Regression of Carotid Atherosclerosis by Control of Postprandial Hyperglycemia in Type 2 Diabetes Mellitus

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Background—Postprandial hyperglycemia may be a risk factor for cardiovascular disease. We compared the effects of two insulin secretagogues, repaglinide and glyburide, known to have different efficacy on postprandial hyperglycemia, on carotid intima-media thickness (CIMT) and markers of systemic vascular inflammation in type 2 diabetic patients.

Methods and Results—We performed a randomized, single-blind trial on 175 drug-naive patients with type 2 diabetes mellitus (93 men and 82 women), 35 to 70 years of age, selected from a population of 401 patients who participated in an epidemiological analysis assessing the relation of postprandial hyperglycemia to surrogate measures of atherosclerosis. Eighty-eight patients were randomly assigned to receive repaglinide and 87 patients to glyburide, with a titration period of 6 to 8 weeks for optimization of drug dosage and a subsequent 12-month treatment period. The effects of repaglinide (1.5 to 12 mg/d) and glyburide (5 to 20 mg/d) on CIMT were compared by using blinded, serial assessments of the far wall. After 12 months, postprandial glucose peak was 148±28 mg/dL in the repaglinide group and 180±32 mg/dL in the glyburide group (P<0.01). HbA1c showed a similar decrease in both groups (−0.9%). CIMT regression, defined as a decrease of >0.020 mm, was observed in 52% of diabetics receiving repaglinide and in 18% of those receiving glyburide (P<0.01). Interleukin-6 (P=0.04) and C-reactive protein (P=0.02) decreased more in the repaglinide group than in the glyburide group. The reduction in CIMT was associated with changes in postprandial but not fasting hyperglycemia.

Conclusions—Reduction of postprandial hyperglycemia in type 2 diabetic patients is associated with CIMT regression.

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Key Words: diabetes mellitus ■ atherosclerosis ■ interleukins ■ carotid arteries

Cardiovascular disease is the leading cause of death among type 2 diabetic subjects.1 Recent epidemiological studies suggest that postprandial hyperglycemia might be an independent risk factor of cardiovascular disease beyond and more powerful than fasting hyperglycemia.2 However, it is not clear whether pharmacological interventions that target postprandial hyperglycemia provide unique benefits relative to other pharmacological therapies that lower HbA1c comparably.3

The Campanian Postprandial Hyperglycemia Study was conducted to assess the relation of postprandial hyperglycemia to carotid intima-media thickness (CIMT), a validated surrogate cardiovascular end point,4–6 and circulating inflammatory markers (interleukin [IL]-6, IL-18, IL-10, and C-reactive protein [CRP]) in a population of patients with type 2 diabetes mellitus. Moreover, we compared the effects of two insulin secretagogues, repaglinide and glyburide, on CIMT and circulating markers of vascular inflammation. Repaglinide, a carbamoylmethyl benzoic acid derivative, is a rapid-onset/short-duration insulinotropic agent, whereas glyburide is a long-acting sulfonylurea. Repaglinide selectively increases meal-related early insulin secretion and may result in better control of postprandial hyperglycemia than glyburide.7–9

Methods

Epidemiological Study

We screened type 2 diabetic patients regularly attending 14 diabetes clinics located in the area of Naples and Caserta, two towns of the Campania county, South Italy. Among them, we selected those with a diagnosis of type 2 diabetes for ≥6 months but <10 years, 35 to 70 years of age, a body mass index (BMI) of ≥24, a value of HbA1c of ≥6.5%, and treated with diet or oral drugs. Criteria for exclusion were need for insulin use, concomitant chronic diseases, including kidney, liver, and cardiovascular diseases, recent acute illness, or change in diet, treatment, or lifestyle within the 3 months before the study. The 401 diabetic patients enrolled in the study were compared with 150 subjects recruited by newspaper advertisements among the population near the clinics. Criteria for inclusion were the absence of diabetes or glucose intolerance (assessed by an oral glucose tolerance test), apparent good health (assessed by absence of self-reported
follow-up studies were performed in a standard fashion by a single specialist physician who was specifically trained to perform the prescribed study examination and blinded to treatment group. All images were electronically stored. The measurement was made in the 1-cm segment proximal to the dilation of the carotid bulb and always in plaque-free segments. For each patient, 3 measurements on both sides were performed on the anterior, lateral, and posterior projections of the far wall; the readings were then averaged. An independent observer who was blinded to treatment group and trained in the interpretation of CIMT images performed off-line analysis of B-mode ultrasound images. Both patients and providers were blinded to the CIMT results until 1-year follow-up examination was completed. Paired CIMT measurements in the same arteries showed a high degree of reproducibility, with a mean difference in CIMT of 0.020 mm, and an intraclass correlation coefficient of 0.97 ($P<0.001$). CIMT regression was defined as a decrease of >0.020 mm in mean CIMT at 12 months.

**Laboratory Analysis**

All analyses were performed in the reference center, except for postmeal blood glucose monitoring, which was performed at home with the same devices through the study (One Touch, Lifescan). Plasma glucose and serum lipids were measured by enzymatic assays in the hospital’s chemistry laboratory. HbA$_1c$, by nephelometry, and serum insulin by radioimmunoassay (Pharmacia). Serum samples for inflammatory markers were stored at −80°C until assay. Serum concentrations of IL-6, IL-10, and IL-18 were determined in duplicate with commercially available kits (Quantikine HS, R&D Systems). All samples for the same patient were measured in the same assay. The interassay coefficient of variation was <6% for all kits. High-sensitivity CRP was assayed in duplicate by immunonephelometry on a Behring Nephelometer 2 (Dade Behring).

**Statistical Analysis**

Data are presented as mean±SD unless stated otherwise. Baseline comparison was made by means of a $t$ test and Wilcoxon test as appropriate. Glucose peak was defined as the maximal increase in blood glucose obtained at any point after the meal. The incremental area under the curve (AUC) for glucose was calculated by the trapezoidal method. The correlation of selected variables to CIMT was assessed by using Pearson or Spearman correlation coefficients, as appropriate, and a stepwise multiple regression analysis was then used to evaluate the independent association of these variables with CIMT. In the randomized trial, data were analyzed by intention-to-treat on all randomly assigned subjects, by imputing no change in CIMT or any other variable to the dropouts. Changes in glucose, HbA$_1c$, lipids, IL-6, IL-18, IL-10, and CRP over time were evaluated by using either a paired $t$ test or Wilcoxon signed-rank test, as appropriate. Comparison of the treatment effect between experimental groups for the changes in the primary outcome at 12 months was performed with a $t$ test for independent groups. The $x^2$ test was used for comparing proportions of patients in the two groups that demonstrated regression of mean CIMT. A value of $P<0.05$ was considered significant. All statistical analyses were performed with the use of SPSS software (version 10.05, SPSS Inc).

**Results**

The baseline characteristics of type 2 diabetic patients and control subjects are given in Table 1. Forty-eight percent of diabetic patients were treated with oral drugs, including a sulfonylurea (16%), metformin (10%), or combined therapy (22%). Moreover, statins, ACE inhibitors, and aspirin were used in 8%, 18%, and 15% of patients, respectively.

The mean value of postmeal incremental glucose peak was 70±42 mg/dL, with a wide range (0 to 213 mg/dL). The interclass correlation coefficient between the 3 postmeal glucose curves obtained in the same patient was 0.85 ($P<0.001$). In univariate analysis adjusted for sex and age,
glucose parameters were significantly correlated to CIMT: HbA1c, \( r = 0.19, P = 0.02 \); glucose peak, \( r = 0.21, P = 0.01 \); and fasting glucose, \( r = 0.12, P = 0.04 \). There was a significant correlation between CIMT and IL-6 \( (r = 0.31, P = 0.002) \), CRP \( (r = 0.24, P = 0.01) \), and IL-18 \( (r = 0.16, P = 0.04) \). In a multivariate analysis including CIMT as a dependent variable and candidate risk factors (age, sex, BMI, smoking, blood pressure, lipid and glucose parameters, IL-6, IL-18, and CRP) as independent variables, we found that glucose peak, IL-6, and CRP were significant independent determinants of CIMT and explained 49% of the variability (20%, 12%, and 17%, respectively, \( P < 0.05 \)).

Intervention Study

The two experimental groups (repaglinide and glyburide) had similar baseline characteristics (Table 2). At the end of the trial, 19% of patients were at dose level 1, 12% were at dose level 2, 10% were at dose level 3, and 59% were at dose level 4; this distribution was not significantly different between the two treatments. There was a similar course in HbA1c concentration during the study in both treatment groups; the fasting glucose concentration decreased significantly more among patients in the glyburide group, whereas the glucose peak and AUC decreased significantly more among the patients in the repaglinide group (Table 3 and Figure 2). AUC for glucose at the end of the study was 2370 ± 565 mg/dL · h in the repaglinide group and 4020 ± 790 mg/dL · h in the glyburide group \( (P = 0.01) \). Twenty-four percent of patients in the repaglinide group and 48% of patients in the glyburide group achieved a fasting glucose level <110 mg/dL \( (P = 0.01) \); by contrast, 43% of patients in the repaglinide group and 21% of patients in the glyburide group achieved a fasting glucose level <70 mg/dL \( (P = 0.01) \).

Compared with glyburide, repaglinide resulted in significantly greater reductions in IL-6 and CRP concentrations (Table 3). Changes in IL-6 and CRP concentrations after treatment were related to reductions in postprandial glucose peaks \( (r = 0.35, P < 0.001, r = 0.26, P = 0.01) \), respectively in both groups but not to changes in fasting glucose or HbA1c. Repaglinide induced progressive mean CIMT regression over 12 months, whereas mean CIMT was stable in the glyburide group (Table 3 and Figure 3). CIMT regression was observed in 52% of diabetic patients receiving repaglinide and in 18% of diabetic patients receiving glyburide \( (P = 0.01) \). There was no difference observed between treatment groups in any of the 6-month CIMT measurements. No significant changes from baseline in lipid and blood pressure parameters occurred in either group (Table 3).

For evaluating the independent association of changes in CIMT with changes in glucose parameters and inflammatory markers, a multivariate analysis was performed in which CIMT was the dependent variable and fasting glucose, glucose peak, HbA1c, IL-6, IL-18, and CRP were the inde-
The model explained 60% of variability in the change of CIMT with changes of glucose peak (28%, \( P < 0.002 \)), HbA1c (15%, \( P = 0.03 \)), and CRP (17%, \( P = 0.01 \)) concentrations.

The number of patients who had hypoglycemic events was similar in the repaglinide and glyburide groups (9% and 13% of patients, respectively). During the study, 14 patients (8%) withdrew (7 patients in each group). Of these patients, 10 withdrew for personal reasons, 2 withdrew because of severe illness, and 2 could not be contacted.

**TABLE 3.** Changes in Selected Variables and Carotid Intima-Media Thickness From Baseline in Repaglinide and Glyburide Groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Repaglinide (n=88)</th>
<th>Glyburide (n=87)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI, kg/m²</td>
<td>-0.3±0.4</td>
<td>-0.2 to 0.7</td>
<td>0.22</td>
</tr>
<tr>
<td>Glucose, mg/dL</td>
<td>Fasting -24±18</td>
<td>-38 to -10</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Peak -70±58</td>
<td>-98 to -42</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>AUC, mg/dL · 2 h</td>
<td>-398±1035</td>
<td>0.01</td>
</tr>
<tr>
<td>HbA1c, %</td>
<td>-0.9±0.5</td>
<td>-1.1 to -0.7</td>
<td>0.13</td>
</tr>
<tr>
<td>Serum lipids, mg/dL</td>
<td>Total cholesterol -5±10</td>
<td>-12 to 3</td>
<td>0.18</td>
</tr>
<tr>
<td></td>
<td>HDL cholesterol 3±4</td>
<td>-2 to 8</td>
<td>0.28</td>
</tr>
<tr>
<td></td>
<td>Triglycerides -15±19</td>
<td>-39 to 10</td>
<td>0.34</td>
</tr>
<tr>
<td>Blood pressure, mm Hg</td>
<td>Systolic -2±2</td>
<td>-5 to 3</td>
<td>0.17</td>
</tr>
<tr>
<td></td>
<td>Diastolic -1±2</td>
<td>-3 to 2</td>
<td>0.20</td>
</tr>
<tr>
<td>Serum cytokines, pg/mL</td>
<td>IL-6 -0.5±0.8</td>
<td>-0.9 to -0.1</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>IL-18 -17±27</td>
<td>-35 to 1</td>
<td>0.09</td>
</tr>
<tr>
<td></td>
<td>IL-10 0.4±0.5</td>
<td>-0.1 to 0.9</td>
<td>0.15</td>
</tr>
<tr>
<td></td>
<td>CRP -0.7±0.7</td>
<td>-1.2 to -0.2</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>CIMT -0.029±0.021</td>
<td>-0.041 to -0.017</td>
<td>0.02</td>
</tr>
</tbody>
</table>

A total of 14 patients withdrew from the study, 7 in each group. Probability values were determined by 2-tailed \( t \) test for difference between groups.

**Discussion**

This study provides evidence that progression of carotid atherosclerosis can be prevented by the control of postprandial hyperglycemia in type 2 diabetic patients. In particular, at the same level of HbA1c, amelioration of postprandial glucose peaks was more effective in reducing CIMT than amelioration of fasting hyperglycemia. Although a nonglycemic effect (yet unknown) of repaglinide on CIMT regression cannot be

**Figure 2.** Glucose peaks (top) and glucose curves (bottom) after main meal of the day according to assigned treatment (repaglinide or glyburide) in diabetic patients of the intervention study.

**Figure 3.** Individual CIMT measurements in diabetic patients assigned to repaglinide or glyburide treatment. Box plots indicate median and interquartile range.
ruled out, these results suggest that excessive excursions of plasma glucose in the postprandial state are harmful for the vascular tree and that postprandial hyperglycemia should be considered a treatment target of therapy.

We found that postprandial hyperglycemia assessed at home in a free-living condition was more strongly associated with CIMT than fasting glucose and HbA1c. A similar association was reported with the plasma glucose peak after an oral glucose tolerance test. Several experimental studies provide a plausible pathophysiological explanation for this association. In diabetic patients, hyperglycemia after meals causes an overproduction of free radicals and thrombin proportional to blood glucose levels. Moreover, acute elevations of glucose levels in both normal subjects and type 2 diabetic patients induce vasoconstriction and increase the circulating levels of some cellular adhesion molecules and proinflammatory cytokines. Baseline concentrations of the proinflammatory cytokines IL-6 and IL-18 were lower, whereas those of the antiinflammatory cytokine IL-10 were lower in diabetic patients as compared with control subjects. Such a profile of circulating cytokine concentration may be dangerous for cardiovascular health because elevated circulating concentrations of IL-6 predict future myocardial infarction among apparently healthy men and elevated IL-18 concentrations predict future cardiovascular events and death in patients with documented coronary artery disease, whereas lower serum IL-10 concentrations have been found in patients with unstable angina compared with those who had chronic stable angina.

Although several epidemiological studies have found associations of cardiovascular disease with glyceria over a broad range of glucose tolerance, from normal to diabetic, interventional studies have not demonstrated a convincing beneficial effect of glucose lowering on cardiovascular outcomes. In those studies, however, no attention was paid to control of postprandial hyperglycemia, which also contributes to blood glucose levels. Moreover, the majority of patients with diabetes fail to achieve their glycemic goals. In our study, most of the drug-naive, diabetic patients assigned to treatment obtained HbA1c values below the recommended value of 7%. Moreover, patients who had the greatest reduction of postprandial hyperglycemia had the largest regression of CIMT.

In our study, diabetic patients had higher values of CIMT than did nondiabetic subjects; this was associated with higher serum concentrations of proinflammatory cytokines and CRP. CRP has been directly related to the rate of progression of carotid atherosclerosis. Emerging data suggest that besides being a marker of cardiovascular risk, CRP may be a mediator of atherogenesis by quenching nitric oxide. Interestingly enough, acute hyperglycemia also reduces nitric oxide bioavailability, pointing to the intriguing possibility that the combined effect of raised CRP concentrations and increased postprandial glucose levels in diabetic patients may act synergistically to diminish nitric oxide bioactivity. A positive association between dietary glycemic load and circulating CRP levels has been reported, suggesting that a high intake of rapidly digested and adsorbed carbohydrates, which leads to larger postprandial glycemic excursions, may exacerbate the inflammatory process.

This study does have limitations. First, because the epidemiological study is cross-sectional, the directionality of associations cannot be conclusively explained. However, the results of the intervention study shows that near-normalization of glucose control with optimal sulfonylurea dosages causes CIMT regression or stabilization. Second, the randomized clinical trial used open-label administration of the study drug; however, the concealment of allocation and the use of an objective, blinded, end point assessment strengthened the significance of results. Finally, because of the limited follow-up, we could not evaluate clinical events. However, decreasing postprandial hyperglycemia with the α-glucosidase inhibitor acarbose, even at a much lower level than that obtained in the present study, is associated with a significant reduction in the incidence of cardiovascular disease and hypertension in patients with impaired glucose tolerance characterized by moderate postprandial hyperglycemia.

In type 2 diabetic patients, amelioration of postprandial hyperglycemia provides superior efficacy for atherosclerosis regression in the distal common carotid artery at 1 year compared with amelioration of fasting hyperglycemia. These results suggest that control of excessive glucose excursions, especially in the postprandial state, may provide clinical benefit in type 2 diabetic patients.

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Appendix

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References
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