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

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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), defined as log(TG/HDL-C), 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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Patients with type 2 diabetes are at high risk for and have a higher mortality from coronary heart disease (CHD)3 (1, 2). A cluster of cardiovascular risk factors associated with insulin resistance, a core defect in this disease, contributes to this increased risk for CHD (3). Dyslipidemia, very common in patients with type 2 diabetes, is one of these risk factors (4). Diabetic dyslipidemia is generally characterized by increased plasma triglyceride (TG) and decreased high-density lipoprotein (HDL)-cholesterol (HDL-C) concentrations, a preponderance of small, dense low-density lipoprotein (LDL), and an increased apolipoprotein B concentration. Although the major focus on the connection between lipids and CHD is on LDL-cholesterol (LDL-C), the Adult Treatment Panel III has recognized the important roles of HDL-C and TGs, calling this combination an atherogenic dyslipidemia (5).

Dobiasova and Frohlich (6) proposed the term Atherogenic Index of Plasma (AIP), defined as log(TG/HDL-C), on the basis that people with high AIP have a higher risk for CHD than those with low AIP, that AIP is positively correlated with the fractional esterification rate of HDL (FER\textsubscript{HDL}), and that AIP is inversely correlated with LDL particle size. Because FER\textsubscript{HDL} predicts particle size in HDL and LDL, which in turn predicts CHD risk, the simultaneous use of TGs and HDL-C (both readily available in a plasma lipoprotein profile) as AIP may be useful in predicting plasma atherogenicity. Furthermore, insulin resistance (decreased insulin sensitivity), which is often accompanied by increased CHD risk, is also often associated with increased TG and decreased HDL-C concentrations and a predominance of small, dense LDL particles. Reducing insulin resistance (enhancing insulin sensitivity) can potentially correct this dyslipidemia and, in so doing, AIP. We therefore studied the effect of pioglitazone, a thiazolidinedione that reduces insulin resistance, on the AIP of patients with type 2 diabetes.
Clinical Chemistry 50, No. 7, 2004 1185

**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 antihyperglycemia 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:

\[
\text{AIP} = \log(\text{TG/HDLC})
\]

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/HDLC 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/HDLC 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 significantly different from their respective placebo (or active controls) controls in reducing AIP.

A comparison of overall \(P\) values from analyses of AIP and TG/HDLC is shown in Table 2. The overall \(P\) values for drug effect were lower than those of the TG/HDLC 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/HDLC. 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 indices as well as measures of insulin sensitivity at the end of
the study are shown in Table 3. AIP was inversely and significantly correlated with insulin sensitivity measures (HOMA-S and QUICKI). In contrast, AIP was not significantly correlated with HbA1c. In two of the four studies, AIP was significantly correlated with FPG.

**Discussion**

Several lipoprotein-related indices [plasma concentrations 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.

The ratio TG/HDL-C was further characterized by Dobiasova and Frohlich (6) into log(TG/HDL-C). They called it AIP and provided three reasons to support it as a marker for plasma 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 $FER_{HDL}$, which is increased in patients at risk for or with CHD (15), and a predominance of small HDL$_{2b,c}$ particles increases $FER_{HDL}$ whereas increased HDL$_{2b}$ particles decrease it (16); and (c) there was a significant inverse correlation between LDL particle size and $FER_{HDL}$ ($r = -0.82$) 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 $FER_{HDL}$ compared with nondiabetic individuals, and there is a direct correlation between $FER_{HDL}$ and waistship 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 atherogeneity 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 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 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

<table>
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<th>Study</th>
<th>HbA1c (P value)</th>
<th>FPG (P value)</th>
<th>HOMA-S (P value)</th>
<th>QUICKI (P value)</th>
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Table 3. Pearson correlation coefficients (P values) between AIP and glycemic control (HbA1c and FPG) and insulin sensitivity (HOMA-S and QUICKI).
underway to determine whether therapy with pioglitazone in patients with type 2 diabetes reduces cardiovascular events (26). Recently, it was reported that FER_{\text{HDL}} was a significant predictor of the presence of angiographically documented CHD (27). If only laboratory tests were used in the multivariate analysis, FER_{\text{HDL}} was the sole predictor of CHD. When FER_{\text{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.

We thank Anthony Reitz, Neeraj Gupta, and Dr. Christopher Konkoy for assistance in the preparation of this manuscript and the investigators from Study Groups 001, 010, 014, and 027 (7–10).

References