Pioglitazone Reduces Atherogenic Index of Plasma in Patients with Type 2 Diabetes

Meng H. Tan,1* Don Johns,1 and N. Bradley Glazer2

Background: Insulin resistance is often associated with increased triglyceride (TG) and decreased HDL-cholesterol (HDL-C) concentrations and increased small LDL particles. The Atherogenic Index of Plasma (AIP) has recently been proposed as a marker of plasma atherogenicity because it is increased in people at higher risk for coronary heart disease and is inversely correlated with LDL particle size. We studied the effect of pioglitazone, a thiazolidinedione that reduces insulin resistance, on the AIP of patients with type 2 diabetes.

Methods: The data for the analysis of AIP in this report were obtained from four randomized, double-blind, multicenter, parallel-group, placebo-controlled clinical trials. Pioglitazone was used as monotherapy in one study and in combination therapy in three studies. Fasting glucose, insulin, HDL-C, and TGs plus glycohemoglobin (HbA1C) were measured at baseline and various points during each study.

Results: Patients in this study population with type 2 diabetes had high AIP values at baseline. Pioglitazone treatment significantly decreased AIP from baseline in each of the study groups. Pioglitazone treatment groups had a significantly lower AIP compared with their respective placebo controls. Finally, AIP was inversely and significantly correlated with measures of insulin sensitivity, such as the homeostasis model assessment and quantitative insulin sensitivity check index. In contrast, AIP was not significantly correlated with HbA1C.

Conclusions: Pioglitazone reduced AIP when used as monotherapy or in combination therapy with sulfonylurea, metformin, or insulin. AIP was inversely correlated with measures of insulin sensitivity.

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Materials and Methods

Patients
The data for the analysis of AIP in this report were obtained from four randomized, double-blind, multicenter, parallel-group, placebo-controlled clinical trials conducted in the United States (7–10). Because all four studies have been reported previously, we will provide only brief outlines of the studies. Inclusion criteria for these studies included (a) diagnosis of type 2 diabetes mellitus based on diagnostic criteria of the National Diabetes Data Group; (b) age 30–75 years; (c) glycohemoglobin (HbA1C) ≥8.0% at baseline (≥7.0% for study 001); (d) fasting plasma glucose (FPG) ≥7.8 mmol/L; (e) fasting C-peptide ≥0.331 nmol/L; and (f) body mass index of 25–45 kg/m².

One study (study 001) examined the efficacy of pioglitazone as monotherapy, and three studies examined the efficacy of pioglitazone when added to sulfonylurea (study 010), metformin (study 027), or insulin (study 014) therapy, respectively. In each study, patients received a single-blind placebo for 5–10 weeks before randomization to allow washout of previous antihyperglycemic medications or to stabilize the dose of companion medication in the combination-therapy studies. Brief descriptions of the studies are presented in Table 1.

FPG, fasting serum insulin, and fasting serum lipids (total cholesterol, HDL-C, and TGs) were measured at a central laboratory (Covance) as described previously (7–10). Insulin sensitivity was calculated by the homeostasis model assessment (HOMA-S) and by the quantitative insulin sensitivity check index (QUICKI) in studies 001, 010 and 027. Values for HOMA-S were derived from fasting serum insulin and FPG and calculated using a computer program (11). QUICKI was calculated as 1/(log₁₀ fasting serum insulin + log₁₀ fasting blood glucose) (12).

Statistical Analysis
Each study was analyzed separately. AIP was computed for each patient at baseline and at each subsequent visit according to the following equation:

\[
\text{AIP} = \log(\text{TG/HDL-C})
\]

with units for TG and HDL-C in mmol/L.

For missing post-baseline values, the previous post-baseline observation was used in a last-observation-carried-forward method. The statistical model used for analysis was a single slope analysis of covariance

\[
y_{ijk} = \mu + \tau_i + \rho_j + \beta x_{ijk} + \epsilon_{ijk}
\]

where \(y_{ijk}\) is the response (change in AIP) of the \(k\)th patient on the \(i\)th treatment at the \(j\)th center; \(\mu\) is the overall mean; \(\tau_i\) is the effect of the \(i\)th treatment; \(\rho_j\) is the effect of the \(j\)th center; \(\beta\) is the linear regression coefficient representing the dependence of \(y_{ijk}\) on \(x_{ijk}\), the baseline value of the response variable; and \(\epsilon_{ijk}\) is the residual error term. Adjusted (least-squares) treatment means were obtained from the model. Within-group changes from baseline were tested with Student t-tests. Each of the pioglitazone treatments was compared with placebo. In studies with more than two treatment groups, Dunnett’s procedure was used to adjust for multiple comparisons between pioglitazone and placebo. An analysis of the TG/HDL ratio was performed, using the same statistical model.

The fundamental assumption for analysis of variance (covariance) is that the underlying distribution of the residual errors is gaussian; thus, to compare the results of the AIP analysis with analysis of the TG/HDL-C ratio, an analysis of the residual errors was conducted and normal probability plots for each model were constructed. The correlation between standardized residuals and the expected residuals formed the basis of each comparison.

The correlation between AIP and glycemic control indices (HbA1C and FPG) and measures of insulin sensitivity (HOMA-S and QUICKI) were examined within pioglitazone-treated patients by use of Pearson correlation coefficients.

Results

Baseline Characteristics
The baseline patient characteristics have been reported previously in detail (7–10). At baseline, AIP values were similar between the placebo and pioglitazone groups (Table 1).

AIP Results
A summary of the AIP results is shown in Table 1. All pioglitazone treatments had statistically significant decreases from baseline in AIP. In addition, pioglitazone treatment groups were statistically significant from their respective placebo (or active controls) controls in reducing AIP.

A comparison of overall \(P\) values from analyses of AIP and TG/HDL-C are shown in Table 2. The overall \(P\) values for drug effect were lower than those of the TG/HDL-C analyses in three of the four studies. In addition, normal probability plots showing the relationship of the residual error to the expected residuals from a gaussian distribution are shown in Fig. 1. A straight line and high \(r^2\) value indicate adherence to the assumption of an underlying gaussian distribution. The correlations between standardized and expected residuals were higher in each study for AIP than for TG/HDL-C. The higher correlations and normal probability plots indicated that the AIP analyses better met the fundamental assumption for analysis of variance, i.e., that residual error terms have a gaussian distribution.

The changes in glycemic control (HbA1C and FPG) for the intent-to-treat sample in each of the four studies have been reported previously (7–10). In studies 001 (monotherapy), 010 (combination with sulfonylurea), and 027 (combination with metformin), pioglitazone increased insulin sensitivity as calculated by HOMA-S and QUICKI. The correlations between AIP and glycemic control indi-
AIP was significantly correlated with FPG. Study (14) was a significant independent predictor of CHD (13), indicating good predictive value for future cardiovascular events. Changes in cholesterol/HDL-C and LDL-C/HDL-C molar ratios have been used to predict CHD risk. The total compositions of lipids (LDL-C, HDL-C, and TGs), molar ratios (TG/HDL-C and LDL-C/HDL-C), and particle size (LDL and HDL) have been used to predict CHD risk. The total cholesterol/HDL-C and LDL-C/HDL-C molar ratios have good predictive value for future cardiovascular events (13). Another molar ratio, log TG/HDL-C, is also a significant independent predictor of CHD (14). In the study by Gaziano et al. (14), compared with those in the lowest quartile, those in the highest quartile had a 16.0-fold increased risk of myocardial infarction.

Log TG/HDL-C was further characterized by Dobia and Frohlich (6) into log(TG/HDL-C). They called it FERHDL, which is increased in patients at risk for or with CHD (15). A predominance of small HDL3b,c particles increases FERHDL, whereas increased HDL2b particles decrease it (16); and (c) there was a significant inverse correlation between LDL particle size and FERHDL (r = −0.82) and AIP (r = −0.78). Patients with small, dense LDL particles are at higher risk for CHD (17). Patients with type 2 diabetes have the highest AIP (6); they also have a higher FERHDL compared with nondiabetic individuals, and there is a direct correlation between FERHDL and waist:hip ratio in these patients (18). In addition, they are more likely to have a predominance of small, dense LDL particles compared with nondiabetic controls (19). All of these factors suggest that AIP is a suitable marker for plasma atherogenicity in patients with type 2 diabetes. We provide new information on the changes in AIP in patients with type 2 diabetes treated with pioglitazone.

We also demonstrated by use of normal probability plots and correlations between residual error and expected residual error terms that AIP is preferable to the TG/HDL-C ratio for use in statistical analyses such as analysis of covariance for comparing treatments. AIP is, of course, a transformation of TG/HDL-C that better meets the assumption of normality of the errors in the statistical model being used to describe the treatment effects than does the untransformed variable.

Cross-sectional studies have reported that patients with type 2 diabetes and cardiovascular disease have fasting hyperinsulinemia compared with those without cardiovascular disease (20). Because hyperinsulinemia is

Table 1. Summary of change from baseline in AIP.

<table>
<thead>
<tr>
<th>Monotherapy (study 001)</th>
<th>n</th>
<th>Baseline</th>
<th>Change from baseline</th>
<th>SE</th>
<th>P vs baseline*</th>
<th>P vs placebob</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>79</td>
<td>0.34</td>
<td>−0.04</td>
<td>0.021</td>
<td>0.0816</td>
<td></td>
</tr>
<tr>
<td>15 mg Pio*</td>
<td>79</td>
<td>0.38</td>
<td>−0.12</td>
<td>0.021</td>
<td>0.0001</td>
<td>0.0124</td>
</tr>
<tr>
<td>30 mg Pio</td>
<td>83</td>
<td>0.35</td>
<td>−0.12</td>
<td>0.020</td>
<td>0.0001</td>
<td>0.0169</td>
</tr>
<tr>
<td>45 mg Pio</td>
<td>77</td>
<td>0.36</td>
<td>−0.13</td>
<td>0.021</td>
<td>0.0001</td>
<td>0.0034</td>
</tr>
<tr>
<td>Combination with SU (study 010)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo + SU</td>
<td>175</td>
<td>0.30</td>
<td>0.01</td>
<td>0.013</td>
<td>0.3772</td>
<td></td>
</tr>
<tr>
<td>15 mg Pio + SU</td>
<td>171</td>
<td>0.32</td>
<td>−0.07</td>
<td>0.013</td>
<td>0.0001</td>
<td>0.0001</td>
</tr>
<tr>
<td>30 mg Pio + SU</td>
<td>179</td>
<td>0.32</td>
<td>−0.14</td>
<td>0.013</td>
<td>0.0001</td>
<td>0.0001</td>
</tr>
<tr>
<td>Combination with metformin (study 027)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo + Met</td>
<td>143</td>
<td>0.33</td>
<td>0.00</td>
<td>0.017</td>
<td>0.9281</td>
<td></td>
</tr>
<tr>
<td>30 mg Pio + Met</td>
<td>158</td>
<td>0.34</td>
<td>−0.09</td>
<td>0.016</td>
<td>0.0001</td>
<td>0.0001</td>
</tr>
<tr>
<td>Combination with insulin (study 014)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo + Ins</td>
<td>173</td>
<td>0.26</td>
<td>0.02</td>
<td>0.016</td>
<td>0.2499</td>
<td></td>
</tr>
<tr>
<td>15 mg Pio + Ins</td>
<td>173</td>
<td>0.27</td>
<td>−0.09</td>
<td>0.016</td>
<td>0.0001</td>
<td>0.0001</td>
</tr>
<tr>
<td>30 mg Pio + Ins</td>
<td>179</td>
<td>0.28</td>
<td>−0.12</td>
<td>0.016</td>
<td>0.0001</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

a Student one-sample t test.

b Adjusted for multiple comparisons if more than two treatments (Dunnett’s procedure).

c Pio, pioglitazone; SU, sulfonylurea; Met, metformin; Ins, insulin.

d For plasma lipid atherogenicity: (a) AIP was directly related to a cohort’s risk for atherosclerosis; (b) there was a strong positive correlation (r = 0.803) between AIP and the FERHDL, which is increased in patients at risk for or with CHD (15), and a predominance of small HDL3b,c particles increases FERHDL, whereas increased HDL2b particles decrease it (16); and (c) there was a significant inverse correlation between LDL particle size and FERHDL (r = −0.82) and AIP (r = −0.78). Patients with small, dense LDL particles are at higher risk for CHD (17). Patients with type 2 diabetes have the highest AIP (6); they also have a higher FERHDL compared with nondiabetic individuals, and there is a direct correlation between FERHDL and waist:hip ratio in these patients (18). In addition, they are more likely to have a predominance of small, dense LDL particles compared with nondiabetic controls (19). All of these factors suggest that AIP is a suitable marker for plasma atherogenicity in patients with type 2 diabetes. We provide new information on the changes in AIP in patients with type 2 diabetes treated with pioglitazone.

Table 2. Comparison of AIP analyses with TG/HDL-C analyses.

<table>
<thead>
<tr>
<th>Overall test for drug effect (P)</th>
<th>Correlation between standardized and expected residuals*</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIP</td>
<td>TG/HDL-C</td>
</tr>
<tr>
<td>Study</td>
<td></td>
</tr>
<tr>
<td>001</td>
<td>0.0013</td>
</tr>
<tr>
<td>010</td>
<td>0.0001</td>
</tr>
<tr>
<td>027</td>
<td>0.0001</td>
</tr>
<tr>
<td>014</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

* Pearson correlation coefficients.
often clustered with other cardiovascular risk factors, the presence of endogenous hyperinsulinemia combined with hypertriglyceridemia, increased body mass index, and a decreased HDL-C increases the risk of CHD death in patients with type 2 diabetes (21). Despres et al. (22) also reported that people with hyperinsulinemia and high TGs have an increased risk for CHD.

AIP is inversely and significantly correlated with measures of insulin sensitivity. Previously, AIP has been reported to correlate with insulin resistance (HOMA IR) in Bermudians (23). We report here that pioglitazone therapy also reduces AIP in patients with type 2 diabetes whether it is used as monotherapy or in combination therapy with sulfonylurea, metformin, or insulin.

Patients with type 2 diabetes treated with fibrates (increases HDL and decreases TG concentrations) have

<table>
<thead>
<tr>
<th>Study</th>
<th>HbA1c</th>
<th>FPG</th>
<th>HOMA-S</th>
<th>QUICKI</th>
</tr>
</thead>
<tbody>
<tr>
<td>001</td>
<td>0.111 (0.2298)</td>
<td>0.128 (0.1700)</td>
<td>-0.269 (0.0035)</td>
<td>-0.253 (0.0061)</td>
</tr>
<tr>
<td>010</td>
<td>0.095 (0.0948)</td>
<td>0.156 (0.0059)</td>
<td>-0.263 (0.0001)</td>
<td>-0.299 (0.0001)</td>
</tr>
<tr>
<td>027</td>
<td>-0.010 (0.9101)</td>
<td>0.079 (0.3761)</td>
<td>-0.277 (0.0017)</td>
<td>-0.323 (0.0002)</td>
</tr>
<tr>
<td>014</td>
<td>0.084 (0.1379)</td>
<td>0.281 (0.0001)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Fig. 1. Normal probability plots of analyses of covariance for AIP and TG/HDL-C.
Std, standardized.
decreased cardiovascular risk (24, 25). Fibrates are peroxisome proliferator-activated receptor-α agonists, which lower plasma TG and increase HDL-C concentrations. Whether therapy with a peroxisome proliferator-activated receptor-γ agonist such as pioglitazone, which reduces insulin resistance in addition to lowering plasma TG and increasing HDL-C concentrations (thus reducing AIP), will lead to decreased cardiovascular morbidity and mortality remains to be established. A large study is currently underway to determine whether therapy with pioglitazone in patients with type 2 diabetes reduces cardiovascular events (26). Recently, it was reported thatFER_{HDL} age, smoking, and diabetes are significant predictors of the presence of angiographically documented CHD (27). If only laboratory tests were used in the multivariate analysis, FER_{HDL} was the sole predictor of CHD. When FER_{HDL} was omitted from the multivariate analysis, AIP was an independent predictor of CHD.

In summary, pioglitazone, a thiazolidinedione that reduces insulin resistance in type 2 diabetes, decreases AIP when used as monotherapy or in combination therapy with sulfonylurea, metformin, or insulin. AIP is inversely correlated with measures of insulin sensitivity.

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References


