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Peroxisome proliferator–activated receptor-γ agonist rosiglitazone reduces clinical inflammatory responses in type 2 diabetes with coronary artery disease after coronary angioplasty

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Abstract

Rosiglitazone, an agonist of peroxisome proliferator–activated receptor-γ (PPARγ), is an insulin-sensitizing antidiabetic agent and inhibits restenosis in animal blood vessels. However, its benefit for patients with type 2 diabetes and coronary artery disease (CAD) after percutaneous coronary intervention is unknown. Patients with diabetes and CAD who had undergone percutaneous coronary intervention were randomized to either receive or not receive rosiglitazone (4 mg/d) for 6 months. After 6 months of rosiglitazone treatment, the plasma levels of fasting glucose and insulin and those of hemoglobin A1C and homeostasis model assessment of insulin resistance were significantly decreased in the rosiglitazone group as compared with baseline levels and those in the control group. After 2 and 6 months of rosiglitazone treatment, the plasma level of high-density lipoprotein was significantly increased in the rosiglitazone group. In addition, plasma levels of monocyte chemoattractant protein-1 and C-reactive protein and hyperresponsiveness of low-dose lipopolysaccharide-induced monocyte chemoattractant protein-1 secretion from monocytes were reduced. Furthermore, the occurrence of coronary events was significantly decreased in the rosiglitazone group at 6-month follow-up. Our data indicate that rosiglitazone may protect the vascular wall through not only improving the features of metabolic disorders but also reducing proinflammatory responses and the occurrence of coronary events in patients with diabetes and CAD after percutaneous coronary intervention.

1. Introduction

Atherosclerosis is a multifactorial disease in which the occurrence of lesions may result in ischemia of the heart, which results in myocardial infarction. Recently, chronic subclinical inflammation is increasingly recognized as possibly contributing to the progression of atherosclerosis and restenosis after percutaneous coronary intervention [1,2]. The formation of atherosclerotic lesions involves accumulation of monocytes and T lymphocytes. Endothelial cell expression of inflammatory mediators such as chemokines and adhesion molecules and adhesion of leukocytes to endothelial cells are essential steps in atherosclerosis [3,4]. In addition, several prospective studies have demonstrated that the plasma level of C-reactive protein is associated with risk of atherosclerosis and may reflect the body's response to inflammatory reactions in atherosclerotic vessels [5,6].

Type 2 diabetes is characterized by insulin resistance and impaired glucose tolerance. Insulin resistance is often associated with dyslipidemia, hypertension, and atherosclerosis. Although the exact cause of atherosclerosis is not clear, improving the features of metabolic disorders characterized by insulin resistance can significantly decrease its risk.

Peroxisome proliferator–activated receptors (PPARs) are ligand-activated transcription factors that are a subfamily of the nuclear receptor gene family. The subfamily of PPARs consists of isoforms, α, β, and γ. The rosiglitazones are a class of pharmacological compounds with high affinity to PPARγ and enhance insulin-mediated glucose transport into

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adipose and skeletal muscle. They are clinically used for type 2 diabetes. Peroxisome proliferator–activated receptor-γ agonists have been shown in various animal models to decrease the risk of atherosclerosis by directly affecting the formation of atherosclerotic lesions through regulating gene expression of glucose and lipid metabolism [7-9]. Peroxisome proliferator–activated receptor-γ agonists suppress the migration and proliferation of vascular smooth muscle cells, inhibit the interaction between leukocyte endothelial cells, and decrease the expression of the vascular cell adhesion molecule-1 and intercellular adhesion molecule-1 in activated endothelial cells [10,11]. Furthermore, PPARγ agonists inhibit the production of monocyte inflammatory cytokines [12] and monocyte chemoattractant protein-1 (MCP-1)–directed transendothelial migration of monocytes [10,11]. Our previous study demonstrated that PPARγ agonists significantly reduce homocysteine-induced reactive oxygen species and secretion of MCP-1 and interleukin-8 in human monocytes [13]. Recently, clinical studies demonstrated that serum levels of metalloproteinase-9 and C-reactive protein in diabetic patients with or without coronary artery disease (CAD) were reduced after treatment with rosiglitazone [14,15]. However, whether PPARγ agonists can benefit patients with diabetes and CAD after percutaneous coronary intervention and, if so, what the underlying mechanisms are are still unclear. Our results showed that 4 mg/d rosiglitazone treatment for 6 months not only decreased insulin resistance but also reduced proinflammatory responses from monocytes and the occurrence of coronary events in patients with diabetes and CAD after percutaneous coronary intervention.

2. Material and methods

2.1. Subjects

Patients were selected from the cardiovascular internal medicine practice at the Peking University Third Hospital from October 2002 to May 2003. We included 71 patients, aged 50 to 73 years old, with a diagnosis of CAD (>50% stenosis as proven on angiography) and established type 2 diabetes mellitus. Patients with acute myocardial infarction during the preceding 12 weeks, cardiac insufficiency, renal function impairment, liver function impairment, systemic inflammatory disease, infectious disease, cancer, or a serious illness that would affect their participation or who were under insulin treatment were excluded.

2.2. Study design

All 71 patients had undergone angiography and percutaneous coronary intervention. The patients were randomly divided into 2 groups, the control group (n = 35) and the rosiglitazone treatment group (n = 35), which received 4 mg rosiglitazone daily for 6 months. One patient in the treatment group withdrew during follow-up. Blood was sampled before and after angiography at 2 and 6 months for analysis of clinical chemistry and inflammatory factors. Plasma was separated and stored at −70°C for further analysis.

All subjects gave their written informed consent. This study was approved by the ethics committee of the Health Science Center of the Peking University.

Table 1
Baseline clinical characteristics of patients with diabetes and CAD after percutaneous coronary intervention

	Control group (n = 35)	Rosiglitazone group (n = 35)
Character		
Age	62.2 ± 8.6	60.1 ± 8.5
Body mass index	25.6 ± 2.7	26.1 ± 2.5
Sex (M/F)	28:7	30:5
Risk factors (n)		
Hyperlipidemia	14	14
Hypertension	30	32
Smoking	21	25
Parameters (levels)		
Cholesterol (mmol/L)	5.1 ± 0.2	5.2 ± 0.2
HDL (mmol/L)	0.95 ± 0.05	0.95 ± 0.04
LDL (mmol/L)	2.94 ± 0.13	3.06 ± 0.12
Triglycerides (mmol/L)	2.06 ± 0.16	1.89 ± 0.25
Fasting insulin (mmol/L)	12.38 ± 0.64	13.88 ± 0.70
Fasting plasma glucose (mmol/L)	7.89 ± 0.39	7.8 ± 0.4
HbA1c (%)	7.33 ± 0.17	7.29 ± 0.17
HOMA-IR	4.86 ± 0.37	4.78 ± 0.36
CRP (mg/L)	1.49 (0.44-3.63)	1.61 (0.94-3.22)
MCP-1 (pg/mL)	169.5 (69.3-245.7)	183.6 (84-230.6)
sICAM-1 (ng/mL)	396.0 (320-482.2)	392.7 (366.0-513.1)
sP-selectin (ng/mL)	179.0 (118.7-283.1)	195.7 (124.0-235.8)
No. of lesions in the vessels	68	65
RCA/LCX/LAD	18:21:29	13:20:32
No. of target vessel revascularization	42	44
PTCA/stenting	5:37	6:38
Medication		
Aspirin	35	35
β-blocker	31	32
Lipid-lowering drugs	30	33
Nitrates	16	13
Ca antagonists	3	4
Angiotensin-converting enzyme inhibitors	33	33
Other antidiabetic drugs	16	13

Unless otherwise stated, values are mean ± SD or median (interquartile range).

Summarization of the clinical characteristics and laboratory findings of the study participants in the control group (n = 35) and rosiglitazone treatment group (n = 35). Statistical analysis indicates that the control and rosiglitazone groups had no significant difference from each other with respect to age, sex, body mass index, and smoking. The prevalence of hypertension, diabetes, and hypercholesterolemia was similar in the rosiglitazone and control groups, and the baseline laboratory values had no significant differences between these 2 groups. The number of lesions in the coronary artery vessels and target vessel revascularization also had no significant differences between the 2 groups. CRP indicates C-reactive protein; sICAM-1, soluble intercellular adhesion molecule-1; HbA1c, hemoglobin A1C; RCA, right coronary artery; LCX, left circumflex; LAD, left anterior descending artery; PTCA, percutaneous transluminal coronary angioplasty.

2.3. Responsiveness of monocytes to lipopolysaccharide

Venous blood samples were obtained from fasting subjects after 6 months to evaluate the effect of in vivo rosiglitazone treatment on chemokine MCP-1 production in isolated monocytes induced by low-dose lipopolysaccharide (LPS). Whole blood was separated into peripheral blood mononuclear cells and neutrophils by use of Nycoprep 1.077 (Life Technologies, Carlsbad, Calif), and then monocytes were isolated by their adherence to flasks. Adherent cells were then detached and resuspended in RPMI-1640 medium containing 5% autologous plasma. Freshly isolated monocytes (5×10^5) were incubated at 37°C with or without LPS (final concentration, 0.01 μg/mL) for 24 hours. The supernatant was harvested and stored at −70°C for further MCP-1 analysis.

2.4. Laboratory measurements

Levels of MCP-1 were measured by enzyme-linked immunosorbent assay (ELISA; R&D Systems Inc, Minneapolis, Minn), and plasma levels of soluble intercellular adhesion molecule-1 and soluble P selectin (sP-selectin) were measured by ELISA (GeneMay, Inc, San Diego, Calif) according to the manufacturer's protocols. The estimate of insulin resistance by homeostasis model assessment (HOMA-IR) was as follows: IR = [fasting insulin (μU/mL) × fasting glucose (mmol/L)]/22.5.

2.5. Statistical analysis

Within-treatment changes in levels from baseline to 2 and 6 months for MCP-1, C-reactive protein, soluble intercellular adhesion molecule-1, and sP-selectin were analyzed with use of the Wilcoxon matched-pairs signed ranks test. The difference between groups was analyzed by use of the Mann-Whitney tests. Values were expressed as median and ranges. Age, body mass index, and plasma levels of cholesterol, triglycerides, and glucose were analyzed with use of the Student t test and expressed as mean ± SD. Proportions were analyzed by use of the χ^2 test. A P value of less than .05 (2 tailed) was considered statistically significant.

3. Results

3.1. Clinical characteristics of patients

The characteristics of patients are summarized in Table 1. The control and rosiglitazone groups did not differ significantly in age, sex, and body mass index. The prevalence of smoking was similar, as was use of other medications. The baseline laboratory values and plasma levels of inflammatory factors were not significantly different. The prevalence of hypertension, diabetes, and hypercholesterolemia was similar in both groups. The number of lesions in the coronary

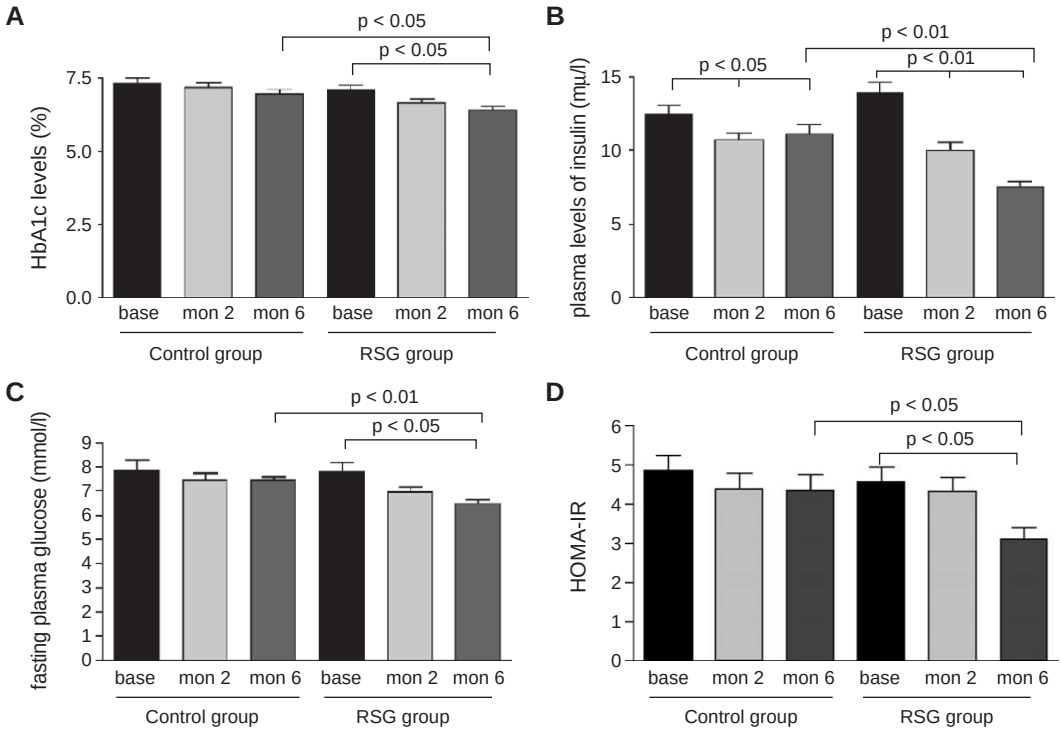

Fig. 1. Changes in levels of hemoglobin A1C (A), fasting plasma insulin (B) and glucose (C), and HOMA-IR (D) at 2 and 6 months of rosiglitazone treatment. Data are mean ± SEM. HbA1C indicates hemoglobin A1C; RSG, rosiglitazone.

artery vessel and target vessel revascularization also did not differ. Data on treatment drugs among the study groups are also presented in Table 1. At baseline and follow-up period, there were no significant differences in the proportion of patients receiving other drugs.

3.2. Effects of rosiglitazone treatment on diabetes features

As shown in Figs. 1A-C, after 6 months of rosiglitazone treatment, the levels of hemoglobin A1C and fasting plasma insulin and glucose were significantly decreased in the rosiglitazone group. Similarly, rosiglitazone significantly decreased the level of HOMA-IR after 6 months of treatment (Fig. 1D), as expected. In addition, 2 months of treatment led to fasting plasma insulin levels lower than baseline levels. However, hemoglobin A1C and fasting plasma glucose levels showed only a trend of improvement after 2 months of rosiglitazone treatment (Figs. 1A and C).

The levels of plasma lipid protein before and after rosiglitazone treatment are summarized in Figs. 2A-D. After 2 and 6 months of rosiglitazone treatment, the plasma levels of high-density lipoprotein (HDL) were significantly increased in the rosiglitazone group. In addition, 2 months of rosiglitazone treatment produced plasma HDL levels higher than those of the control group. However, total cholesterol, low-density lipoprotein (LDL), and triglyceride levels did not show a significant difference after 2 and 6 months of rosiglitazone treatment (Figs. 2A-D).

Weight gain can be a major drawback in treatment with a PPARγ agonist [16]. However, body weight after 6 months of rosiglitazone treatment was not significantly different from the baseline level and from that of the control group (data not shown).

3.3. Rosiglitazone effect on plasma levels of MCP-1 and C-reactive protein

The levels of MCP-1 in the plasma before and after rosiglitazone treatment are summarized in Fig. 3A. Plasma MCP-1 levels were significantly decreased in the rosiglitazone group compared with baseline levels and with those of the control group after 6 months of treatment (median, 146.7 vs 183.6 or 189.0 pg/mL, respectively). However, no significant differences were seen after 2 months of treatment (Fig. 3A).

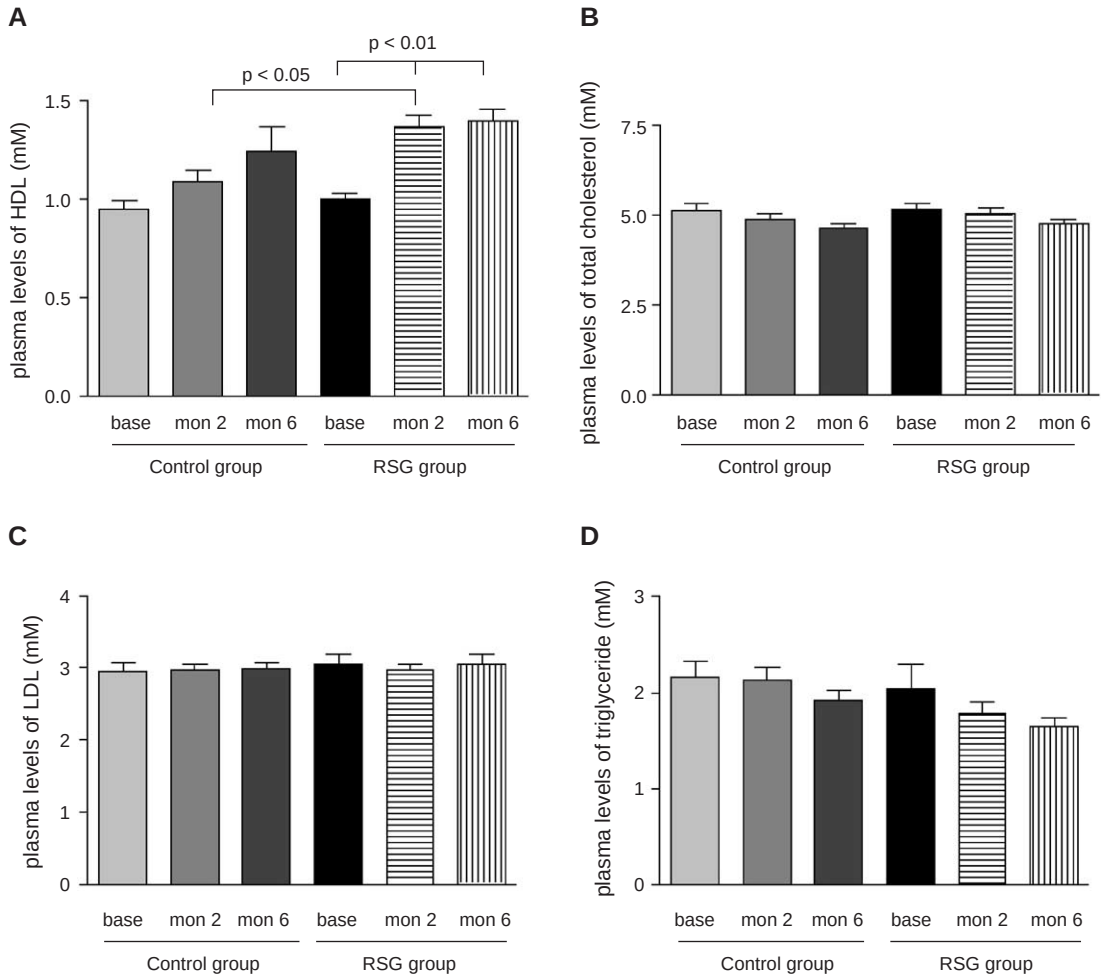

Fig. 2. Changes in levels of HDL (A), total cholesterol (B), LDL (C), and triglyceride (D) at 2 and 6 months of rosiglitazone treatment. Data are mean ± SEM.

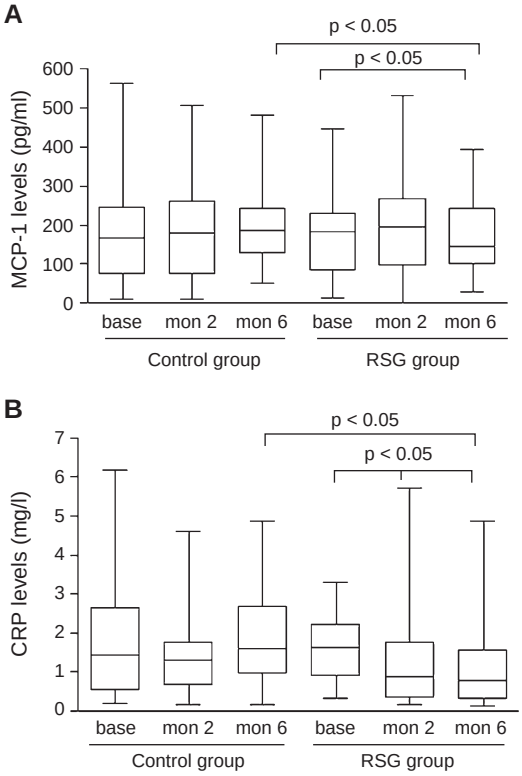

Fig. 3. Effect of rosiglitazone treatment on plasma levels of MCP-1 and C-reactive protein in patients with diabetes and CAD after percutaneous coronary intervention. The plasma levels of MCP-1 and C-reactive protein were assessed by ELISA. Data are medians and ranges. CRP: C-reactive protein; MCP-1: monocyte chemoattractant protein-1; PCI indicates percutaneous coronary intervention.

The levels of C-reactive protein in the plasma before and after rosiglitazone treatment are summarized in Fig. 3B. Plasma C-reactive protein levels in the rosiglitazone group were significantly reduced, from 1.62 to 0.89 and 0.77 mg/L after 2 and 6 months of treatment, respectively. Furthermore, plasma C-reactive protein levels were significantly decreased in the rosiglitazone group compared with the control group after 6 months of treatment (median, 1.59 vs 0.77 mg/L). C-reactive protein levels in the control group did not differ from baseline levels after 2 and 6 months.

However, rosiglitazone treatment had no significant effect on plasma levels of soluble intercellular adhesion molecule-1 and sP-selectin (data not shown).

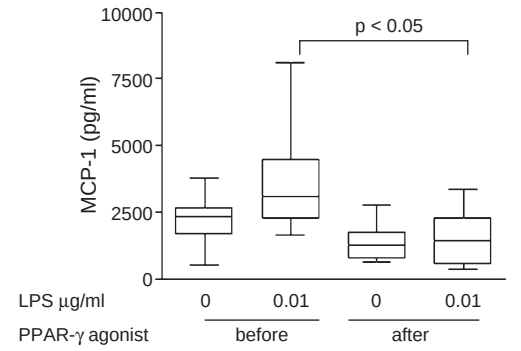

Fig. 4. Effect of rosiglitazone on LPS-induced MCP-1 production in isolated monocytes from patients with diabetes and CAD after percutaneous coronary intervention. Monocytes were isolated from patients before and after 6 months of 4 mg/d rosiglitazone treatment. The production of MCP-1 from isolated monocytes after stimulation with LPS (0.01 μg/mL) for 24 hours was assessed by ELISA. Data are medians and ranges. n = 8.

Table 2
Coronary events 6 months after rosiglitazone treatment

	Control group (n = 35)	Rosiglitazone group (n = 35)
Death	0	0
Recurrent MI	0	0
Recurrent angina	5	3
Target vessel repeat PCI	2	0
Any vessel PCI	1	0
CABG	4	1
Composite (death, MI, recurrent angina, CABG, PCI)	12	4*

MI indicates myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft.
* $P < .05$ vs control group.

3.4. Chemokine secretion from isolated monocytes in response to LPS

To test whether monocytes isolated from patients with diabetes and CAD show enhanced inflammatory response, peripheral monocytes were incubated with LPS (0.01-0.1 μg/mL) for 24 hours. As observed previously, LPS at 0.01 μg/mL but not at 0.1 μg/mL induced greater MCP-1 secretion in patients with diabetes and CAD than in control subjects (data not shown). To test whether enhanced MCP-1 secretion in isolated monocytes could be suppressed by rosiglitazone treatment, monocytes were incubated with LPS (0.01 μg/mL) for 24 hours. As shown in Fig. 4, rosiglitazone treatment for 6 months significantly lowered the low-dose LPS-induced secretion of MCP-1 (2450 to 3119 pg/mL vs 700 to 895 pg/mL). These results suggest that rosiglitazone treatment may benefit patients with diabetes and CAD, at least in part through the mechanism of anti-inflammation by inhibiting the hyperresponsiveness of LPS-induced chemokine secretion from monocytes.

3.5. Effect of rosiglitazone on coronary events after percutaneous coronary intervention

Four patients in the rosiglitazone group had coronary events (recurrent angina in 3 and coronary artery bypass graft in 1) vs 12 patients in the control group (recurrent angina in 5, target-vessel repeated percutaneous translational coronary angioplasty in 3, and coronary artery bypass graft in 4) at 6-month follow-up ($P < .01$; Table 2).

4. Discussion

Our study demonstrates that 6 months of rosiglitazone treatment significantly improved metabolic features, includ-

ing the levels of fasting plasma glucose, insulin, and hemoglobin A1C, in patients with diabetes and CAD. In addition to improving metabolic features, rosiglitazone treatment significantly decreased the levels of plasma MCP-1 and C-reactive protein compared with baseline levels and those of control subjects. Furthermore, it significantly reduced the hyperresponsiveness of low-dose LPS-induced secretion of MCP-1 from monocytes. Finally, the occurrence of coronary events was significantly reduced in the rosiglitazone group at 6-month follow-up.

Atherosclerosis is characterized by the recruitment of monocytes and lymphocytes to the artery wall. A number of studies have determined the important role of MCP-1 in atherosclerotic plaque formation and development [17]. Several perspective studies have demonstrated that plasma levels of the inflammatory marker C-reactive protein are positively associated with risk of cardiovascular disease and clinical events. C-reactive protein may reflect the body's response to inflammatory reactions in atherosclerotic vessels. However, it may exert a direct effect in promoting the progression of atherosclerosis and plaque vulnerability [6,18]. Pasceri et al [19] reported that C-reactive protein induces the expression of MCP-1 in human umbilical vein endothelial cells. As a regulator of lipid and glucose metabolism, PPARγ decreases plasma levels of cholesterol and glucose, which contribute to major risk factors for CAD. Peroxisome proliferator–activated receptor-γ is expressed in most cells of the vascular wall and atherosclerotic lesions [20,21]. Early in vitro studies of PPARγ in macrophages identified its anti-inflammatory and potentially antiatherogenic activities, including inhibiting cytokine production in the endothelium and expression of the transcription factors active protein-1 and nuclear factor-Kb [11]. Moreover, PPARγ has been shown to inhibit the production of inflammatory factors interlukin-6 and tumor necrosis factor-α in activated monocytes and to decrease MCP-1 gene expression [11,12]. These results suggest that rosiglitazone regulates the expression of key inflammatory factors involved in atherosclerosis. Recently, we showed that PPARγ agonists significantly reduce the homocysteine-induced formation of reactive oxygen species and expression of MCP-1 and interleukin-8 in human monocytes [13]. The C-reactive protein–mediated expression of MCP-1 is also decreased by the PPARγ ligand in human endothelial cells [19]. The binding of monocytes to adhesion molecules expressed on the surface of endothelial cells and their infiltration into the subendothelial may be reduced by PPARγ agonists. The expression of vascular cell adhesion molecule-1 and intercellular adhesion molecule-1 and the transendothelial migration of monocytes mediated by MCP-1 are inhibited by PPARγ agonists. A study by Marx et al [14] revealed that rosiglitazone reduces the levels of serum metalloproteinase-9 and tumor necrosis factor-α in patients with diabetes and CAD. Similarly, rosiglitazone treatment significantly reduced the levels of metalloproteinase-9 and C-reactive protein in patients with type 2 diabetes [15].

In the present study, we demonstrated further that rosiglitazone significantly decreases plasma MCP-1 levels and activates monocyte MCP-1 secretion in patients with diabetes and CAD after percutaneous coronary intervention. Given that chronic inflammation is important in atherosclerosis and restenosis after percutaneous coronary intervention, reducing hyperresponsiveness in monocytes and inhibiting MCP-1 and C-reactive protein levels by rosiglitazone might have potentially beneficial effects in patients with type 2 diabetes and CAD.

Despite the in vivo results found by Marx et al [14], we found that rosiglitazone had no significant effect on levels of soluble intercellular adhesion molecule-1 and sP-selectin.

Numerous studies have indicated that insulin resistance plays a central role in the development of type 2 diabetes mellitus. Patients with insulin resistance also have an enhanced risk of developing atherosclerosis. Rosiglitazone appears to enhance insulin action by modulating the activity of the PPARγ, which results in changes in the expression of a number of genes that are critically involved in glucose and lipid metabolism. Thiazolidinedione, a PPARγ agonist, has been shown to improve insulin action, decrease insulin levels, and lower blood glucose levels in fasting diabetic animal models and patients with diabetes [22]. Treatment with thiazolidinedione not only improved insulin sensitivity but also reduced triglyceride levels and increased HDL levels [23]. These changes are associated with the reversal of many components of the insulin resistance syndrome. Recently, Marx et al [14] reported that rosiglitazone treatment decreased hemoglobin A1C levels significantly, demonstrating that rosiglitazone exhibits its metabolic effects. Lebovitz et al [24] reported that rosiglitazone decreased mean hemoglobin A1C levels by 1.5% and reduced fasting plasma glucose levels by 3.2 mmol/L. Homeostasis model assessment estimates indicate that rosiglitazone reduces insulin resistance by 24%. Our results, together with previous ones, show that fasting plasma glucose and insulin and hemoglobin A1C levels are all decreased significantly by 6 months of rosiglitazone treatment. Thus, the reversal of the insulin resistance syndrome is associated with improved cardiovascular risk factors in patients with diabetes and CAD after percutaneous coronary intervention.

In addition to glucose lowering, the PPARγ agonist rosiglitazone influences lipid metabolism, likely by a PPARγ-mediated change in adipocyte metabolism and insulin sensitivity. In the present study, the plasma level of HDL was significantly increased in the rosiglitazone group compared with baseline levels and with that of the control group. However, the plasma levels of LDL, triglycerides, and total cholesterol did not change significantly after rosiglitazone treatment. One possible explanation is that reverse cholesterol transport and cholesterol efflux from foam cells are increased by upregulated liver X receptor-α expression [25]. Another possible explanation is that nearly all patients during the study are also taking statins, a class of

lipid-lowering drugs that mainly reduce triglycerides, LDL, and total cholesterol [26].

In recent years, PPARγ agonists have been used increasingly to treat patients with type 2 diabetes mellitus. Treatment of these patients is aimed at reducing not only plasma levels of glucose but also the incidence of complications, including CAD and myocardial infarction. Animal studies have shown that the PPARγ agonist troglitazone inhibits atherosclerosis in apolipoprotein E knockout mice [27]. Clinical studies have shown that troglitazone decreases the intimal and medial thickness of carotid arteries [28,29]. Furthermore, Takagi et al [30], through intravascular ultrasound study, demonstrated that troglitazone reduces intimal hyperplasia after coronary stent implantation in patients with type 2 diabetes mellitus. In the present study, we demonstrated that rosiglitazone treatment significantly reduced the occurrence of coronary events in patients with diabetes and CAD after percutaneous coronary intervention. Precisely how it decreases the events is still unclear; however, the effect of rosiglitazone on anti-inflammation and improved metabolism most likely contributes to its cardiovascular beneficial role.

Taken together, these results indicate that PPARγ may influence several key steps of atherosclerosis such as monocyte migration and activation, glucose metabolism, and local inflammatory response; therefore, the PPARγ agonist rosiglitazone may play an important role in protecting vasculature indirectly by normalizing the metabolic disorders of diabetes mellitus and depressing chronic inflammation of the vascular wall, eventually reducing the occurrence of coronary events in patients with type 2 diabetes and CAD after clinical percutaneous coronary intervention.

Acknowledgments

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