Pioglitazone Improves Insulin Sensitivity Among Nondiabetic Patients With a Recent Transient Ischemic Attack or Ischemic Stroke

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Background and Purpose—The aim of this study was to determine the effectiveness of pioglitazone compared with placebo for improving insulin sensitivity among nondiabetic patients with a recent transient ischemic attack (TIA) or nondisabling ischemic stroke and impaired insulin sensitivity.

Methods—Eligible subjects were men and women >45 years of age who had no history of diabetes, fasting glucose <7.0 mmol/L, and impaired insulin sensitivity according to an index calculated from insulin and glucose blood levels obtained during an oral glucose tolerance test. Eligible subjects were randomized to pioglitazone 45 mg/d or placebo. After 3 months of therapy, the glucose tolerance test was repeated.

Results—Between July 2000 and June 2001, we performed oral glucose tolerance tests on 75 patients with no history of diabetes, among whom 36 (50%) were found to have impaired insulin sensitivity and fasting glucose <7.0 mmol/L. Among these 36, 20 consented to the trial. Patients assigned to pioglitazone (n=10) and placebo (n=10) were similar in insulin sensitivity, age, obesity, and index event (stroke compared with TIA), but patients assigned to pioglitazone were less likely to be male (4 compared with 9). The mean proportional increase in insulin sensitivity was 62% among patients assigned to pioglitazone compared with a –1% decline among patients assigned to placebo (P=0.0006). Mean C-reactive protein concentration declined from 0.30 to 0.20 mg/L among patients assigned to pioglitazone and increased from 0.41 to 0.45 mg/L among patients assigned to placebo (P=0.06 for comparison of mean change).

Conclusions—Pioglitazone is effective for improving insulin sensitivity among patients with recent TIA or stroke and impaired insulin sensitivity. (Stroke. 2003;34:1431-1436.)

Key Words: cerebrovascular disorders ■ cerebral ischemia, transient ■ insulin ■ insulin resistance ■ pioglitazone ■ prevention ■ randomized controlled trials ■ risk factors ■ stroke, ischemic

Impaired insulin sensitivity (ie, insulin resistance) has emerged as a potentially important risk factor for vascular disease. In separate investigations, it has been associated with risk for coronary artery disease,1 carotid atherosclerosis,2-5 and stroke.6 The mechanism for the association is not completely understood but may involve hyperglycemia,7 dyslipidemia,7 hypertension,8 hypercoagulability,9 and endothelial dysfunction.10

Because impaired insulin sensitivity has been associated with increased stroke risk in epidemiological research, investigators have recently become interested in determining whether improving insulin sensitivity with drugs or lifestyle interventions can reduce the risk for initial or recurrent stroke (and other vascular events). In preparation for a clinical trial on this question, we conducted a randomized controlled trial to determine whether pioglitazone is effective in improving insulin sensitivity among nondiabetic patients with symptomatic cerebrovascular disease and impaired insulin sensitivity. Pioglitazone, a thiazolidinedione, has been shown to improve insulin sensitivity among diabetic patients, but its effectiveness has not been tested in nondiabetic individuals with vascular disease.

Methods

Study Participants

Study participants were nondiabetic men and women who were >45 years of age and admitted to 1 of 3 participating hospitals from July 2000 through June 2001 for transient ischemic attack (TIA) or nondisabling ischemic stroke. A nondisabling stroke was recognized when a patient was able to communicate verbally, move the fingers of both hands, and take 3 steps without the assistance of another person. Patients were excluded if their cerebrovascular event was related to trauma, medical instrumentation, or embolism from an
artificial heart valve. Patients were also excluded if they were taking oral corticosteroids or had irreversible medical conditions that were likely to affect short-term survival or their ability to participate in the study protocol. Because insulin sensitivity may be perturbed by the physical stress of illness, patients could not enter the study before 2 months had elapsed since their stroke event.11

Patients who met the preliminary eligibility criteria were invited to undergo testing of insulin sensitivity. Insulin sensitivity was estimated with the Composite Insulin Sensitivity Index described by Matsuda and DeFronzo.12 This composite index is based on insulin and glucose measures during an oral glucose tolerance test. After a 10-hour fast, patients underwent phlebotomy for baseline laboratory tests. They then consumed 75 g glucose orally. Glucose and insulin concentrations were obtained at 30, 60, 90, and 120 minutes after glucose administration. The composite index is calculated as follows:

\[ \text{Composite index} = \frac{10,000/\text{fasting plasma glucose} (\text{mg/dL}) \times \text{fasting plasma insulin} (\mu\text{U/mL})}{\text{mean glucose concentration} (\text{mg/dL}) \times \text{mean insulin concentration} (\mu\text{U/mL})} \]

Higher composite index values indicate greater insulin sensitivity (ie, less insulin resistance). Plasma glucose concentrations were measured by a glucose oxidation method (Glucose Analyzer II, Beckman Instruments) immediately after phlebotomy. Plasma insulin was measured with a commercial radioimmunoassay kit (Linco Research). This assay does not cross-react with human proinsulin.

**Criterion for Impaired Insulin Sensitivity**

There is no accepted, standard criterion for impaired insulin sensitivity based on the composite index or any other measure. For this research, we derived a criterion by analysis of epidemiological data and the distribution of values for the composite index in a population from San Antonio (Tex).12 Epidemiological data suggest that persons in the 20% to 25% of the population with the lowest insulin sensitivity have increased risk for vascular disease, including stroke.13,14 Their insulin sensitivity, furthermore, is comparable to that of patients with diabetes.15 In the population from San Antonio, the lowest third was identified by a composite index value of ≤2.5. This population comprised 62 persons (mean age, 37 years) with normal glucose tolerance who volunteered for metabolic studies. Most participants were Hispanic (personal communication, R.A. DeFronzo, April 26, 2001). The median composite index value was 3.0, with tertiles defined by values of 0 to 2.5, 2.6 to 4.5, and 4.6 to 12.12 Because Hispanic ethnicity is associated with increased risk for impaired insulin sensitivity, this population is likely to have lower composite index values than a white population.16 We estimated that the composite index value demarcating the lower tertile of insulin sensitivity in San Antonio (ie, ≤2.5) will demarcate the lowest 20% in a representative population at average risk for impaired insulin sensitivity. Accordingly, we defined impaired insulin sensitivity by a composite index value of ≤2.5. The Composite Insulin Sensitivity Index was used successfully to measure treatment effect in another trial of pioglitazone.17

In addition to having a composite index score ≤2.5, eligible patients were required to be nondiabetic according to their fasting glucose value at the time of oral glucose tolerance testing. We classified a person as nondiabetic if the glucose value was <7.0 mmol/L (126 mg/dL).18

As a secondary assessment of insulin sensitivity, we calculated the Homeostatic Model Assessment (HOMA). This is a simple measure of insulin sensitivity based on the fasting glucose and insulin concentrations and calculated as follows:

\[ \text{HOMA} = \frac{\text{fasting plasma glucose (mmol/L}) \times \text{fasting plasma insulin} (\mu\text{U/mL})}{22.5} \]

Although it is less accurate than the composite index, it is becoming popular as a more convenient measure. Lower HOMA values indicate greater insulin sensitivity (ie, less insulin resistance).

**Prerandomization Assessment**

Patients who met all eligibility criteria, including impaired insulin sensitivity and fasting glucose <7.0 mmol/L, were invited to participate in the clinical trial. If they consented, they underwent a structured interview and physical examination before randomization. The physical examination included anthropomorphic measures (weight, height), blood pressure, and neurological status assessment (National Institutes of Health Stroke Scale).19 Blood tests included aspartate transaminase, alanine transaminase, alkaline phosphatase, direct bilirubin, indirect bilirubin, creatinine, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, total cholesterol, and triglycerides. C-reactive protein concentration was measured on plasma stored at -20°C for up to 1 year from the date of collection with a latex particle–enhanced immunoturbidimetric assay (Kamiya Biomedical Co).

All patients had to be randomized within 30 days of the baseline oral glucose tolerance test. If >30 days elapsed, patients were required to have a repeated test to establish a pretreatment baseline.

**Randomization**

At the start of the trial, a master schedule of computer-generated random treatment assignments (placebo or pioglitazone) was stored at the Investigational Pharmacy at Yale–New Haven Hospital. Randomization was blocked to equalize treatment assignments after 20 subjects. After confirmation of eligibility, a research associate contacted the investigational pharmacist, who assigned the participant to the next available treatment as specified by the master schedule. The pharmacist then dispensed a full supply of tablets containing pioglitazone 15 mg or matching placebo. Patients were instructed to take 1 pill daily for the first 2 weeks, 2 pills daily for the next 2 weeks, and then 3 pills daily thereafter. Research staff, investigators, and patients were blinded to treatment assignment throughout the study.

**Follow-Up Procedures**

Every 2 weeks, a research nurse telephoned each participant to promote compliance and to assess side effects. As a safety precaution, blood was obtained for measurement of alanine transaminase 2 months after randomization. At 3 months, participants returned to the General Clinical Research Center for a repeated oral glucose tolerance test.

**Statistical Power and Analysis**

The primary research outcome was change in insulin sensitivity index. The sample size of 20 subjects was based on the following assumptions: a mean baseline composite index value of 1.8 among enrolled patients, 40% improvement in the composite index among patients assigned to pioglitazone, and an SD of 0.5 around the mean composite index in the 2 treatment groups at baseline and exit. This baseline composite index of 1.8 is the mean value of the lowest tertile of the composite index among normal subjects studied by Matsuda and DeFronzo.12 The 40% treatment effect was based on previous studies showing that insulin sensitivity is improved by 30% to 50% with troglitazone22,23 and 33% to 43% with pioglitazone.24 Among nondiabetic obese patients, troglitazone increased insulin sensitivity (based on a glucose tolerance test) by 228%.23

Stroke type was classified according to the method used in North American Symptomatic Endarterectomy Trial.25 Hypertension was defined by self-reported history. Obesity was defined as a body mass index >30 kg/m².26

Analyses for all trial outcomes used the intention-to-treat principle. Baseline, exit, and change in insulin sensitivity index in each treatment group were compared through the use of analysis of variance. Patients provided written, informed consent, and the study protocol was approved by Investigational Review boards at all participating institutions. The study was funded by an investigator-initiated grant from Takeda Pharmaceuticals North America. Takeda had no involvement in data collection, data analysis, or report composition. By contract, Takeda could not suppress publication of this report.

**Results**

**Participants**

Between July 2002 and June 2001, we recruited 75 nondiabetic patients with cerebrovascular disease for insulin sensi-
TABLE 1. Baseline Characteristics of Participants

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Pioglitazone Group (n=10)</th>
<th>Placebo Group (n=10)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sociodemographic characteristics</td>
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<td></td>
<td></td>
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<tr>
<td>Age, y</td>
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<tr>
<td>Black</td>
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<tr>
<td>Clinical characteristics</td>
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<td>Myocardial infarction, n</td>
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<td>Hypertension, n</td>
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<tr>
<td>Obesity (BMI &gt;30 kg/m²), n</td>
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<td>3</td>
<td>1.00</td>
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<td>LDL-C (median), mmol/L†</td>
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<td>2.44</td>
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<td>Triglycerides (median), mmol/L†</td>
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<td>Neurological characteristics</td>
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<td>Lacune</td>
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<tr>
<td>NIH Stroke Scale ≥0</td>
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<td>1.00</td>
</tr>
</tbody>
</table>

BMI indicates body mass index; HDL-C, HDL cholesterol; LDL-C, LDL cholesterol; and NIH, National Institutes of Health.

*Continuity-adjusted χ² probability value for comparison of proportions; †t test probability value for comparison of means; Wilcoxon rank-sum test for comparison of medians.

†One subject in pioglitazone group did not have HDL, LDL, or triglycerides measured.

The mean composite index increased from 2.1 to 3.2 among patients assigned to pioglitazone compared with a decrease from 1.8 to 1.7 among patients assigned to placebo (P=0.0003). The mean proportional changes in the pioglitazone and placebo groups were 62% and −1%, respectively (P=0.0006) (Table 2). In addition to the composite index, we calculated mean change in HOMA. A fall in the HOMA score indicates an increase in insulin sensitivity. The mean HOMA score declined from 4.2 to 2.8 among patients assigned to pioglitazone compared with an increase from 4.6 to 5.0 among patients assigned to placebo (P=0.01 for comparison of mean change). The mean proportional changes in the pioglitazone and placebo groups were −29% and 10%, respectively (P=0.01).

To illustrate the effects of pioglitazone and placebo on concentrations of glucose and insulin, the Figure shows mean change in both measures from baseline to exit at all times during oral glucose tolerance testing. The mean decline in insulin and glucose was greater for patients assigned to pioglitazone compared with placebo at all time points. Among patients who received placebo, the mean change in insulin and glucose measures was nearly zero at all times.
points except for 120 minutes when the mean change in insulin was 51.1 μU/mL. This last result was heavily influenced by 1 subject who had a recurrent stroke 5 days before the exit oral glucose tolerance test. His insulin concentrations at baseline and 30, 60, 90, and 120 minutes after glucose were 32, 275, 183, 253, and 645 μU/mL. When this patient is excluded, the mean change in 120-minute insulin concentration from baseline to exit among placebo recipients was 1.3 μU/mL. Changes in both measures of insulin sensitivity were still significantly greater in the pioglitazone group compared with the placebo group after exclusion of this subject (5.6% mean proportional change in composite index for the placebo group, \( P = 0.001 \) for comparison with pioglitazone group, 1.1% mean proportional change in HOMA for placebo group, \( P = 0.01 \) for comparison with pioglitazone group).

As expected, we observed no significant difference between treatment groups for change in systolic blood pressure, diastolic blood pressure, LDL cholesterol, HDL cholesterol, or triglyceride concentration. Our study was not powered to detect changes in these measures of the magnitude reported in current literature (eg, 5–mm Hg decline in systolic blood pressure and 36-mg/dL decline in triglycerides). Mean C-reactive protein concentration declined from 0.30 to 0.20 mg/L (−32%) among patients assigned to pioglitazone compared with an increase of 0.37 to 1.24 mg/L among patients assigned to placebo (\( P = 0.27 \) for comparison of mean change). One patient in the placebo group demonstrated a very large increase in C-reactive protein (from 0.09 to 8.36 mg/dL). Eliminating this outlier resulted in a mean C-reactive protein increase among the placebo group from 0.41 to 0.45 mg/L and a reduction to \( P = 0.06 \) for the comparison of mean change between treatment groups. (Eliminating the outlier resulted in a more normal distribution of change scores. Results of the \( t \) test were confirmed with the Wilcoxon rank-sum test, which yielded an exact value of \( P = 0.05 \) with the outlier included and \( P = 0.09 \) with the outlier excluded.)

Adherence to the study medication, as determined by pill counts, was high in both treatment groups. Patients assigned to pioglitazone took 88.5% of their pills. Patients assigned to placebo took 94.4% of their pills. No patients were lost to follow-up.

The study medication was well tolerated, with no patient permanently discontinuing his or her treatment. Reported side effects, however, were more common among pioglitazone patients, especially for nausea (3 versus 0), self-reported edema (2 versus 0), muscle aches (2 versus 0), sore throat (2 versus 0), and dizziness (2 versus 0). A total of 10 patients on pioglitazone and 4 patients on placebo reported any side effect. The median weight gain was 2 lb among patients receiving pioglitazone compared with 1 lb among patients receiving placebo.

**Discussion**

The results of this study indicate that pioglitazone given at a dose of 45 mg/d improves insulin sensitivity among nondiabetic patients with recent TIA or ischemic stroke and impaired insulin sensitivity. Compared with placebo, pioglitazone therapy was associated with a small, nonsignificant decrease in mean fasting plasma glucose but a large, significant decrease in mean fasting plasma insulin concentration.

Our findings are consistent with other published randomized trials of thiazolidinedione therapy in nondiabetic patients with gestational diabetes, obesity, polycystic ovary disease. In these studies, all involving troglitazone, active therapy was associated with a 23% to 128% increase in insulin sensitivity. Ours is the first study, however, to examine the effect of pioglitazone in nondiabetic patients and to enroll patients on the basis of vascular disease and impaired insulin sensitivity.

In this small, short-duration study, we observed no significant effect of pioglitazone on blood pressure or serum lipids, but we did observe a favorable effect on C-reactive protein that approached statistical significance. Other studies among diabetic patients suggest that thiazolidinediones may lower blood pressure and triglycerides and raise HDL cholesterol. These effects, however, are small compared with the effect on insulin sensitivity and could not have been detected in our study because of a lack of statistical power.
C-reactive protein, a marker for systemic inflammation, has been associated with increased risk for TIA, stroke, and other manifestations of vascular disease.\textsuperscript{30,31} The effect of thiazolidinediones on markers of inflammation, however, has not been previously studied in randomized, placebo-controlled trials. In 1 trial comparing metformin with troglitazone, however, both agents reduced C-reactive protein after 4 months of therapy.\textsuperscript{32} If confirmed, our finding that pioglitazone reduces C-reactive protein would suggest a mechanism, in addition to improving insulin sensitivity, by which this agent may have a favorable effect on risk for vascular disease.

Pioglitazone therapy was well tolerated in this study, although symptoms of nausea, edema, myalgia, sore throat, and dizziness were more commonly reported among patients assigned to pioglitazone than among patients assigned to placebo. Only 3 placebo-controlled trials of pioglitazone, including 790 patients, have been published in the peer-review literature.\textsuperscript{17,33,34} Most of the safety data are therefore from unpublished trials sponsored by the manufacturer\textsuperscript{35} (Takeda Pharmaceuticals America, Lincolnshire, Ill). In these trials of patients with type 2 diabetes, the 45-mg dose of pioglitazone was associated with a median weight gain of 2.6 kg, and edema was reported in 4.8% of patients receiving pioglitazone compared with 1.2% of patients receiving placebo. For most other adverse events, rates were similar among treatment groups.

Although our sample size was small, it was designed to provide adequate power (80%) to detect a clinically significant effect of pioglitazone on insulin sensitivity. The observed effect (62% proportional change in the composite index) exceeded our proposed effect (40%), suggesting that our sample size calculation was conservative. The stability of our findings is supported by the results of an analysis in which we eliminated a placebo recipient who demonstrated marked insulin resistance during the exit test. A larger sample size would have provided a more precise estimate of the treatment effect but not a more rigorous test of the research hypothesis.

Because pioglitazone is effective and safe for increasing insulin sensitivity in patients with cerebrovascular disease who have impaired insulin sensitivity, our results suggest that a larger trial with clinical end points is feasible. Finding patients for such a trial would not be difficult. In this research, we found that 50% of nondiabetic patients with cerebrovascular disease had impaired insulin sensitivity. This is consistent with recent estimates that 24% of adults in the United States have the metabolic syndrome (in which impaired insulin sensitivity is the basic defect)\textsuperscript{36} and that impaired insulin sensitivity is increased in older age, hypertension, and vascular disease. Because the prevalence of impaired insulin sensitivity is high among patients with stroke, the determination that thiazolidinediones improve outcome after stroke would have a major effect on the morbidity and mortality of this disease.

Since this article was submitted for publication, Haffner and colleagues\textsuperscript{37} have published evidence that thiazolidinedione therapy (rosiglitazone) reduces C-reactive protein among patients with type 2 diabetes. Our study provides further evidence for this drug effect and extends the finding to nondiabetic patients.


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