Insulin response and glycemic effects of meals in non-insulin-dependent diabetes1-3

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ABSTRACT Glycemic and hormonal responses to two breakfast mixed meals were studied in six obese subjects with NIDDM. The study evaluated a high-glycemic-effect (HGE) and a low-glycemic-effect (LGE) meal, each with ~600 kcal and 12% protein, 15% fat, and 73% carbohydrate. Plasma insulin and counterregulatory hormones were measured at baseline and at 30-min intervals for 5 h after meals. Mean fasting plasma glucose and insulin concentrations were similar before both studies: for the LGE meal, 11.9 ± 1.8 mmol/L and 261.9 ± 50.1 pmol/L; for the HGE meal, 11.9 ± 2.0 mmol/L and 262.6 ± 43.1 pmol/L. Peak plasma glucose concentrations were ~25% lower with the LGE meal and the area under the glucose curve was 63% of that obtained for the HGE meal (p < 0.05). Although the integrated insulin responses of the two meals did not differ, the peak occurred 60 min earlier in the LGE meal (p < 0.05). The LGE meal may produce a lower glycemic response, in part because of earlier insulin secretion. Am J Clin Nutr 1990;52:519-23.

KEY WORDS Glycemic index, insulin response, non-insulin-dependent diabetes mellitus, counterregulatory hormones

Introduction

Factors that limit the postprandial rise in blood glucose have become important in normalizing blood glucose concentration (1). Postprandial glucose concentrations reflect hepatic glucose release as well as digestion and absorption of ingested food. Insulin and counterregulatory responses to specific food and meals need to be considered as possible determinants of glucose concentrations.

The ranking of specific foods based on the blood glucose response was first proposed by Jenkins et al (2). Mixing carbohydrate foods of different glycemic indices has resulted the observed glycemic index of the mixed meal to within 2% of the expected value (3). The effect of high- and low-carbohydrate meals on insulin and glucagon was evaluated in subjects with normal glucose tolerance and with non-insulin-dependent diabetes (NIDDM) (4). The glycemic impact of various sources of carbohydrate has been evaluated in many studies (3, 5-16).

Low-glycemic-index foods including fructose significantly reduced plasma glucose response (5, 8, 13) and also reduced insulin responses (13). Insulin response to fructose-supplemented meals has not been studied in depth, but the response to glucose was demonstrated to be highly variable (17, 18). Crapo et al (14) noted that the glucagon concentrations in subjects with impaired glucose tolerance are relatively nonsuppressible after glucose ingestion and yet increase after fructose ingestion.

In addition to insulin and glucagon secretory changes, other hormones may be important in regulating blood glucose concentrations (19-21). Few studies have examined range of the hormonal factors involved (4, 6-8). This study was undertaken to evaluate blood glucose, blood insulin, and counterregulatory responses to two breakfast meals with similar macronutrient composition and different glycemic effect.

Subjects and methods

Six obese diabetic subjects (three men and three women) who met the National Diabetes Data Group Criteria (22) for the diagnosis of NIDDM (confirmed with glucose tolerance tests) were studied at the Clinical Research Center of the Albert Einstein College of Medicine (AECOM). Mean age was 61 y (range 53-65 y), mean body weight was 97.7 kg (range 78.2-120.5 kg), and percent desirable body weight (23) was 152 ± 18% (*SEM). The clinical characteristics of the subjects are shown in Table 1. Five of the patients were taking oral hypoglycemic agents that were withheld 24 h before the tests.

The subjects signed an informed-consent form, and the study was approved by the Clinical Investigation Committee of AECOM. All the participants remained on their usual diabetes diets but fasted overnight before the study.

After an overnight fast of 8-10 h, an indwelling catheter was inserted into an antecubital vein and kept patent with saline. After baseline measurements of glucose and hormone concentrations at −10 and 0 min, the subject was given a breakfast meal. Two studies were done on each patient in random order 1 wk apart. The patients did not know the anticipated glycemic effect of each meal.

Study 1 [high-glycemic-effect (HGE) meal] and study 2 [low-
glycemic-effect (LGE) meal] were calculated to differ in weighted glycemic effect by 50%. The glycemic effect (GE) was calculated by multiplying the glycemic index of each food item by the percent of total carbohydrate contributed. The values for glycemic index were taken from those published by Jenkins et al (2).

The meals were isocaloric and had equal amounts of protein, carbohydrate, and fat but differed in the source of carbohydrate. The meals were prepared by the research dietitian (Table 2). Macronutrient composition was calculated by using data from Agriculture Handbook no. 456 (24). Weights of foods in the HGE meal were based on average portion size (24); the LGE meal was of similar macronutrient composition but was chosen to produce of only half the area under the glycemic response curve based on glycemic indices provided by Jenkins et al (2). Glycemic indices are based on the incremental glucose-response curve (2). The foods were weighed to the nearest 0.1 g on an electronic balance. The composition of the meals were virtually identical (HGE meal: 11.9% protein, 14.8% fat, and 73.34% carbohydrate; LGE meal: 12.3% protein, 14.7% fat, and 73.2% carbohydrate).

Blood samples were obtained at −10 and 0 min, and the test breakfast was eaten under supervision within 15 min. Further blood samples were drawn at intervals of 30 min for a total of 5 h. The separated plasma was frozen at −20 °C for subsequent assay.

Plasma glucose was determined by a glucose oxidase method with a glucose analyzer (Beckman Instruments, Fullerton, CA). Plasma insulin was measured by using a double-antibody technique (25). Plasma glucagon was assayed in plasma treated with aprotinin (Trasylol, FBA Pharmaceutical, New York) (26). Plasma epinephrine and norepinephrine were measured by using an isotope-derivative method (27).

Student’s two-tailed t test for paired variables was used for analysis of statistical significance. Significance was established at p ≤ 0.05. Data are presented as the mean ± SEM.

**TABLE 1**
Characteristics of subjects

<table>
<thead>
<tr>
<th>Subject</th>
<th>Sex</th>
<th>Age</th>
<th>Percent desirable body weight</th>
<th>Daily treatment*</th>
<th>HGE meal</th>
<th>LGE meal</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>53</td>
<td>130</td>
<td>D 250 mg qd</td>
<td>8.2</td>
<td>7.8</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>65</td>
<td>165</td>
<td>Diet only</td>
<td>11.3</td>
<td>13.5</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>58</td>
<td>133</td>
<td>D 250 mg bid</td>
<td>14.1</td>
<td>13.6</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>62</td>
<td>173</td>
<td>D 250 mg bid</td>
<td>7.4</td>
<td>8.0</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>64</td>
<td>161</td>
<td>T 500 mg tid</td>
<td>20.5</td>
<td>19.5</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>65</td>
<td>154</td>
<td>D 250 mg bid</td>
<td>9.8</td>
<td>9.2</td>
</tr>
<tr>
<td>x ± SEM</td>
<td></td>
<td></td>
<td>61.0 ± 4.7</td>
<td>152 ± 17.5</td>
<td>11.9 ± 2.0</td>
<td>11.9 ± 1.8</td>
</tr>
</tbody>
</table>

* HGE, high-glycemic-effect meal; LGE, low-glycemic-effect meal; D, diabenase; T, tolbutamide.

**TABLE 2**
Test meals

<table>
<thead>
<tr>
<th>Weight*</th>
<th>Energy</th>
<th>Protein</th>
<th>Fat</th>
<th>Carbohydrate</th>
<th>GI†</th>
<th>Calculated GE‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>g</td>
<td>kcal</td>
<td>g</td>
<td>g</td>
<td>g</td>
<td>g</td>
<td>g</td>
</tr>
<tr>
<td>HGE meal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corn flakes</td>
<td>37.5</td>
<td>142.0</td>
<td>53.0</td>
<td>—</td>
<td>31.5</td>
<td>80</td>
</tr>
<tr>
<td>Whole-wheat bread</td>
<td>56.0</td>
<td>134.0</td>
<td>5.2</td>
<td>1.4</td>
<td>27.6</td>
<td>72</td>
</tr>
<tr>
<td>Margarine</td>
<td>10.0</td>
<td>72.0</td>
<td>—</td>
<td>8.2</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Skim milk</td>
<td>245.0</td>
<td>88.0</td>
<td>8.8</td>
<td>0.2</td>
<td>12.5</td>
<td>32</td>
</tr>
<tr>
<td>Orange juice</td>
<td>124.5</td>
<td>60.0</td>
<td>1.0</td>
<td>0.2</td>
<td>14.0</td>
<td>46</td>
</tr>
<tr>
<td>Dextrose (polyose)</td>
<td>28.7</td>
<td>110.0</td>
<td>—</td>
<td>—</td>
<td>27.0</td>
<td>100</td>
</tr>
<tr>
<td>Total</td>
<td>501.7</td>
<td>606.0</td>
<td>68</td>
<td>10</td>
<td>112.6</td>
<td>—</td>
</tr>
<tr>
<td>LGE meal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oatmeal</td>
<td>180.0</td>
<td>99.0</td>
<td>3.6</td>
<td>1.8</td>
<td>17.5</td>
<td>49</td>
</tr>
<tr>
<td>Apple, golden</td>
<td>192.5</td>
<td>112.0</td>
<td>0.4</td>
<td>1.2</td>
<td>28.0</td>
<td>39</td>
</tr>
<tr>
<td>Yogurt, plain</td>
<td>184.0</td>
<td>114.0</td>
<td>5.5</td>
<td>6.2</td>
<td>9.0</td>
<td>36</td>
</tr>
<tr>
<td>Skim milk</td>
<td>245.5</td>
<td>88.0</td>
<td>8.8</td>
<td>0.2</td>
<td>12.5</td>
<td>32</td>
</tr>
<tr>
<td>Orange juice</td>
<td>124.0</td>
<td>60.0</td>
<td>1.0</td>
<td>0.3</td>
<td>14.0</td>
<td>46</td>
</tr>
<tr>
<td>Fructose</td>
<td>31.0</td>
<td>124.0</td>
<td>—</td>
<td>—</td>
<td>31.0</td>
<td>20</td>
</tr>
<tr>
<td>Total</td>
<td>957.0</td>
<td>597.0</td>
<td>19.3</td>
<td>9.7</td>
<td>112.0</td>
<td>—</td>
</tr>
</tbody>
</table>

* Based on edible portion.
† Glycemic index based on 50 g carbohydrate with glucose as reference.
‡ Calculated glycemic effect: GI of food item multiplied by percent of carbohydrate contributed by each food item.
FIG 1. Plasma glucose for the high-glycemic-effect meal (●) and for the low-glycemic-effect meal (○). x ± SEM; n = 6.

Results

The glucose response curve is shown in Figure 1. The mean fasting plasma glucose concentrations were similar before both studies (LGE meal 11.9 ± 1.8 mmol/L; HGE meal 11.9 ± 2.0 mmol/L). After ingestion of the HGE meal, plasma glucose concentration increased to a peak value of 19.0 ± 2.3 mmol/L at 90 min. After 5 h plasma glucose remained above the baseline value at 13.6 ± 2.7 mmol/L. The LGE meal rose to a peak value of 15.6 ± 2.0 mmol/L and fell below baseline at 5 h (10.6 ± 2.2 mmol/L). The mean glucose area integrated over the 5 h of study after the LGE meal was 63% of that of the HGE meal (p < 0.05).

The insulin response curves are shown in Figure 2. Before the meal plasma insulin was 261.9 ± 50.1 pmol/L for study 2 group and 262.6 ± 43.1 pmol/L for the study 1 group. After the ingestion of the HGE meal, plasma insulin rose to a peak value of 846.7 ± 240.4 pmol/L at 90 min and was 432.7 ± 78.9 pmol/L at 5 h. The LGE meal elicited a rise in insulin to a peak of 1291.5 ± 416.2 pmol/L, returning to a final value of 317.9 ± 50.2 pmol/L at 5 h. The mean insulin area integrated over the 5 h was 101 ± 5 mmol/L x 300 min for the LGE meal and was 122 ± 8 mmol/L x 300 min for the HGE meal, which was borderline significant (p = 0.1). However, the peak insulin response occurred significantly earlier for the LGE meal (90 min) than for the HGE meal (150 min; p < 0.05). Table 3 lists the time to peak insulin concentrations for both test meals in all subjects.

The plasma glucagon values in the two studies did not differ significantly as is shown in Figure 3. Similarly, plasma epinephrine norepinephrine, cortisol, and growth hormone, which are shown in Figure 4, after the two meals did not differ significantly.

Discussion

The test meals produced the anticipated glycemic response in this study: the area under the glucose response curve for the LGE meal was lower (by 63%) than that of the HGE meal. Our results appear to be consistent with the findings of Wolter et al (3). However, the predictive ability of the glycemic index for carbohydrate-containing foods has been questioned. One study by Coulston et al (16) did not find differences in postprandial glucose and insulin responses to test meals, with 40% of calories from fat, that were calculated to produce high, intermediate, and low glycemic responses. However, in another study, also with 40% of calories from fat, Coulston et al (15) found that a meal containing potato elicited higher glycemic and insulin responses than did meals containing lentils. All of the test meals used by Wolter et al (3) were low in fat, which suggests that high fat per se may blunt glucose differences found in foods in

![Figure 2](image2.png)

**FIG 2.** Plasma insulin for the high-glycemic-effect meal (●) and for the low-glycemic-effect meal (○). x ± SEM; n = 6.

![Figure 3](image3.png)

**FIG 3.** Plasma glucagon for the high-glycemic-effect meal (●) and for the low-glycemic-effect meal (○). x ± SEM; n = 6.
a mixed meal. However, differences in glycemic response were found to high-fat meals in studies by Collier et al (28) and Bornet et al (29) although fat did not affect insulin response in either study.

Our most interesting observation was the insulin response, notably the early insulin peak that occurred after the LGE meal. Insulin responses to a standard glucose-tolerance test may vary over a 10-fold range, unrelated to factors such as sex, deviation from ideal body weight, and age (18). Nevertheless, the individual response is a major issue. Early work by Crapo et al (6) evaluating glucose and insulin response to various carbohydrates demonstrated that different sources of carbohydrate produced different glycemic-response curves, but there was no significant difference in the insulin responses for carbohydrate sources. Coulston et al reported with no differences in insulin secretion in response to meals with various sources of carbohydrate (16) but reported increased glucose and insulin responses to a potato meal compared with other meals (15). Therefore, it was not surprising that the area under the insulin curve was actually somewhat greater after the HGE meal. We find it interesting that the insulin peak occurs earlier in the LGE meal and suggest that this may be a possible mechanism for the lower glucose response to the LGE meal. Whether this represents the effect of lowered glucose or is a direct fructose effect is unknown.

Changes in counterregulatory hormone secretion do not appear to be a major factor in the blood glucose and insulin responses to the LGE meal. Though there was an apparent difference in the early plasma glucagon response to these meals, this difference was not significant. Indeed, plasma glucagon tended to be higher in the LGE meal. Similarly, the changes in other counterregulatory hormones could not explain our results. Although after a glucose-tolerance test selective changes that blunt the decline in plasma glucose may occur in plasma concentrations of growth hormone and epinephrine (17), we were not able to show any significant difference in counterregulatory hormone secretion after the two meals. This occurred despite the fall in plasma glucose below the baseline in the LGE studies.

Abnormal patterns of insulin secretion may be important in NIDDM. The almost universal impairment of early (first-phase) insulin secretion in response to meals in such patients has led to conventional recommendations about dietary carbohydrate. Thus, dietary factors that are associated with a difference in insulin secretion pattern may improve postprandial glycemia. However, we cannot determine from our results whether the earlier insulin response to the LGE meal caused reduced hyperglycemia or, conversely, whether the greater hyperglycemia of the HGE meal caused the delay in insulin secretion. Furthermore, whether fructose per se has any direct influence on determining insulin secretory responses is not established. Although there is considerable controversy about the importance of dietary carbohydrate constituents on postprandial glucose response, our study was specifically designed to produce clear-cut differences in glycemia to allow for evaluation of the normal factors.
Therefore, we conclude that in NIDDM the lower glycemic responses to certain foods may not be simply due to the interplay of factors related to the complexity and absorption of nutrients and may be related to the dynamics of insulin secretion. In NIDDM the LGE meal may be associated with an improved glycemic response because of the induction of earlier insulin secretion.

We are grateful to Helene Leiberman for planning and preparing the meals and to Robin Sgueglia for her assistance in the laboratory.

References