Attenuation of Progression of Insulin Resistance in Patients With Coronary Artery Disease by Bezafibrate

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Background: Development of insulin resistance (IR) may be important in the pathogenesis of both metabolic syndrome and type 2 diabetes mellitus. Few data are available regarding the short-term efficacy of the peroxisome proliferator–activated receptor ligand bezafibrate on IR, and its long-term effect is unknown. The present analysis aimed to investigate the effect of bezafibrate on IR in patients with coronary artery disease enrolled in the Bezafibrate Infarction Prevention Study.

Methods: Metabolic and inflammatory parameters were analyzed from stored frozen plasma samples obtained from patients who completed a 2-year, randomized, double-blind, placebo-controlled study. The homeostatic indexes of IR (HOMA-IRs) were calculated according to the homeostasis model of assessment.

Results: Both the patients taking bezafibrate (n = 1262) and those taking placebo (n = 1242) displayed similar baseline characteristics. The HOMA-IRs significantly correlated at baseline and during follow-up with glucose (r = 0.35 and 0.31, respectively) and triglycerides (r = 0.16 and 0.19, respectively). In a subgroup of 351 patients with diabetes, HOMA-IR at baseline was 88% higher than in their counterparts with normal glucose levels (P < .001). In the placebo group, during follow-up there was a significant 34.4% rise in HOMA-IR. In contrast, in the bezafibrate group there was only a nonsignificant 6.6% change in HOMA-IR. The intergroup differences in percentage changes of HOMA-IR were in favor of bezafibrate (P < .001).

Conclusions: In patients with coronary artery disease enrolled in our study, as represented by the placebo group, HOMA-IR increased over time. During the 2 years of the follow-up, bezafibrate significantly attenuated this process.

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DEVELOPMENT OF INSULIN resistance (IR) has been considered an important stage in the pathogenesis of metabolic syndrome, diabetes, and probably coronary artery disease (CAD), in which its effect is partially mediated by traditional cardiovascular risk factors. Moreover, IR has several possible pleiotropic effects, including dyslipidemia and direct promotion of atherosclerosis.

The fibric acid derivative bezafibrate is a nonselective ligand for peroxisome proliferator–activated receptor α (PPAR-α) with triglyceride-lowering and high-density lipoprotein cholesterol (HDL-C)–raising effects, resulting in decreased systemic availability of fatty acid and diminished fatty acid uptake by muscle. We have recently shown that the long-term use of bezafibrate in patients with CAD can reduce the incidence of diabetes. We hypothesized that this effect may be based on an improvement in insulin sensitization. Currently, few data are available regarding the short-term efficacy of bezafibrate on IR in clinical settings, and its long-term effect is unknown. The present study aimed to investigate the effect of bezafibrate on IR in patients with CAD enrolled in the Bezafibrate Infarction Prevention (BIP) Study.

METHODS

Metabolic and inflammatory parameters were analyzed from stored frozen plasma samples obtained from patients who completed a 2-year, randomized, double-blind, placebo-controlled prospective study. The major inclusion and exclusion criteria for the BIP study, as well as the ethical guidelines, have been previously reported. In brief, inclusion criteria for men and women included the following: age 45 to 74 years, history of myocardial infarction no less than 6 months and not more than 5 years before enrollment into the study, and/or stable angina supported by coronary angiography and/or radionuclear studies or standard exercise tests. In addition, a lipid profile of serum total cholesterol level between 180 and 250 mg/dL (4.66-6.48 mmol/L), low-density lipoprotein cholesterol (LDL-C) level of 180 mg/dL or less (<4.66 mmol/L), triglycerides (≤160 mg/dL [≤4.14 mmol/L] for patients younger than 50 years), HDL-C level
of 45 mg/dL or less (≤1.17 mmol/L), and triglyceride level of 150 mg/dL or less (≤1.7 mmol/L) was required. The major exclusion criteria for the BIP study were as follows: permanent pacemaker implantation, cerebrovascular disease, chronic hepatic or renal disease, peripheral vascular disease, malignant diseases, estrogen replacement therapy, type 1 diabetes mellitus, and current use of a lipid-modifying drug. The study was a multicenter prospective trial, performed in 18 university-affiliated hospitals. The trial was approved by the Helsinki Committee of each center and the central national Helsinki Committee. There were 3122 eligible patients who were included in the main BIP study. Among them, 81 died during the 2-year follow-up, and in 337, data were missing regarding baseline and/or follow-up level of fasting blood glucose (FBG) and/or insulin; all of these patients were excluded from this analysis. Thus, the final study sample for the current analysis included 2904 patients.

The patients received either 400 mg of bezafibrate retard or placebo once a day. Patients continued their prescribed medications for cardiac and other conditions except for lipid-lowering drugs. Routine visits to the clinics were scheduled bi-monthly for study medication distribution and compliance assessment by tablet count, every 4 months for clinical evaluation, and every year for blood analyses.

CRITERIA OF DIABETES AND IMPAIRED FBG

Table 1. Baseline Characteristics of the Study Population*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Bezafibrate (n = 1262)</th>
<th>Placebo (n = 1242)</th>
<th>P</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>60.2 ± 6.8</td>
<td>60.3 ± 6.7</td>
<td>.80</td>
<td></td>
</tr>
<tr>
<td>Body mass index</td>
<td>26.6 ± 3.3</td>
<td>26.6 ± 3.2</td>
<td>.90</td>
<td></td>
</tr>
<tr>
<td>Men, No. (%)</td>
<td>1152 (91)</td>
<td>1132 (91)</td>
<td>.90</td>
<td></td>
</tr>
<tr>
<td>Diabetes, No. (%)</td>
<td>168 (13.3)</td>
<td>183 (14.7)</td>
<td>.20</td>
<td></td>
</tr>
<tr>
<td>Past myocardial infarction, No. (%)</td>
<td>978 (78)</td>
<td>954 (77)</td>
<td>.60</td>
<td></td>
</tr>
<tr>
<td>Angina, No. (%)</td>
<td>702 (56)</td>
<td>702 (57)</td>
<td>.70</td>
<td></td>
</tr>
<tr>
<td>NYHA class ≥2, No. (%)</td>
<td>290 (24)</td>
<td>309 (25)</td>
<td>.70</td>
<td></td>
</tr>
<tr>
<td>Hypertension, No. (%)</td>
<td>393 (31)</td>
<td>426 (34)</td>
<td>.10</td>
<td></td>
</tr>
<tr>
<td>Current or past smokers, No. (%)</td>
<td>896 (71)</td>
<td>875 (71)</td>
<td>.90</td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>134 ± 18</td>
<td>133 ± 18</td>
<td>.20</td>
<td></td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>81.1 ± 6.9</td>
<td>80.6 ± 6.9</td>
<td>.10</td>
<td></td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>70.9 ± 9.0</td>
<td>69.8 ± 9.0</td>
<td>.60</td>
<td></td>
</tr>
<tr>
<td>Glucose, mg/dL</td>
<td>100 ± 17</td>
<td>100 ± 17</td>
<td>.40</td>
<td></td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>212 ± 17</td>
<td>214 ± 18</td>
<td>.40</td>
<td></td>
</tr>
<tr>
<td>HDL-C, mg/dL</td>
<td>34.6 ± 5.5</td>
<td>33.7 ± 5.3</td>
<td>.40</td>
<td></td>
</tr>
<tr>
<td>LDL-C, mg/dL</td>
<td>149 ± 16</td>
<td>150 ± 15</td>
<td>.50</td>
<td></td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>144 ± 51</td>
<td>145 ± 50</td>
<td>.80</td>
<td></td>
</tr>
<tr>
<td>CRP, mg/dL</td>
<td>5.25 ± 5.8</td>
<td>5.67 ± 7.6</td>
<td>.10</td>
<td></td>
</tr>
<tr>
<td>Fibrinogen, mg/dL</td>
<td>348 ± 70</td>
<td>349 ± 73</td>
<td>.60</td>
<td></td>
</tr>
<tr>
<td>Insulin, µIU/mL</td>
<td>5.32 ± 4.4</td>
<td>5.51 ± 5.4</td>
<td>.30</td>
<td></td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>1.35 ± 1.2</td>
<td>1.41 ± 1.5</td>
<td>.20</td>
<td></td>
</tr>
<tr>
<td>HOMA-BCF</td>
<td>59.6 ± 5.7</td>
<td>60.0 ± 6.2</td>
<td>.80</td>
<td></td>
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</tbody>
</table>

Table 1. Baseline Characteristics of the Study Population*

Abbreviations: CRP, C-reactive protein; HDL-C, high-density lipoprotein cholesterol; HOMA-BCF, homeostatic index of percentage of β-cell function; HOMA-IR, homeostatic index of insulin resistance; LDL-C, low-density lipoprotein cholesterol; NYHA, New York Heart Association.

*Data are presented as mean ± SD unless otherwise indicated.
†Calculated as weight in kilograms divided by height in meters squared.
‡Calculated as weight in kilograms divided by height in meters squared.

The diagnosis of diabetes at baseline was made by the referring physician and confirmed in the framework of a university hospital based on the reported history and medical records. In addition, in accordance with the American Diabetes Association classification,16 we classified all patients with FBG levels at baseline of 126 mg/dL or higher (≥7 mmol/L) or receiving any type of pharmacologic antidiabetic treatment as diabetic patients. In patients without diabetes at baseline, we defined glucose levels of 110 to 125 mg/dL (6.1-6.9 mmol/L) as impaired fasting glucose (IFG). There were 351 patients with diabetes. 247 patients with IFG, and 1906 patients without diabetes or IFG at baseline.

LABORATORY ANALYSIS

Detailed data on laboratory methods were given in a previous report.13 A central laboratory performed all biochemical determinations. For the purpose of the present study, plasma citrate samples, which had been obtained at baseline from each study participant and stored at −70°C, were thawed and assayed for insulin level (Immulate 2000 analyzer, Diagnostic Products Corporation, Los Angeles, Calif) with the manufacturer’s reagents—solid-phase, 2-site, chemiluminescent enzyme–labeled immunometric assay. This assay uses monoclonal and polyclonal antibodies for the capture and detection, respectively, of insulin. The interobserver and intraobserver variabilities of the insulin test in our study were 6.1% and 7.9%, respectively.

The homeostatic index of IR (HOMA-IR) and the homeostatic index of percentage of β-cell function (HOMA-BCF) were calculated according to the homeostasis model of assessment as follows17:

HOMA-IR = Fasting Insulin (µIU/mL) × FBG (mmol/L)/22.5 (or FBG [mg/dL]/405)
HOMA-BCF = 20 × Fasting Insulin (µIU/mL)/[FBG (mg/dL)/18 – 3.3].

STATISTICAL ANALYSIS

Data were analyzed using SAS statistical software (SAS Institute Inc, Cary, NC). Continuous variables at baseline were presented as mean ± SD. Comparisons between groups were made using χ² tests for discrete variables and the t test or Wilcoxon rank sum test for continuous variables.

Pearson correlation coefficients were calculated to examine the relationships between metabolic and inflammatory analytes at baseline and changes during follow-up for the study population as a whole. Log-transformed data were used for determination of Pearson correlation coefficients.

Because of their skewed distribution, insulin, HOMA-IR, and HOMA-BCF were presented as geometric mean (GM) and 95% confidence interval (CI). For the assessment of differences after 2 years between the bezafibrate and placebo groups, an analysis of covariance with terms for treatment and baseline values was used based on log-transformed data. Percent changes from baseline to 2 years were presented as GM and interquartile range and compared using the Wilcoxon rank sum test. P <.05 (2-sided) was considered statistically significant.

RESULTS

BASELINE DATA

Our population included 2 groups: the bezafibrate group (1262 patients) and the placebo group (1242 patients). Patients in the placebo and bezafibrate groups were well balanced in terms of clinical and laboratory baseline characteristics and concomitant medications (Table 1). The
study groups were similar in regard to age, sex, and the prevalence of the most relevant cardiovascular diseases and risk factors (myocardial infarction in the past, hypertension, heart failure, peripheral vascular disease, anginal syndrome, and chronic obstructive pulmonary disease). No significant differences between the groups were found for the following values: all types of cholesterol, apolipoproteins, blood pressure, heart rate, FBG, triglycerides, fibrinogen, C-reactive protein, creatinine, fasting insulin, HOMA-IR, HOMA-BCF, and body mass index (BMI; calculated as weight in kilograms divided by the square of height in meters). There were no differences between the placebo and bezafibrate groups in the proportion of patients receiving all types of cardiovascular drugs. Nitrates (50%), calcium antagonists (51%), β-blockers (39%), antiplatelet drugs (70%), diuretics (13%), and angiotensin-converting enzyme inhibitors (12%) were the most commonly used medications. The use of all types of cardiovascular drugs did not change significantly during the 2-year follow-up period.

**PATIENTS WITH DIABETES AND IFG**

In the subgroup of 351 patients with diabetes (168 taking bezafibrate and 183 taking placebo), HOMA-IR (presented as GM [95% CI]) was significantly higher (Table 2), whereas HOMA-BCF was lower than in patients with normal glucose levels (<110 mg/dL [≤0.26 mmol/L]): 1.49 (1.30-1.71) vs 0.83 (0.78-0.88) and 28.2 (24.4-32.6) vs 46.1 (43.4-48.9), respectively, in the bezafibrate group (P<.001 for both) and 1.62 (1.41-1.86) vs 0.83 (0.78-0.88) and 30.5 (26.6-35.1) vs 45.8 (43.1-48.6), respectively, in the placebo group (P<.001 for both). In 247 patients with IFG (glucose level, 110-125 mg/dL [6.11-6.94 mmol/L]), HOMA-IR and HOMA-BCF presented intermediate values: 1.27 (1.09-1.49) and 30.5 (26.1-35.7), respectively, in the bezafibrate group and 1.52 (1.29-1.78) and 36.6 (31.2-43.1), respectively, in the placebo group. Pooling the bezafibrate and placebo groups together, in patients with diabetes, HOMA-IR was 88% higher and HOMA-BCF was 36% lower than in their counterparts with normal glucose levels (P<.001 for both).

**INTERRELATIONSHIP OF BASELINE METABOLIC AND INFLAMMATORY VALUES**

The natural logarithm (ln) of HOMA-IR at baseline was significantly positively correlated with ln FBG (r = 0.35), ln BMI (r = 0.30), ln triglycerides (r = 0.16), and ln C-reactive protein (r = 0.13) and inversely correlated with ln HDL-C (r = -0.11). Similar correlations were shown for insulin. Baseline ln HOMA-BCF was correlated positively with BMI (r = 0.20) and negatively with ln FBG (r = -0.27).

**CORRELATIONS BETWEEN CHANGES IN METABOLIC AND INFLAMMATORY VALUES DURING FOLLOW-UP**

The change in ln HOMA-IR from baseline to 2 years of follow-up was significantly positively correlated with changes in ln HOMA-BCF (r = 0.82), ln FBG (r = 0.31), ln triglycerides (r = 0.19), ln fibrinogen (r = 0.17), ln total cholesterol (r = 0.13), and ln BMI (r = 0.11) and inversely correlated with changes in ln HDL-C (r = -0.13). The change in ln HOMA-BCF was positively correlated with changes in ln insulin (r = 0.90) and inversely correlated with changes in ln FBG cholesterol (r = -0.26). There was a relatively weak but significant correlation between the percent changes in ln BMI, ln insulin, ln total cholesterol, and ln triglycerides.

**EFFECT OF TREATMENT ON CHANGES OF INSULIN, FBG, HOMA-IR, HOMA-BCF, AND BMI**

Changes in insulin, HOMA-IR, and HOMA-BCF from baseline to 2 years of follow-up (bezafibrate vs placebo) are given in Table 3 and Table 4. No significant differences between the groups were found for these parameters at baseline. During follow-up, in the placebo group there was a significant 30.3% rise in GM of percentage change in insulin level, 15.2% in FBG, and 34.4% in HOMA-IR. In contrast, changes in the bezafibrate group were nonsignificant (7.8%, 2.1%, and 6.6%, respectively). The intergroup differences in percentage changes were in favor of bezafibrate (P<.001 for all). The HOMA-BCF values have increased during follow-up in patients of both groups but were more pronounced in patients taking placebo (P<.02). The BMI during 2-year follow-up increased significantly and similarly in patients taking bezafibrate and those taking placebo (1.4% and 1.2%, respectively; P<.001 for both).

There are 2 major findings in our study. First, the obtained data demonstrated that in patients with CAD, as represented by the placebo group, HOMA-IR increases over time. Second, the PPAR ligand bezafibrate can sig-

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**Table 2. Insulin, HOMA-IR, and HOMA-BCF at Baseline in Accordance With Glucose Level or Presence of Diabetes***

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Normal Glucose Level (n = 1906)</th>
<th>IFG (n = 247)</th>
<th>Diabetes (n = 351)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin, µIU/mL</td>
<td>3.63 (3.48-3.79)</td>
<td>4.86 (4.35-5.44)</td>
<td>4.98 (4.53-5.47)</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>0.83 (0.80-0.87)</td>
<td>1.39 (1.24-1.55)</td>
<td>1.56 (1.41-1.72)</td>
</tr>
<tr>
<td>HOMA-BCF</td>
<td>45.9 (44.0-47.9)</td>
<td>33.4 (29.8-37.4)</td>
<td>29.4 (26.6-32.5)</td>
</tr>
</tbody>
</table>

Abbreviations: HOMA-BCF, homeostatic index of percentage of β-cell function; HOMA-IR, homeostatic index of insulin resistance; IFG, impaired fasting glucose.

*Conversion factor: To convert insulin to picomoles per liter, multiply by 6.946.

*Data are presented as geometric mean (95% confidence interval) for bezafibrate and placebo groups pooled together. P for trend <.001 for all groups.
correlation between BMI, both at baseline and during follow-up with HOMA-IR. Because BMI values during the 2-year follow-up have increased slightly but significantly in patients taking bezafibrate (1.4%) and those taking placebo (1.2%), this mechanism should be taken into consideration. Second, the BIP study population was characterized by a low baseline HDL-C level (since it was one of the inclusion criteria). Consistent with previous reports, our study has shown that HDL-C and its longitudinal changes are inversely associated with IR and hyperinsulinemia. These observations may partially explain the potential beneficial effect of bezafibrate. Third, it has been shown that the use of \(\beta\)-blockers and diuretics, cardiovascular drugs widely used in patients with CAD, may be associated with impaired insulin sensitivity. In the current analysis, 39% of the patients were taking \(\beta\)-blockers and 13% were taking diuretics, and their use did not change significantly during the 2-year follow-up period. One could presume that long-term metabolic effects of \(\beta\)-blockers and diuretics may be reflected by longitudinal changes in HOMA-IR.

Some of the patients with CAD, particularly those with more advanced myocardial dysfunction, diminish their exercise activity and are prone to development of IR. Moreover, impaired myocardial performance results in activation of the neurohormonal (mainly sympathetic) systems. Therefore, higher catecholamine levels can be another reason for the progression of IR in some of the patients with CAD.

Fibrates are the pharmacologic ligands for PPAR-\(\alpha\), which controls primarily the expression of genes involved in lipid metabolism. However, PPAR-\(\alpha\) (in addition to PPAR-\(\gamma\)) also plays a role in glucose homeostasis and in the development of IR. Some of the patients with CAD, particularly those with more advanced myocardial dysfunction, diminish their exercise activity and are prone to development of IR. Moreover, impaired myocardial performance results in activation of the neurohormonal (mainly sympathetic) systems. Therefore, higher catecholamine levels can be another reason for the progression of IR in some of the patients with CAD.

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brate on insulin sensitivity were beneficial or neutral. The data regarding favorable effects of bezafibrate on glucose metabolism are consistent. We reported earlier that bezafibrate reduces the incidence of myocardial infarction in subgroups of patients with metabolic syndrome during long-term follow-up. This may be explained by observations that bezafibrate operated as a pan-agonist for all 3 PPARs (α, β/δ, and γ) isoforms. Therefore, it has the potential to directly improve insulin sensitization via PPAR-γ activation.

To the best of our knowledge, the present study is the first large-scale report regarding the long-term effect of bezafibrate on IR. Moreover, our placebo group (1242 patients) represents one of the first large populations in which long-term changes of IR in patients with CAD were evaluated. However, whether our results could be generalized to other populations of patients with CAD remains to be determined. Furthermore, our work was the secondary analysis of the BIP study, which was not designed to evaluate longitudinal changes in IR. Therefore, further studies are required to confirm our observation that IR in patients with CAD increases over time.

In conclusion, in patients with CAD enrolled in our study, as represented by the placebo group, HOMA-IR increased over time. During the 2 years of follow-up, bezafibrate significantly attenuated this process.

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Author Contributions: Dr Tenenbaum had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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