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# Pioglitazone Decreases Coronary Artery Inflammation in Impaired Glucose Tolerance and Diabetes Mellitus

## Evaluation by FDG-PET/CT Imaging

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OBJECTIVES The aim of this study was to compare the effect of pioglitazone with glimepiride on coronary arterial inflammation with serial $^{18}$F-fluorodeoxyglucose (FDG)–positron emission tomography (PET) combined with computed tomography (CT) angiography.

BACKGROUND Recent studies have shown that FDG-PET combined with CT is a reliable tool to visualize and quantify vascular inflammation. Although pioglitazone significantly prevented the progression of coronary atherosclerosis and reduced the recurrence of myocardial infarction in patients with type 2 diabetes mellitus (DM), it remains unclear whether pioglitazone could attenuate coronary artery inflammation.

METHODS Fifty atherosclerotic patients with impaired glucose tolerance or type 2 DM underwent determination of blood chemistries, anthropometric and inflammatory variables, and FDG-PET/CT angiography, and then were randomized to receive either pioglitazone or glimepiride for 16 weeks. Effects of the treatments on vascular inflammation of the left main trunk were evaluated by FDG-PET/CT angiography at baseline and end of the study. Vascular inflammation of the left main trunk was measured by blood-normalized standardized uptake value, known as a target-to-background ratio.

RESULTS Three patients dropped out of the study during the assessment or treatment. Finally, 25 pioglitazone-treated patients and 22 glimepiride-treated patients (37 men; mean age: 68.1 ± 8.3 years; glycosylated hemoglobin: 6.72 ± 0.70%) completed the study. After 16-week treatments, fasting plasma glucose and glycosylated hemoglobin values were comparably reduced in both groups. Changes in target-to-background ratio values from baseline were significantly greater in the pioglitazone group than in the glimepiride group (–0.12 ± 0.06 vs. 0.09 ± 0.07, $p = 0.032$), as well as changes in high-sensitivity C-reactive protein (pioglitazone vs. glimepiride group: median: –0.24 [interquartile range (IQR): –1.58 to –0.04] mg/l vs. 0.08 [IQR: –0.07 to 0.79] mg/l, $p = 0.031$).

CONCLUSIONS Our study indicated that pioglitazone attenuated left main trunk inflammation in patients with impaired glucose tolerance or DM in a glucose-lowering independent manner, suggesting that pioglitazone may protect against cardiac events in patients with impaired glucose tolerance or DM by suppressing coronary inflammation. (Anti-Inflammatory Effects of Pioglitazone; NCT00722631) (J Am Coll Cardiol Img 2013;6:1172–82) © 2013 by the American College of Cardiology Foundation

Rupture of atherosclerotic plaques in the coronary artery could lead to the clinical manifestation of acute coronary syndrome (1–4). Accumulation of macrophages in the atherosclerotic vessels is among the characteristic features of vulnerable plaques (1–4). Therefore, development of novel imaging modality to assess the macrophage content and its activity in the coronary artery would be required to facilitate a screening of high-risk patients and identify those with vulnerable atherosclerotic plaques.

$^{18}$F-Fluorodeoxyglucose (FDG) imaging by positron emission tomography (PET) is commonly employed for the screening and detection of occult tumors (5–7). Recently, it has been used to identify the extent of vasculitis for both Takayasu and Kawasaki diseases (8–10) and to evaluate the carotid plaque inflammation in high-risk patients (11–16). Rudd et al. (11) reported that most of the FDG accumulations in carotid arteries corresponded to the macrophage-rich area of the atherosclerotic plaques in patients with symptomatic carotid atherosclerosis. FDG uptake in the carotid artery has also been shown to correlate with macrophage staining from the corresponding histological sections in patients who subsequently underwent carotid endarterectomy (12). These observations have suggested that FDG-PET is a noninvasive tool to evaluate the vascular inflammation and identify the macrophage-rich, vulnerable atherosclerotic plaques in humans.

Coronary artery disease is more prevalent and severe in patients with type 2 diabetes mellitus (DM) or impaired glucose tolerance (IGT) than in subjects with normal glucose tolerance (17,18). Pioglitazone, a peroxisome proliferator-activated receptor-gamma agonist, is a widely used drug for the treatment of DM (19). It improves insulin resistance and subsequently decreases plasma glucose as well as glycosylated hemoglobin (HbA1c) values in patients with DM (19). In addition, several clinical studies have shown that pioglitazone may have atheroprotective properties in humans (20–24). The CHICAGO (Carotid Intima Media Thickness in Atherosclerosis Using Pioglitazone) (23) and PERISCOPE (Pioglitazone Effect on Regression of Intravascular Sonographic Coronary Obstruction Prospective Evaluation) (24) studies have demonstrated that pioglitazone, compared with an equipotent glucose-lowering agent, glimepiride, significantly prevents the progression of coronary atherosclerosis. In the PROACTIVE (Prospective Pioglitazone Clinical Trial in Macrovascular Events) studies, pioglitazone remarkably reduced the recurrence of stroke and acute coronary syndrome in high-risk diabetic patients (20–22). We also demonstrated by FDG-PET that pioglitazone attenuated the inflammation of carotid arteries and aortas (16). These findings suggest that pioglitazone may suppress coronary inflammation and have a plaque-stabilizing effect. Therefore, in this study, we examined whether pioglitazone could attenuate left main trunk (LMT) inflammation in patients with IGT or type 2 DM by using serial FDG-PET and computed tomography (CT) angiography.

**ABBREVIATIONS AND ACRONYMS**

**CT** = computed tomography
**DM** = diabetes mellitus
**FDG** = $^{18}$F-fluorodeoxyglucose
**FPG** = fasting plasma glucose
**HbA1c** = glycosylated hemoglobin
**hsCRP** = high-sensitivity C-reactive protein
**IGT** = impaired glucose tolerance
**IQR** = interquartile range
**LMT** = left main trunk
**PET** = positron emission tomography
**SUV** = standardized uptake value
**TBR** = target-to-background ratio

## METHODS

**Design and subjects.** This study was a prospective, randomized, active comparator-controlled, single-center trial to look at coronary artery inflammation a priori involving 16 weeks of study-drug administration and follow-up, although some subjects were enrolled in our previous carotid study (16). We screened patients with IGT or type 2 DM who had ultrasonic evidence of carotid atherosclerosis. We excluded any patients with a history of hypersensitivity reactions to iodinated contrast media, with acute coronary syndrome, with symptomatic stroke within at least 6 months before the enrollment, with uncontrolled diabetes (fasting plasma glucose [FPG] ≥200 mg/dl), with insulin treatment, with left ventricular dysfunction (left ventricular ejection fraction <40%) or heart failure (New York Heart Association functional class ≥II), with neoplastic disorders, and with active inflammatory diseases. Fifty-seven patients underwent FDG-PET. Myocardial FDG uptake was visually evaluated by a quantitative analysis of scores 0 to 3 (0 = no uptake; 1 = mild uptake; 2 = moderate uptake; and

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3 = severe uptake). Patients whose score was ≥2 were also excluded because coronary artery inflammation cannot be evaluated under such intense myocardial FDG uptakes (25–28). Fifty atherosclerotic patients were randomized to receive either pioglitazone or glimepiride for 16 weeks. Three patients dropped out of the study during the assessment or treatment. Finally, 47 patients were evaluated at baseline and 16 weeks of follow-up with FDG-PET/CT angiography examinations. The disposition of patients in the study is shown in Figure 1. The study protocol was approved by the Ethics Committee of Kurume University. All subjects provided written informed consent.

**Carotid ultrasonography.** The carotid wall thickness of the bilateral carotid arteries was measured by duplex ultrasonography (SSA-380A, Toshiba Medical Systems Corp., Tochigi, Japan) with a 10-MHz transducer as described previously (14,15). Longitudinal B-mode images at the diastolic phase of the cardiac cycle were recorded by a single trained technician, who was blinded to the subject's background. The images were magnified and printed using a high-resolution line recorder (LSR-100A, Toshiba Medical Systems Corp.). The maximum intima-media thickness was measured at the thickest wall of internal and common carotid arteries. The presence of atherosclerosis was defined as a thickening of the maximum intima-media thickness >1.1 mm (29).

**Treatments.** Eligible patients were randomly assigned to receive either pioglitazone 15 to 30 mg daily (n = 25) or glimepiride 0.5 to 4 mg daily as an active comparator (n = 22) for 16 weeks. The initial dose of study drugs was based on fasting glucose level, and then doses of pioglitazone or glimepiride were titrated to obtain target glycemic control defined as a FPG level of 110 mg/dl or lower. Other medications for hypertension, diabetes, or dyslipidemia or antiplatelet agents were not altered within the past 16 weeks and remained unchanged during the course of the study period.

**Data collection.** Presence of smoking habit, medical history, use of medication, and family history of cardiovascular disease were assessed by a questionnaire. Smoking was classified as current habitual use or not. Waist circumference was measured at the umbilical level in the late exhalation phase as an index of the presence or absence of abdominal obesity. Blood pressure was measured in the sitting position using an upright standard sphygmomanometer. Vigorous physical activity and smoking were avoided for at least 30 min before measurements of resting blood pressure and heart rate. Blood was drawn on the same day of FDG-PET image acquisition after 12-h fasting from the antecubital vein in the morning for the determinations of blood chemistries: total cholesterol, low-density lipoprotein cholesterol, triglycerides, and high-density lipoprotein cholesterol; FPG, fasting serum immunoreactive insulin, HbA1c, and high-sensitivity C-reactive protein (hsCRP). These blood chemistries were measured with standard methods at a commercially available laboratory (The Kyodo Igaku Laboratory, Fukuoka, Japan) as described previously (13–16).

**FDG-PET and CT angiography.** FDG-PET and CT angiography was performed as described previously (16). In brief, after at least a 12-h fasting prior to PET scanning, patients received a single intravenous bolus injection of FDG (4.2 MBq [0.12 mCi]/kg body weight) via the antecubital vein. PET scan was performed 3 h after the FDG administration. The patients rested for 3 h in a comfortable position in a quiet room and were then conveyed to the scanning suite. Three hours after the FDG injection, contrast medium on a dose-by-weight basis was administered and 3-dimensional cardiac PET and CT angiography were carried out using an integrated full-ring PET/CT scanner (Gemini-GXL 16, Philips Medical Systems, Inc., Cleveland, Ohio). Sixteen-slice multidetector CT was used in this study. For the contrast-enhanced scan, 100 ml of contrast media (Iohexol, Daiichi Sankyo, Tokyo, Japan) was injected at 3.0 ml/s with biphasic injection of a 20-ml saline chaser. The CT data were used for attenuation correction and lesion localization. After both the transmission and emission images were obtained, the images were reconstructed using the 3-dimensional line-of-response row-action maximum likelihood algorithm (Philips, Eindhoven, the Netherlands). The PET images were appropriately coregistered with CT angiography images by a nuclear investigator using a strategy of prioritizing the registration of the ascending aorta given that it is discernable on both PET and CT image for reproducible evaluation. Two independent experienced cardiologists, who were blinded to the patients' clinical history and classification, engaged in the process of coregistration and reviewed the PET/CT scans for myocardial and coronary FDG uptakes.

**Evaluation of vascular inflammation of the LMT.** To minimize the myocardial glucose uptake for better visualization of coronary artery FDG uptake, FDG-PET image was acquired after at least a 12-h period of fasting. Analyses were performed on the LMT just before the bifurcation to avoid spillover of activity from the aorta or myocardium (Fig. 2). The position of the LMT was identified by the CT

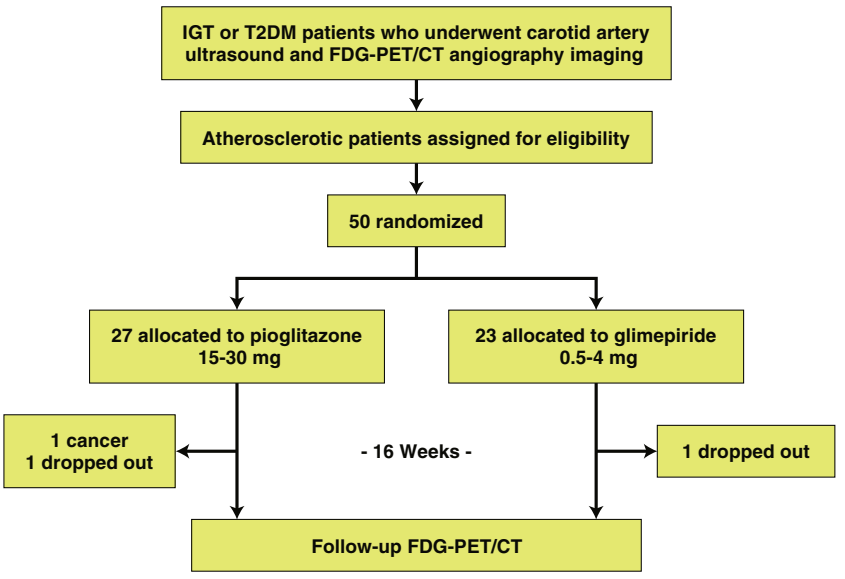


**Figure 1. Disposition of Patients**

CT = computed tomography; FDG = $^{18}$F-fluorodeoxyglucose; IGT = impaired glucose tolerance; PET = positron emission tomography; T2DM = type 2 diabetes mellitus.

angiography (Fig. 2). The intensity of FDG uptake was quantified by measuring the standardized uptake value (SUV) corrected for body weight and injected FDG dose. The SUV was calculated by using the maximum pixel activity value within the region of interest placed on the entire vasculature obtained from the consecutive coregistered sagittal FDG-PET and CT angiography images (Fig. 2). The SUV score was determined as the average of SUV of the LMT obtained from consecutive 5 PET/CT images, each separated by 4 mm in length. The SUV score of the LM was corrected for blood activity by dividing by the average blood SUV estimated from the inferior vena cava to produce a blood-corrected artery SUV known as a target-to-background ratio (TBR). For assessment of intra- and inter-reader reproducibility, TBR values were measured in all patients by 2 cardiologists who were blind to patients' clinical information. The blinded intraobserver and interobserver reliability analysis for the TBR values revealed intraclass correlation coefficients between readers of 0.97 and 0.93, respectively, in the LMT.

**Statistical methods.** Data were presented as mean ± SD or median (interquartile range [IQR]). We performed the Shapiro-Wilk test to evaluate the assumption of normality. Statistical analysis was performed by means of appropriate parametric and nonparametric methods. Treatment groups were compared at baseline by using an unpaired Student *t* test for continuous variables and chi-square for categorical variables. First, paired Student *t* test was performed for comparisons between the baseline and post-treatment values. Second, the changes from baseline were compared by unpaired Student *t* test between the 2 groups. Values of $p < 0.05$ were considered to indicate statistical significance. All statistical analyses were performed with the use of the SPSS system (SPSS Inc., Chicago, Illinois).

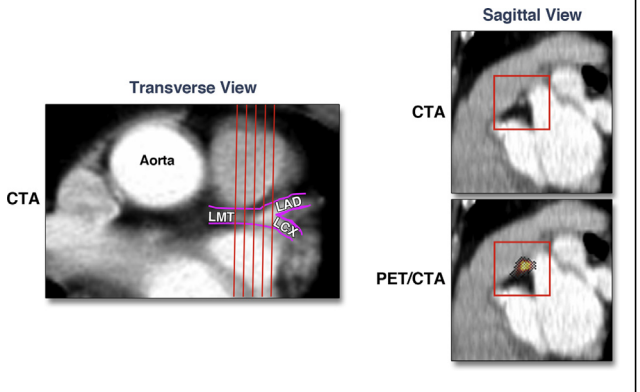


**Figure 2. FDG-PET and CT Angiography**

$^{18}$F-fluorodeoxyglucose accumulation was quantified in the left main trunk (LMT). CTA = computed tomography angiography; LAD = left anterior descending; LCX = left circumflex artery; other abbreviations as in Figure 1.

**Table 1. Patient Characteristics**

| | Pioglitazone (n = 25) | Glimepiride (n = 22) | p Value |
|---|---|---|---|
| Male | 19 | 18 | 0.897 |
| Age, yrs | 68.8 ± 7.2 | 67.3 ± 9.3 | 0.563 |
| Waist circumference, cm | 64.4 ± 12.5 | 65.3 ± 10.8 | 0.794 |
| Maximum carotid IMT, mm | 1.84 ± 0.76 | 1.95 ± 1.06 | 0.669 |
| Systolic blood pressure, mm Hg | 128.0 ± 12.3 | 123.5 ± 13.3 | 0.239 |
| Diastolic blood pressure, mm Hg | 70.8 ± 9.0 | 69.0 ± 9.3 | 0.511 |
| Lipid profile | | | |
| LDL cholesterol, mg/dl | 108.4 ± 23.8 | 117.6 ± 24.8 | 0.210 |
| HDL cholesterol, mg/dl | 49.9 ± 12.8 | 51.3 ± 13.0 | 0.723 |
| Triglycerides, mg/dl | 105.0 (79.5–125.5) | 120.0 (74.8–164.0) | 0.965 |
| Glycemic state | | | |
| Fasting plasma glucose, mg/dl | 121.0 (105.5–140.0) | 129.0 (119.5–145.5) | 0.249 |
| Fasting plasma insulin, μU/ml | 6.80 (4.55–11.20) | 4.85 (3.63–8.45) | 0.157 |
| Hemoglobin A1c, % | 6.61 ± 0.73 | 6.85 ± 0.64 | 0.247 |
| High-sensitivity CRP, mg/dl | 0.78 (0.34–1.93) | 0.61 (0.35–1.47) | 0.466 |
| Risk factor | | | |
| Current smoking | 4 | 4 | 0.849 |
| Hypertension | 23 | 19 | 0.88 |
| Family history of CVD | 10 | 12 | 0.319 |
| Drugs | | | |
| ACE-Is or ARBs | 14 | 16 | 0.234 |
| Beta-blockers | 11 | 9 | 0.831 |
| Calcium channel blockers | 15 | 12 | 0.706 |
| Aspirin | 13 | 16 | 0.145 |
| Statins | 13 | 9 | 0.447 |

Values are n, mean ± SD, or median (interquartile range).
ACE-I = angiotensin-converting enzyme inhibitors; ARB = angiotensin II receptor blockers; CRP = C-reactive protein; CVD = cardiovascular disease; HDL = high-density lipoprotein; IMT = intima-media thickness; LDL = low-density lipoprotein.

## RESULTS

**Clinical characteristics.** Three patients did not complete the assessment or treatment of the study; 47 patients did complete the study (n = 25 in the pioglitazone group and n = 22 in the glimepiride group) (Fig. 1). The average age of patients was 68.1 ± 8.2 years old, and average waist circumference and HbA1c values were 88.6 ± 10.1 cm and 6.72 ± 0.70%, respectively. Demographic characteristics at baseline are summarized in Table 1. As shown in Table 1, there were no significant differences of baseline data between the 2 groups, including anthropometric, metabolic, hemodynamic, and inflammatory variables. Percentages of patients who were taking oral hypoglycemic agents, antihypertensive medication, statins, or aspirin were similar between the 2 groups, and doses of the drugs remained unchanged during the intervention periods.

**Effects of pioglitazone and glimepiride on clinical parameters.** The mean titrated daily dose of glimepiride was 1.3 ± 1.0 mg and that of pioglitazone was 16.2 ± 4.0 mg. Both treatments were well tolerated, and there were no drug-related adverse effects such as heart failure or severe hypoglycemia. Table 2 shows changes of clinical parameters in each treatment group. After 16-week treatments, FPG and HbA1c values were comparably reduced in both groups. There were no differences of changes in other clinical parameters except for hsCRP. The changes of hsCRP values from baseline (ΔhsCRP) in the pioglitazone group were significantly larger than those in glimepiride group (ΔhsCRP: median: −0.24 [IQR: −1.58 to −0.04] mg/l vs. 0.08 [IQR: −0.07 to 0.79] mg/l; p = 0.031).

**Effects pioglitazone and glimepiride on FDG-PET and CT angiography.** Figure 3 shows the representative images of the CT angiography, FDG-PET, and coregistration of FDG-PET and CT angiography in patients treated with pioglitazone or glimepiride. FDG uptakes of the LMT were observed in both groups (lowest panels of Figs. 3A and 3B and upper panels of Fig. 3C, baseline). There was no significant difference in baseline TBR values between pioglitazone and glimepiride groups (1.39 ± 0.32 vs. 1.45 ± 0.29, respectively; p = 0.496) (Fig. 4). As shown in the lowest panels of Figures 3A and 3B and lower panels of Figure 3C, post-treatment, pioglitazone therapy significantly attenuated the FDG uptake of the LMT, but glimepiride did not. Pooled data demonstrated that pioglitazone decreased the TBR values of the LMT (1.39 ± 0.32 to 1.26 ± 0.29; p = 0.033) (Fig. 4A), whereas glimepiride did not affect the values (1.45 ± 0.29 to 1.54 ± 0.35; p = 0.261) (Fig. 4B). The ΔTBR values were significantly greater in the pioglitazone group than in the glimepiride group (−0.12 ± 0.06 vs. 0.09 ± 0.07; p = 0.032) (Fig. 4C). We also examined the effects of pioglitazone and glimepiride on vascular remodeling of LMT, left anterior descending artery, left circumflex artery, and right coronary artery by using CT angiography with 16-slice multidetector. Pioglitazone or glimepiride treatment did not affect vascular remodeling evaluated by vessel diameters or calcification score of each coronary artery (data not shown).

## DISCUSSION

In the present study, we found here for the first time that pioglitazone, but not glimepiride, significantly

**Table 2. Changes in Clinical Parameters After 16-Week Treatments With Pioglitazone and Glimepiride**

| | Pioglitazone | Glimepiride | p Value Between Groups |
|---|---|---|---|
| Weight, kg | | | |
| Baseline | 64.4 ± 12.5 | 65.3 ± 10.8 | 0.794 |
| Post-treatment | 65.1 ± 13.0 | 65.8 ± 10.4 | 0.858 |
| p value vs. baseline | 0.080 | 0.153 | |
| Waist circumference, cm | | | |
| Baseline | 88.3 ± 9.8 | 89.0 ± 10.5 | 0.806 |
| Post-treatment | 89.5 ± 9.5 | 89.4 ± 10.0 | 0.979 |
| p value vs. baseline | 0.058 | 0.484 | |
| Systolic blood pressure, mm Hg | | | |
| Baseline | 128.0 ± 12.3 | 123.5 ± 13.3 | 0.239 |
| Post-treatment | 124.1 ± 14.9 | 123.7 ± 14.1 | 0.936 |
| p value vs. baseline | 0.149 | 0.907 | |
| Diastolic blood pressure, mm Hg | | | |
| Baseline | 70.8 ± 9.0 | 69.0 ± 9.3 | 0.511 |
| Post-treatment | 70.4 ± 9.8 | 68.1 ± 9.8 | 0.452 |
| p value vs. baseline | 0.819 | 0.458 | |
| LDL cholesterol, mg/dl | | | |
| Baseline | 108.4 ± 23.8 | 117.6 ± 24.8 | 0.210 |
| Post-treatment | 106.4 ± 27.7 | 118.1 ± 19.8 | 0.116 |
| p value vs. baseline | 0.714 | 0.903 | |
| HDL cholesterol, mg/dl | | | |
| Baseline | 49.9 ± 12.8 | 51.3 ± 13.0 | 0.723 |
| Post-treatment | 54.6 ± 14.9 | 53.3 ± 12.5 | 0.755 |
| p value vs. baseline | 0.017 | 0.161 | |
| Triglycerides, mg/dl | | | |
| Baseline | 105.0 (79.5–125.5) | 120.0 (74.8–164.0) | 0.965 |
| Post-treatment | 120.0 (80.5–148.5) | 119.5 (85.0–207.8) | 0.611 |
| p value vs. baseline | 0.431 | 0.153 | |
| Fasting plasma glucose, mg/dl | | | |
| Baseline | 121.0 (105.5–140.0) | 129.0 (119.5–145.5) | 0.249 |
| Post-treatment | 110.0 (100.5–120.5) | 120.0 (111.8–133.5) | 0.004 |
| p value vs. baseline | 0.001 | 0.003 | |
| Fasting plasma insulin, μU/ml | | | |
| Baseline | 6.80 (4.55–11.20) | 4.85 (3.63–8.45) | 0.157 |
| Post-treatment | 6.40 (4.20–10.45) | 5.70 (4.10–7.53) | 0.681 |
| p value vs. baseline | 0.144 | 0.592 | |
| Hemoglobin A1c, % | | | |
| Baseline | 6.61 ± 0.73 | 6.85 ± 0.64 | 0.247 |
| Post-treatment | 6.15 ± 0.42 | 6.50 ± 0.51 | 0.014 |
| p value vs. baseline | <0.001 | <0.001 | |
| High-sensitivity CRP, mg/l | | | |
| Baseline | 0.78 (0.34–1.93) | 0.61 (0.35–1.47) | 0.466 |
| Post-treatment | 0.53 (0.27–1.15) | 0.93 (0.45–2.00) | 0.101 |
| p value vs. baseline | 0.228 | 0.018 | |

Values are mean ± SD or median (interquartile range).
Abbreviations as in Table 1.

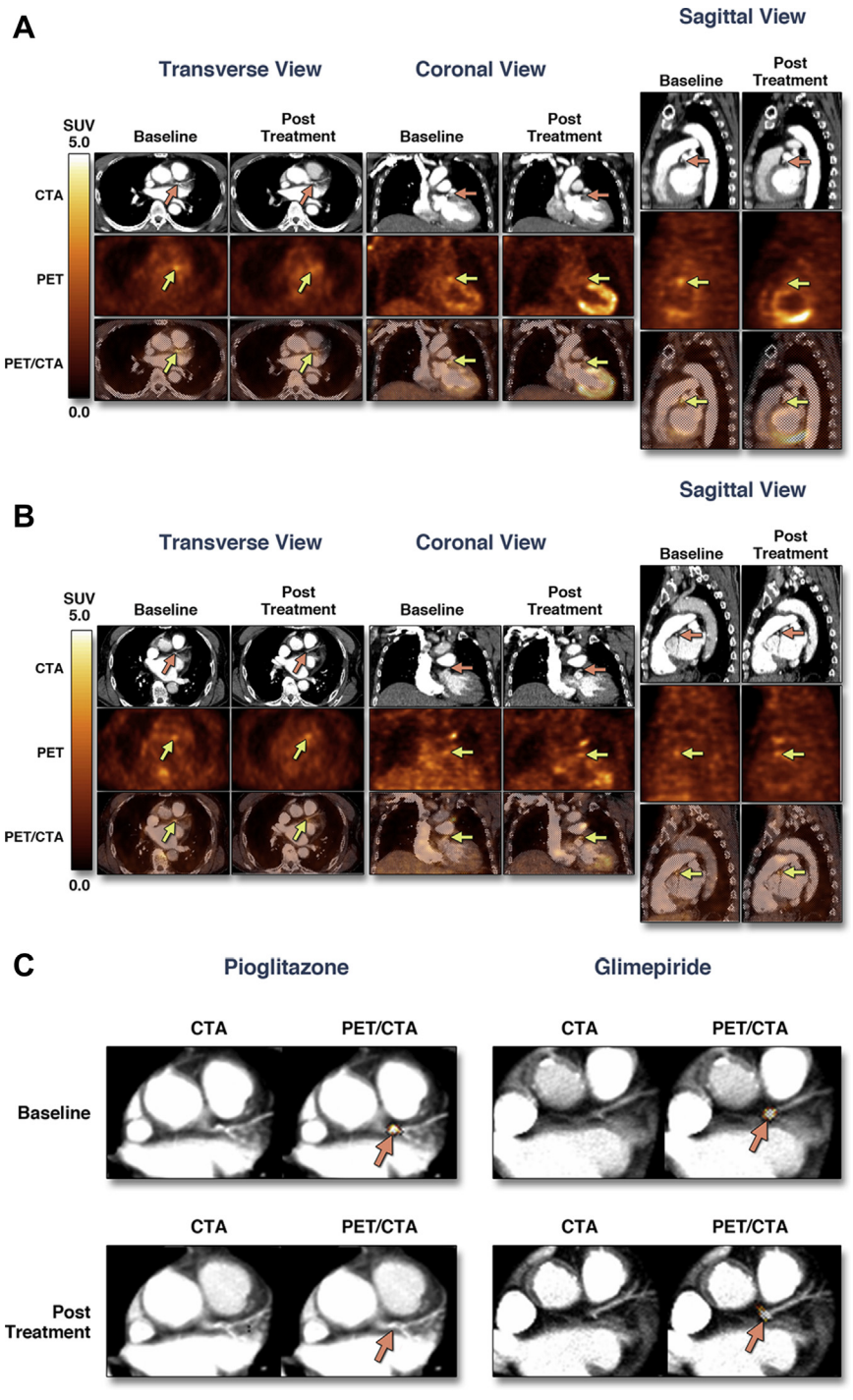


**Figure 3. Representative Cases After Treatment With Pioglitazone or Glimepiride**

Effects of pioglitazone and glimepiride on FDG uptake in the LMT. Representative CT angiography **(top),** FDG-PET **(middle),** and PET/CT angiography **(bottom)** images (transverse, coronal, and sagittal views) at baseline and after 16-week treatment with pioglitazone **(A)** or glimepiride **(B)**. Manipulated PET/CT fused images with background subtraction **(C)**. Note reduction in FDG uptake in the LMT with pioglitazone, but not with glimepiride treatment **(arrows)**. SUV = standardized uptake value; other abbreviations as in Figures 1 and 2.

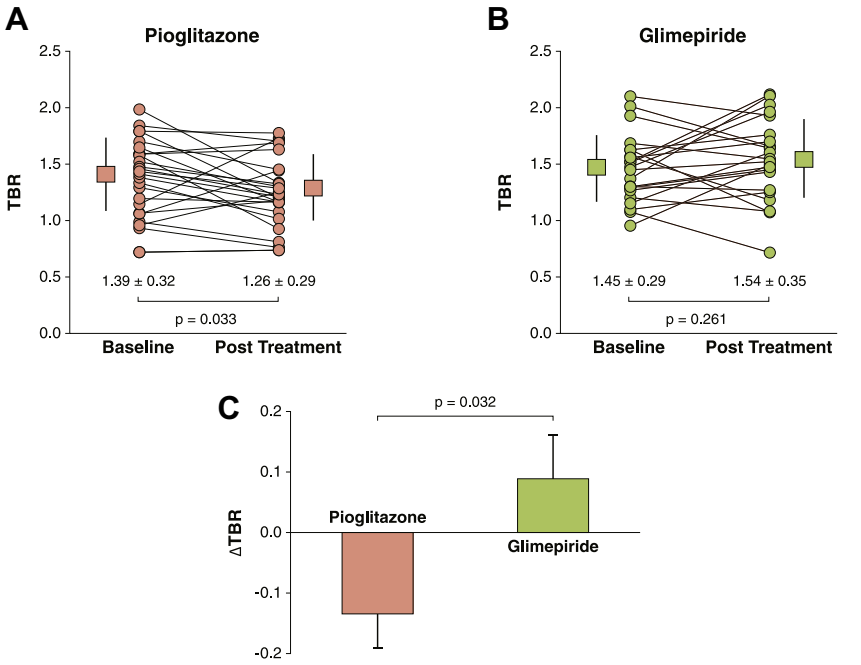


**Figure 4. Changes in Coronary TBR Values After 16-Week Treatment With Pioglitazone or Glimepiride**

Target-to-background ratio (TBR) was evaluated in individual patients at baseline and after 16-week treatments with pioglitazone **(A)** or glimepiride **(B)** for quantitative analysis. **(C)** Changes in TBR from baseline. **Bar** shows standard error.

decreased LMT inflammation evaluated by FDG-PET and CT angiography in atherosclerotic patients with IGT or type 2 DM. We used carotid atherosclerosis as an entry criterion because we would like to compare the effects of each oral hypoglycemic agent on LMT inflammation in high-risk subjects. As there were no significant differences of glucose control between the 2 groups, pioglitazone may have exerted anti-inflammatory effects on the LMT in a glucose-lowering–independent manner. Compared with glimepiride, pioglitazone has been shown to prevent recurrent myocardial infarction in type 2 DM patients with previous myocardial infarction (22). Given the accumulating evidence that inflammatory reactions in the vessels play a central role in the pathogenesis of vulnerable atherosclerotic plaques and thus contribute to acute coronary syndrome (30–32), our present study suggests that pioglitazone may reduce cardiovascular events in patients with type 2 DM or IGT by suppressing the inflammatory reactions in the coronary artery.

In the present study, for the quantitative analysis of vascular inflammation, we measured TBR values of the LMT by FDG-PET. We limited the analyses for LMT (Fig. 2), because FDG uptake of the other portions of the coronary artery is subject to error due to interference by the myocardial FDG uptake and motion of the coronary artery (26). In order to obtain better visualization of FDG accumulation of the LMT, we made the following efforts. First, FDG-PET image was acquired after at least 12-h fasting for minimizing the myocardial FDG uptake. Second, because perfect coregistration of chest structures between the PET and CT images is not feasible because of cardiac and respiratory motion that can potentially swamp FDG signal in coronary arteries, we used a strategy of prioritizing the registration of the ascending aorta given that it is discernable on both PET and CT image for reproducible evaluation (27). As a result, although there was a lack of respiratory and cardiac motion correction for PET analysis, process of observer-dependent image fusion and serial FDG-PET imaging of the LMT inflammation studied here obtained highly reproducible results. It was reported that TBR values (TBR $\geq$2.0) of the culprit lesion were significantly higher in patients with recent acute coronary syndrome than those in patients with stable angina (TBR around 1.6) (27,28). Thus, the relatively low baseline TBR values (1.42 $\pm$ 0.31) in our asymptomatic subjects with atherosclerosis further validated the evaluation of the LMT inflammation by FDG-PET.

In our patients, hsCRP was not very elevated. Nevertheless, pioglitazone treatment significantly decreased hsCRP, whereas an equipotent glucose-lowering agent, glimepiride, had a tendency to increase hsCRP, and there was significant difference in ΔhsCRP between the 2 groups. These observations suggest that pioglitazone may attenuate the LMT inflammation by suppressing systemic inflammation in our subjects. However, in the present study, ΔhsCRP was not significantly correlated with ΔTBR values in pioglitazone-treated patients ($r = 0.223$, $p = 0.307$), whose results were consistent with our previous observations showing that hsCRP was not associated with vascular inflammation of the carotid arteries evaluated by FDG-PET (33). Therefore, regulation by pioglitazone of systemic and local inflammation in the LMT may differ, and pioglitazone could directly attenuate the vascular inflammation by inhibiting macrophage activity within the atherosclerotic area. Carotid FDG activity was strongly correlated with macrophage infiltration in the carotid artery specimens of patients (11,12). Pioglitazone has been shown to not only suppress inflammation in murine carotid atherosclerosis by inhibiting macrophage activation (34), but also to inhibit in-stent restenosis in rabbits by reducing the release of monocyte chemoattractant protein-1 (35). These findings further support the concept that suppression of macrophage activation and infiltration in the coronary arteries may be a molecular target of pioglitazone, by which it could attenuate the LMT inflammation in our patients.

We have previously found that pioglitazone significantly decreases TBR values of carotid arteries and ascending aortas of the aortic arch, whose changes were inversely associated with those in plasma high-density lipoprotein cholesterol levels (16). However, in this study, ΔTBR of the LMT in pioglitazone group were not associated with differences in high-density lipoprotein cholesterol values. The finding may be related to relatively small numbers of patients. However, the differences of patients' characteristics and target vessels (carotid arteries and aortas vs. LMT) between the 2 studies might account for the discrepant results. Recently, it has been reported that markers of atherosclerotic burden at coronary and carotid arteries were not correlated with each other and were distinctly associated with pro-inflammatory cytokines (36). These findings suggest that vascular inflammation in carotid arteries and LMT may be differently regulated by pioglitazone.

**Study limitations.** The small sample size and various comedications may limit and confound the present findings. In the present study, some subjects were enrolled in our previous study (16). However, because baseline LMT TBR values in the pioglitazone versus the glimepiride group ($1.39 \pm 0.32$ vs. $1.45 \pm 0.29$) were almost equal to carotid TBR values of our previous study ($1.40 \pm 0.29$ vs. $1.28 \pm 0.27$) (16), it was unlikely that the present study may be underpowered for coronary PET analysis. Further, although the PERISCOPE trial, using coronary intravascular ultrasonography, demonstrated that pioglitazone, but not glimepiride, treatment for 18 months prevented atherosclerotic plaque progression of coronary arteries (24), CT angiography showed here that pioglitazone or glimepiride treatment for 16 weeks did not affect coronary artery remodeling evaluated by vessel diameters or calcification score. Therefore, a longitudinal study will be needed to address whether plaque inflammation in the LMT evaluated by FDG-PET could be a biomarker to predict atherosclerotic plaque progression and future cardiovascular events in patients with IGT or type 2 DM. Moreover, development of novel PET tracers would provide more specific information for detecting the inflammation in coronary arteries in humans independently of myocardial glucose uptake.

## CONCLUSIONS

Our present study demonstrated that pioglitazone attenuated the LMT inflammation in patients with IGT or type 2 DM in a glucose-lowering–independent manner. Pioglitazone may be a promising strategy for the treatment of high-risk patients, especially subjects with vulnerable atherosclerotic plaques in the coronary arteries.

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**Key Words:** computed tomography angiography ■ coronary artery disease ■ $^{18}$F-fluorodeoxyglucose–positron emission tomography ■ high-sensitivity C-reactive protein ■ pioglitazone ■ vascular inflammation.