Effects of Peroxisome Proliferator-Activated Receptor Ligands, Bezafibrate and Fenofibrate, on Adiponectin Level

Aki Hiuge, Alexander Tenenbaum, Norikazu Maeda, Michal Benderly, Masahiro Kumada, Enrique Z. Fisman, David Tanne, Zipora Matas, Toshiyuki Hibuse, Koichi Fujita, Hitoshi Nishizawa, Yehuda Adler, Michael Motro, Shinji Kihara, Ichiro Shimomura, Solomon Behar, Tohru Funahashi

Objective—Adiponectin is adipose-specific secretory protein and acts as an anti-diabetic and anti-atherosclerotic molecule. We previously found peroxisome proliferators response element element in adiponectin promoter region, suggesting that peroxisome proliferator-activated receptor (PPAR) ligands elevate adiponectin. Fibrates are known to be PPARα ligands and were shown to reduce risks of diabetes and cardiovascular disease. Effect of fibrates on adiponectin has not been clarified, whereas thiazolidinediones enhance adiponectin. Thus, we explored the possibility and mechanism that fibrates enhance adiponectin in humans, mice, and cells.

Methods and Results—Significant increase of serum adiponectin was observed in bezafibrate-treated subjects compared with placebo group in patients enrolled in The Bezafibrate Infarction Prevention study. Higher baseline adiponectin levels were strongly associated with reduced risk of new diabetes. Fibrates, bezafibrate and fenofibrate, significantly elevated adiponectin levels in wild-type mice and 3T3-L1 adipocytes. Such an effect was not observed in PPARα-deficient mice and adipocytes. Fibrates activated adiponectin promoter but failed to enhance its activity when the point mutation occurred in peroxisome proliferators response element site and the endogenous PPARα was knocked down by PPARα-RNAi.

Conclusions—Our results suggest that fibrates enhance adiponectin partly through adipose PPARα and measurement of adiponectin might be a useful tool for searching subjects at high risk for diabetes. (Arterioscler Thromb Vasc Biol. 2007;27:635-641.)

Key Words: adipocyte • adiponectin • fibrate • metabolic syndrome • peroxisome proliferator-activated receptor

Fibrates have been used in clinical practice for >4 decades as a class of agents known to decrease triglyceride levels. Fibrates are also known to be peroxisome proliferator-activated receptor (PPARα) ligands. Several clinical studies of fibrates have been performed in large populations. The Bezafibrate Infarction Prevention study (BIP) suggested that bezafibrate prevented cardiovascular events in the subgroup of coronary artery disease patients with high triglycerides. Moreover, further subanalyses demonstrated that the administrations of bezafibrate significantly reduced new-onset diabetes and myocardial infarction in the patients with the metabolic syndrome (MS). The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study showed that fenofibrate significantly reduced nonfatal myocardial infarctions and coronary revascularizations, a secondary endpoint, among patients with type 2 diabetes. These favorable clinical outcomes in fibrate studies might be explained by not only its triglyceride-lowering effect but also its various PPARα-mediated pleiotropic effects.

Adiponectin is an adipose-specific secretory protein and acts as an anti-diabetic and anti-atherosclerotic molecule. Furthermore, a number of clinical trials showed that subjects with high levels of circulating adiponectin tend to be protected against type 2 diabetes and myocardial infarction. Thiazolidinediones, PPARγ ligands, are well known to increase adiponectin levels in humans via upregulation of adiponectin at the transcriptional level, whereas the effect of PPARα ligands fibrates on adiponectin has not been fully explored.

We performed a subanalysis of the BIP study to investigate the effect of bezafibrate on human adiponectin in serum and the impact of baseline adiponectin levels on new-onset diabetes. We also examined the effect of bezafibrate and fenofibrate on adiponectin by using mice and cultured cells.
Materials and Methods

Subjects
Metabolic and inflammatory parameters were analyzed from stored frozen serum samples obtained from randomly selected patients with the MS who completed a 2-year of prospective, double-blind, placebo-controlled study period. The major inclusion and exclusion criteria for the BIP study, as well as the ethical guidelines, have been previously reported.1 The mean follow-up period of BIP was 6.2±0.8 years (range, 4.7 to 7.6 years).

Definition of the MS and Current Study Population
We applied the cut points for the MS based on the NCEP ATP-III report, with minor modifications as noted previously.4 Out of 1111 nondiabetic patients with the MS, we randomly selected 348 (31%). The full clinical data and paired blood samples were available in 292 patients (146 patients in bezafibrate and 146 in the placebo groups), which comprised the current study population. We used as the criterion for new diabetes, the detection of fasting blood glucose of ≥126 mg/dL (7 mmol/L) and/or initiating of any type of pharmacological antidiabetic treatment during follow-up.

Laboratory Methods of Human Studies
Detailed data on laboratory methods were given in previous reports.1 A central laboratory performed all biochemical determinations. For the purpose of the present study, serum samples, which had been taken at baseline from each study participant and stored at −70°C, were thawed and assayed for adiponectin levels using enzyme-linked immunosorbent assay kits (B-Bridge International, Inc, Sunnyvale, Calif). The inter-assay and intra-assay variability of the adiponectin assay kits (B-Bridge International, Inc, Sunnyvale, Calif). The inter-assay and intra-assay variability of the adiponectin assay kits was 5.9% and 3.2%, respectively. The homeostatic indexes of insulin resistance were calculated according to the homeostasis model of assessment as follows:

\[
\text{HOMA-IR} = \frac{\text{fasting insulin (µU/mL)} \times \text{fasting glucose (mmol/L)}}{22.5} \]

HOMA-IR, homeostatic index of insulin resistance; LDL, low-density lipoproteins; NYHA, New York Heart Association classification.

Data are mean±SD, geometric mean (95% confidence interval) or N (%) of patients.

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<tr>
<th>TABLE 1. Baseline Characteristics of the Study Population</th>
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<td>Body mass index, kg/m²</td>
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<td>Men (%)</td>
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<td>Past myocardial infarction (%)</td>
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<td>HOMA-IR</td>
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HDL indicates high-density lipoprotein; HOMA-IR, homeostatic index of insulin resistance; LDL, low-density lipoproteins; NYHA, New York Heart Association classification.

3T3-L1 Cell Cultures
3T3-L1 cells were maintained and differentiated as previously described.9 On day 4, 3T3-L1 adipocytes were treated with the indicated concentrations of either bezafibrate or fenofibric acid dissolved in dimethyl sulfoxide (DMSO) for 24 hours. An aliquot of the media was subjected to measurement of adiponectin by using enzyme-linked immunosorbent assay kit (Otsuka, Tokushima, Japan). We performed adiponectin promoter analysis as previously described.9,11 PPARα- and RXRα expression vectors were co-transfected in 3T3-L1 preadipocytes, as previously described.12 The sequences of the sense siRNAs were as follows: PPARα-siRNA: 5′-CCUUUGAUAGUACUUUAdTdT-3′. control-siRNA: 5′-UUUCGGCAACUGUACGUtTdT-3′.

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<th>TABLE 2. Distribution of Cardiovascular Drugs Among the Study Patients</th>
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<td>Calcium antagonists (%)</td>
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<td>Antiplatelets (%)</td>
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ACE-I indicates angiotensin-converting enzyme inhibitors. Data are N (%) of patients.
Animal Preparation and Primary Cultures of Stromal Vascular Cells

PPARα knockout (KO) mice were purchased from the Jackson Laboratory (Bar Harbor, Me). At 8 weeks of age, male wild-type (WT) and PPARα KO mice were fed with CRF-1 (Oriental Yeast, Osaka, Japan) containing either 0.3% bezafibrate, 0.1% fenofibrate, or no compound (control group) for 2 weeks. For preparation of stromal vascular cells (SVCs), subcutaneous adipose tissues were isolated from mice, minced into fine pieces in phosphate-buffered saline containing antibiotic antimycotic solution (Sigma-Aldrich Inc, St. Louis, Mo), and incubated in Dulbecco’s modified Eagle medium with 1 mg/mL collagenase type II and antibiotic antimycotic solution at 37°C for 30 minutes. Digested adipose tissues were filtered through sterile 250-μm nylon mesh and centrifuged at 600g for 5 minutes to separate floating adipocytes from pellet of SVCs. SVCs were washed with growth media (10% fetal calf serum + Dulbecco’s modified Eagle medium containing 200 μmol/L of L-ascorbic acid and antibiotic antimycotic solution), centrifuged at 600g for 5 minutes, and resuspended twice. SVCs were seeded onto culture dishes with growth media and differentiated by induction media (growth media with 5 μg/mL of insulin, 250 nM of dexamethasone, 500 μmol/L of 1-methyl-3-isobutyl-xanthine, and 5 μmol/L of tetracaine) after growing confluence. On day 2, the media of SVCs were changed to the maintenance media (growth media with 5 μg/mL of insulin). On day 4, SVC adipocytes were treated with the indicated reagents and harvested after 24 hours of treatment. The experimental protocol was approved by the Ethics Review Committee for Animal Experimentation of Osaka University School of Medicine.

Quantification of mRNA Levels

Total RNAs were extracted by using RNA STAT-60 (Tel-Test Inc, Friendswood, Tex). First-strand cDNA was synthesized from 400 ng of total RNA using ThermoScript reverse-transcription polymerase chain reaction system (Invitrogen Corp, Carlsbad, Calif). Real-time polymerase chain reaction amplification was conducted with the ABI PRISM 7900HT Sequence Detection system and SDS Enterprise Database (Applied Biosystems, Foster City, Calif) using SYBR Green polymerase chain reaction Master Mix (Applied Biosystems). The final result for each sample was normalized to the respective cyclophilin value.

Statistical Analysis for Human Studies

Data were analyzed with SAS software, version 8.2 (SAS Institute, Cary, NC). Comparisons of dichotomous variables and normally distributed continuous variables were performed by χ² test and Student t test, respectively. Geometric means were used for triglycerides, insulin and C-reactive protein to correct for their skewed distribution. Non-normally distributed variables were compared by the nonparametric Mann-Whitney U test, and they were log-transformed for further analysis. Spearman rank correlation coefficients for the study population as a whole were computed for the association between adiponectin levels and other clinical variables.

Because of their skewed distribution, adiponectin was presented as median and interquartile range, and 95% confidence interval (CI). For the assessment of differences after 2 years between bezafibrate and placebo group, an analysis-of-covariance with terms for treatment and baseline values was used based on log-transformed data. Absolute changes (μg/mL) and percent changes of adiponectin from baseline to 2 years were presented as median and interquartile range and compared using Mann-Whitney U test. To explore the risk of clinical events associated with reduced adiponectin levels, we evaluated the development of new diabetes in accordance with tertiles of baseline adiponectin level. Linear trend in crude rates of new diabetes onset was assessed by the Mantel-Haenszel χ² test. Age and multivariable adjusted hazard of developing diabetes were computed with the Cox proportional hazard model to account for differences in length of follow-up and correlation of covariates. The variables included in the analysis were age, gender, adiponectin tertiles, body mass index, glucose, insulin, C-reactive protein, triglycerides (log-transformed), and the use of angiotensin-converting enzyme inhibitors. Model performance was assessed with C-statistics and the area under the receiving operating curve. P<0.05 was considered as statistically significant.

Statistical Analysis for the In Vivo and In Vitro Experiments

Results were expressed as the mean±SEM of n separate experiments. Differences between groups were examined for statistical significance using Student t test or ANOVA with Fisher protected least significant difference test. P<0.05 denoted the presence of a statistically significant difference.

![Figure 1.](https://example.com/figure1.png)
Results

Baseline Data and Correlations in Subjects
Patients in the placebo and bezafibrate groups were well-balanced in terms of clinical and laboratory baseline characteristics (Table 1). The study groups were similar in regard to age, gender, 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). No significant differences between the groups were found for cholesterol, blood pressure, fasting glucose, triglycerides, fibrinogen, C-reactive protein, and homeostatic indexes of insulin resistance. Among patients on placebo, body mass index and fasting insulin were somewhat higher and systolic blood pressure lower than in patients on placebo. Data regarding treatment with cardiovascular drugs among the study groups are presented in Table 2. Nitrates, calcium antagonists, beta blockers, and antiplatelet drugs (mainly aspirin) were the most commonly used medications. The use of angiotensin-converting enzyme inhibitors was somewhat lower in patients on placebo. There were no significant differences in the proportion of patients receiving the other cardiovascular drugs.

The natural logarithm of adiponectin at baseline was significantly positively correlated with age (r=0.22, P=0.0002), high-density lipoprotein cholesterol (r=0.26, P=0.0001) and inversely correlated with natural logarithm of triglycerides (r = −0.15, P=0.009).

Bezafibrate Treatment Elevates Serum Adiponectin Levels in Human Subjects
No significant differences between the placebo and bezafibrate groups were found for adiponectin levels at baseline (placebo group: median, 6.75 µg/mL; interquartile range, 4.97 to 9.83; bezafibrate group: median, 7.64 µg/mL; interquartile range, 5.20 to 10.6; P=0.2). During 2 years of follow-up, there were no significant changes in the adiponec-tin level of placebo group, whereas the median adiponectin level significantly increased in bezafibrate groups (Figure 1A). Percent-changes in adiponectin level of placebo group were non-significant as well. In contrast, the median percent-changes in bezafibrate group increased significantly by 9.8% (interquartile range, −8.54 to 40.8%; P<0.0001). The intergroup differences in percentage changes were in favor of bezafibrate (P=0.02). Adiponectin level of bezafibrate group was also higher than that of placebo group after 2-year follow-up (placebo group: median, 7.03 µg/mL; interquartile range, 5.22 to 9.75; bezafibrate group: median, 8.71 µg/mL; interquartile range, 5.53 to 12.10; P=0.006).

Development of New Diabetes According to Adiponectin Levels at Baseline
Development of new diabetes was recorded in 69 patients during the mean 6.2-year follow-up period: 33 (11.3%) in bezafibrate and 36 (12.3%) in placebo group (P=0.4). A significantly reduced risk for development of new diabetes was demonstrated for the highest tertile of adiponectin (age-adjusted hazard ratio and 95% CI: 0.46 and 0.25 to 0.86). The linear trend across the tertiles was significant and demonstrated a higher risk for development of new diabetes (P=0.025) in the lowest tertile of adiponectin (Figure 1B). Multivariable analysis identified adiponectin as an independent predictor of reduced risk of new diabetes development. Adjusting for age and glucose, hazard ratio estimates (95% CI) were 0.51 (0.29 to 0.90) for comparison of II versus I tertile, and 0.44 (0.24 to 0.83) for III versus I tertile (c=0.81). Further adjustment for gender, insulin, C-reactive protein, triglycerides, body mass index, and use of angiotensin-converting enzyme inhibitors resulted in hazard ratio (95% CI) of 0.35 (0.17 to 0.72) and 0.43 (0.23 to 0.81) for tertiles III and II versus I, respectively (Figure 1C) (c=0.77). Another significant variable associated with future overt type 2 diabetes in patients with MS was glucose level (10 mg/dL increment) with hazard ratio 2.50 (95% CI, 1.96 to 3.19).
Fibrates Enhance Adiponectin at the Transcriptional Levels

Bezafibrate is known to be a pan-PPAR agonist that activates not only PPARα but also PPARγ, and fenofibrate is also shown to possess slight PPARγ activation.13 We previously identified peroxisome proliferators response element (PPRE) site locating on adiponectin gene,11 and thus we investigated in vitro and in vivo whether fibrates elevate adiponectin through PPARα. Tissue distribution of mouse PPARα showed that PPARα mRNAs were highly expressed in heart, liver, and kidney, whereas its mRNA level of white adipose tissue was similar to skeletal muscle (Figure 2A). In cultured 3T3-L1 cells, PPARα mRNA levels were increased in parallel with the adipocytes differentiation, and adiponectin mRNA was also detected on the third day and increased after differentiation (Figure 2B). We observed the significant increase of adiponectin mRNA in bezafibrate-treated and fenofibrate acid-treated 3T3-L1 adipocytes (Figure 2C). Similar results were obtained for changes of adiponectin protein level in media (Figure 2D).

Next, we measured the influence of fibrates on the activity of adiponectin promoter (Adn-promoter) by using 3T3-L1 adipocytes (Figure 3A and 3B) and preadipocytes (Figure 3C). Both 10 and 100 μmol/L of bezafibrate significantly enhanced Adn-promoter activities (Figure 3A, lane 2 versus 4 and 5). Treatment of 10 μmol/L fenofibrate acid tended to elevate Adn-promoter activity, and 100 μmol/L of fenofibrate acid significantly increased its activity (lane 2 versus 9). Pioglitazone (PGZ), as a positive control, also activated Adn-promoter (lane 2 versus 11) as previously described.9 However, these ligand-dependent activations of Adn-promoter were totally abolished when the point mutation occurred in PPRE site (lane 5 versus 6, 9 versus 10, and 11 versus 12). To determine the effect of fibrates on Adn-promoter activity via endogenous PPARα, we knocked down PPARα by using RNAi (Figure 3B). Introduction of PPARα-RNAi caused 0.5-fold decrease of PPARα mRNA level compared with control RNAi (data not shown). Knockdown of PPARα significantly reduced fibrates-induced activations of Adn-promoter (lane 2 to 9), whereas such reduction was not observed in PGZ-treated cells (lane 10 versus 11). Figure 3C showed the effect of fibrates on Adn-promoter in 3T3-L1 preadipocytes. Co-expression of PPARα with RXRα significantly increased Adn-promoter activity (Figure 3C, lane 1 versus 2). Addition of bezafibrate and fenofibrate acid augmented this increase, respectively (lane 2 versus 3 or 4), but PGZ treatment failed to enhance such increase (lane 2 versus 5).

Effect of Fibrates on Adiponectin in WT and PPARα-Deficient Mice and Cultured Adipocytes

To confirm the PPARα-mediated elevation of adiponectin by fibrates, we conducted the fibrates treatment on WT and PPARα KO mice and cells. We found significant increases of plasma adiponectin levels in both bezafibrate-treated and fenofibrate-treated WT mice at 1 and 2 weeks after administration (Figure 4A). Plasma adiponectin levels of bezafibrate-treated PPARα KO mice increased to a larger extent than the control group at 2 weeks, but its elevation was not statistically significant (KO + control versus KO + bezafibrate; \(P=0.0838\)). No significant increase of plasma adiponectin level was observed in fenofibrate-treated PPARα KO mice compared with control group (KO + control versus KO + fenofibrate; \(P=0.7780\)). Adiponectin mRNA levels were significantly elevated in bezafibrate and fenofibrate group compared with control group in WT mice, whereas such elevations were not observed in PPARα KO mice (Figure 4B).

Finally, we tested the elevating effect of fibrates on adiponectin by using SVC adipocytes derived from WT and PPARα KO mice. Bezafibrate and fenofibrate acid significantly increased adiponectin mRNA levels and protein in media in WT mice-derived SVC adipocytes (Figure 4C and 4D, left panel). However, treatments of bezafibrate and fenofibrate acid failed to elevate adiponectin mRNA levels...
transcriptionally increased adiponectin via adipose PPAR. As shown in Figures 3 and 4, fibrates directly and indicates that adipose tissue also might be a target organ of addition, there is no study investigating the effect of fibrates obese rats showed an elevation of adiponectin levels. In animals, one group showed that fenofibrate increased adiponectin whereas another group observed no change of adiponectin in one group showed that fenofibrate increased adiponectin, whereas another group observed no change of adiponectin in WT and PPARα KO mice, treated with 10 μmol/L of bezafibrate or fenofibrate acid for 24 hours. D, Adiponectin protein levels in cultured media of SVC adipocytes, WT indicates wild-type mice; KO, PPARα knockout mice; Cont, control diet; Beza, bezafibrate; Feno, fenofibrate; FenoA, fenofibric acid. Values are mean ± SEM; n=6 for each treatment. *P<0.05; **P<0.01, compared with the values of control group (A, B) or nontreated cells (DMSO) (C, D), respectively.

**Discussion**

In this study, we demonstrated: (1) bezafibrate significantly increased serum adiponectin in coronary artery disease patients with the MS; (2) subjects with the highest tertile of baseline adiponectin tended to escape from the development of new-onset diabetes; (3) fibrates enhanced adiponectin via PPRE site locating on its promoter region; and (4) fibrates elevated adiponectin partly through adipose PPARα.

The data regarding fenofibrate were obtained in small populations (n=10 to 20) and shown conflicting results, whereas we have found no published data about the effect of bezafibrate on human adiponectin. In animal experiments, one group showed that fenofibrate increased adiponectin, whereas another group observed no change of adiponectin in fenofibrate-treated obese rats. Bezafrate-administered obese rats showed an elevation of adiponectin levels. In addition, there is no study investigating the effect of fibrates on adiponectin in cultured adipocytes.

PPARα is abundantly expressed in liver, and investigations of PPARα-null mice and fibrate treatments have indicated that PPARα plays an important role in fatty acid oxidation. Fibrates are allowed to exhibit fatty acid oxidation in muscle as well as liver, but the effect of fibrates on adipocytes has not been noted because adipocytes express a small amount of PPARα. The current study showed that PPARα is expressed in adipose tissues as well as in muscle, and this result indicates that adipose tissue also might be a target organ of fibrates. As shown in Figures 3 and 4, fibrates directly and transcriptionally increased adiponectin via adipose PPARα.

Consistent with our results, another group recently demonstrated that PPARα mRNA was expressed in adipose tissues and 3T3-L1 adipocytes, and others have shown the existence of PPARα protein in human isolated adipocytes. In addition, PPARα ligands directly stimulated lipolysis in WT adipocytes, but such effect was not observed in PPARα-deficient adipocytes. These previous and present results indicate that PPARα functionally works in adipocytes. Bezafrate tended to elevate adiponectin in both PPARα-deficient mice and SVC adipocytes (Figure 4A and 4D), which results might be accounted for the partial PPARα activation induced by bezafibrate known to be a pan-PPAR ligand.

Several clinical studies of PPAR ligands have been conducted in large populations. For example, the PROactive study demonstrated that PGZ improved cardiovascular outcome at main secondary endpoint in patients with type 2 diabetes and also reduced the need to add insulin therapy to glucose-lowering regimens compared with placebo. The BIP and FIELD studies also showed that fibrate treatments achieved beneficial outcomes in selected high-risk groups. These clinical results of PPAR ligands theoretically might be partly explained by the PPAR ligand-dependent induction of adiponectin as one of PPAR-mediated pleiotropic effects.

Recently, subanalysis of BIP study demonstrated that high levels of adiponectin at baseline were associated with low risk of subsequent diabetes in coronary artery disease subjects with impaired fasting glucose. Here we also showed that high baseline concentration of adiponectin was associated with lower risk for new-onset diabetes in patients with the MS. It should be noted that the randomly selected patients in the placebo and bezafibrate groups in our study present some minor differences regarding degree of obesity, insulin concentrations and use of angiotensin-converting enzyme inhibitors. All these potential confounders were included in the multivariable analysis and did not affect the results. More
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randomized control trials and larger longitudinal cohort studies to explore the predictive value of adiponectin measurements in subjects at high risk for diabetes and coronary artery disease are warranted.

In conclusion, fibrates enhance adiponectin partly through adipose PPARα and measurement of adiponectin might be a useful tool for searching for subjects at high risk for diabetes.

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Disclosures

None.

References


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