulin tolerance test in subjects at risk of cardiovascular disease (Frost et al. 1998). We were unable to show a significant effect of a low-GI diet on insulin sensitivity. Differences
in the methods of measuring insulin sensitivity, differences in the populations studied, and lack of statistical power may account for the discrepant results. The power of the present study to detect the observed difference in insulin sensitivity was only about 50%. It was lower than expected not because the effect-size was small but because the variation was high. Based on repeated-measures ANOVA, the within-subject variation in $S_I$ was estimated to be 27% of the mean, about twice the value of 14.4% expected from the literature (Ferrari et al. 1991). The values for FSD were acceptably low showing that experimental errors in the estimation of $S_I$ cannot account for the high variation. This suggests that the within-subject variation of the FSIGTT is greater in IGT subjects than normal. In addition, the IGT subjects we studied were quite heterogeneous; in about 67% of them, low insulin sensitivity was the predominant defect, while in about 33% low pancreatic responsiveness was more important.

Recently, changes in insulin secretion and sensitivity in Pima Indians whose glucose tolerance deteriorated from normal to IGT to diabetes over a 5 year period were compared with those in individuals who remained normal (Weyer et al. 1999). Progression from IGT to diabetes was accompanied by a 19% reduction in insulin sensitivity when measured at high plasma insulin (>13,000 pmol/l). However, when measured at a physiological plasma insulin concentration (840 pmol/l) there was no significant change in insulin sensitivity associated with progression from IGT to diabetes (Weyer et al. 1999). Our inability to detect differences in insulin sensitivity may be related to the relatively low mean peak insulin achieved during the FSIGTT test (1000 pmol/l at 22 min declining to <800 pmol/l at 23 min). Furthermore, improving insulin sensitivity may be less important than maintaining insulin secretion for subjects with IGT, since the main factor associated with conversion from IGT to diabetes was a 51% decrease in insulin secretion (Weyer et al. 1999).

We conclude that the long-term effects of altering source of dietary carbohydrate differ from those of altering amount of carbohydrate. High-carbohydrate–low-GI dietary advice may have beneficial effects on $\beta$-cell function in subjects with IGT, and may, therefore, be useful for the dietary management of IGT.

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References


Fig. 5. Changes in insulin sensitivity (SI; a), glucose effectiveness (SG; b), pancreatic responsivity (AIRGLU; c) and glucose disposition index (DI; d) after 4-months treatment with the high-carbohydrate–low-glycaemic index (high-GI), high-carbohydrate–low-glycaemic index (low-GI) or low-carbohydrate–high-monounsaturated fat (MUFA) diets. The changes have been adjusted for baseline, and the total length of each y axis is 2 times the mean baseline value. Values are means with their standard errors represented by vertical bars. a,b Mean values with unlike superscript letters were significantly different (P<0.05).

Fig. 6. Changes in pancreatic responsivity (AIRgly) relative to changes in insulin sensitivity (SI) in impaired glucose-tolerant subjects before (●) and after (□) high-carbohydrate–high-glycaemic index (high-GI; n 11); before (▲) and after (●) high-carbohydrate–low-glycaemic index (low-GI; n 13) and before (●) and after (●) low-carbohydrate–high-monounsaturated fat (MUFA; n 11) diets for 4 months. The lines represent the prediction line (50th percentile) and the 25th and 5th percentiles of the regression between AIRgly and SI derived from the fifteen control subjects.


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