A Randomized Comparison of Pioglitazone to Inhibit Restenosis After Coronary Stenting in Patients With Type 2 Diabetes

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OBJECTIVE — Recent studies have demonstrated that the treatment with thiazolidinediones reduces in-stent restenosis. The aim of this study was to elucidate the mechanism of the efficacy of pioglitazone for preventing in-stent restenosis in type 2 diabetic patients.

RESEARCH DESIGN AND METHODS — We conducted a prospective, randomized trial involving 54 type 2 diabetic patients referred for coronary stenting who were randomly assigned to either the control or the pioglitazone group. Quantitative coronary angiography was performed at study entry and at 6 months follow-up. Endothelial nitric oxide synthase (eNOS), tumor necrosis factor α, interleukin-6, leptin, and adiponectin were measured at study entry and at 6 months follow-up.

RESULTS — A total of 28 patients were randomly assigned to the control group, and 26 patients were assigned to the pioglitazone group. There were no significant differences in glycemic control levels or in lipid levels in the two groups at baseline or at follow-up. Insulin, homeostasis model assessment of insulin resistance, eNOS, and leptin at follow-up were significantly reduced in the pioglitazone group compared with the control group. The late luminal loss and in-stent restenosis were significantly less in the pioglitazone group than in the control group. Leptin independently correlated with late luminal loss at multiple regression analysis.

CONCLUSIONS — The treatment with pioglitazone in type 2 diabetic patients significantly reduced leptin. This decreased leptin improved insulin resistance and endothelial function with the reduction of insulin. The improved endothelial function affected the reduction of in-stent restenosis.

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It has been reported that hyperinsulinemia is an independent risk factor for ischemic heart disease (1) and induces greater vascular smooth muscle cell proliferation in experimental models (2,3). Insulin resistance with hyperinsulinemia is associated with hypertension, glucose intolerance, obesity, and dyslipoproteinemias of low HDL cholesterol levels or hypertriglyceridemias, which are well-known risk factors for coronary artery disease (4–6).

Recent studies showed that insulin resistance is an independent predictor of early restenosis after coronary stenting (7) and is associated with an increased incidence of myocardial infarction and death (8). Takagi and colleagues (9,10) demonstrated that troglitazone reduces neointimal tissue proliferation after coronary stent implantation, but pioglitazone does not reduce in-stent restenosis significantly. Donghoon et al. (11) showed that treatment with rosiglitazone significantly reduces in-stent restenosis. The efficacy of the thiazolidinediones (TZDs), which are novel insulin-sensitizing agents, against in-stent restenosis remains controversial.

Endothelialization and endothelial function play an important role in coronary artery disease. Endothelial dysfunction has been considered a key element in the development of atherosclerosis and has also been found to be associated with insulin resistance (12).

The aim of this study was to elucidate the mechanism of the efficacy of pioglitazone for preventing in-stent restenosis in type 2 diabetic patients.

RESEARCH DESIGN AND METHODS

— The study was a randomized trial. Patients with acute coronary syndrome and type 2 diabetes who had received coronary stenting were eligible for the study if their homeostasis model assessment of insulin resistance (HOMA-IR) was >2.0 (13). Fifty-four patients were enrolled in this study. A total of 28 patients were randomly assigned to the control group and 26 patients were assigned to the pioglitazone group. Patients were not eligible for enrollment if they had spastic angina pectoris, congestive heart failure, hepatic dysfunction, chronic renal disease, recent stroke, impaired glucose tolerance, insulin-dependent diabetes, familial hypercholesterolemia, thyroid dysfunction, adrenal dysfunction, or an intolerance of aspirin, ticlopidine, heparin, pioglitazone, stainless steel, or contrast material. Subjects were also excluded if they were on any of the following medications: glucocorticoids, antineoplastic agents, psychoactive agents, bronchodilators, or any TZD.

We defined diabetes according to the World Health Organization definition from 1998 (14). Diabetes was defined as fasting plasma glucose (FPG) not <126 mg/dl (7.0 mmol/l) or 2-h blood glucose not <200 mg/dl (11.1 mmol/l).

We defined acute myocardial infarction (AMI) according to criteria jointly

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Abbreviations: AMI, acute myocardial infarction; eNOS, endothelial nitric oxide synthase; FPG, fasting plasma glucose; HOMA-IR, homeostasis model assessment of insulin resistance; TZD, thiazolidinedione.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

recommended by the European Society of Cardiology and the American College of Cardiology (15,16). Patients were diagnosed as having an AMI if they had two values of serum troponin T >0.1 ng/ml or CK-MB >7 ng/ml together with either typical symptoms (chest pain >15 min, pulmonary edema in the absence of valvular heart disease, cardiogenic shock, or arrhythmia, such as ventricular fibrillation or ventricular tachycardia), new Q waves in at least two of the twelve standard electrocardiographic leads, or electrocardiogram changes indicating acute ischemia (ST-elevation, ST-depression, or T wave inversion).

The study population consisted of patients in whom intracoronary stents were successfully placed after percutanerous transluminal coronary angioplasty at our institution. Before undergoing catheterization, 100 mg aspirin and 200 mg ticlopidine were started orally, and all patients intravenously received a 5,000-unit bolus of heparin in the absence of contraindications. Left ventriculography and coronary angiography were performed. Patients were evaluated at 6 months by an angiographic study and laboratory studies. The indications for stenting were extensive coronary artery dissection after percutanerous transluminal coronary angioplasty, complete vessel closure, or residual stenosis of ≥25% of the vessel diameter. All patients in whom stenting was successful (i.e., in whom the stent was placed at the desired position and there was <25% residual stenosis) and who gave their written, informed consent to participate in the study were eligible for randomization. All eligible patients were randomly assigned to a control group and a pioglitazone group in a 1:1 ratio. In patients assigned to pioglitazone therapy, pioglitazone (30 mg once a day), a novel insulin-sensitizing agent, was started 2 weeks after the procedure. The randomization sequence was specified before the study began. The study was carried out according to the principles of the Declaration of Helsinki and was approved by our institutional ethics committee.

Quantitative coronary angiographic evaluation

Coronary angiograms were obtained in multiple views after the intracoronary injection of nitrates. Quantitative analyses of all angiographic data before and after the procedure were performed by operators who were unaware of the study groups to which the patients were assigned. The luminal diameter of the coronary artery and the degree of stenosis were measured before dilation, at the end of the procedure, and at 6 months. Restenosis was defined as stenosis of ≥50% of the luminal diameter. The target lesion was defined as the stented segment plus the 5-mm segments proximal and distal to the stented segment.

Laboratory studies

We measured concentrations of overnight FPG, total cholesterol, HDL cholesterol, triglycerides, insulin, and glycosylated hemoglobin (HbA_{1c}) at study entry and at 6 months follow-up. Endothelial nitric oxide synthase (eNOS) and leptin were measured with enzyme-linked immunosorbent assay kits (R&D Systems). In addition, since studies have also implicated several adipocyte-derived hormones (tumor necrosis factor α [17], interleukin-6 [18], and adiponectin [19]) in causing insulin resistance, we also measured plasma concentrations of these factors. A standardized oral glucose tolerance test with 75 g glucose was taken at 6 months after percutanerous transluminal coronary angioplasty (20). An estimate of insulin resistance was calculated using HOMA-IR as follows: insulin resistance = FPG (mg/dl) × fasting plasma insulin (μU/ml)/405 (21). LDL cholesterol concentrations were estimated with the equation of Friedwald et al. (22).

Study end point

The primary angiographic end point was in-stent luminal late loss, as determined by quantitative angiography. Secondary end points included the percentage of in-stent stenosis of luminal diameter, the rate of restenosis (luminal narrowing of ≥50%), and the minimal luminal diameter of the stented segment and of the 5-mm segments proximal and distal to the stent at 6 months.

The primary clinical end point of the study was a composite of major cardiac events, including death, Q wave or non–Q wave myocardial infarction, coronary artery bypass grafting, and revascularization of the target lesion or vessel after the procedure. A non–Q wave myocardial infarction was defined by an increase in the creatine kinase level to more than twice the upper limit of the normal range, accompanied by an increased level

Table 1—*Clinical characteristics of patients*

	Control group	Pioglitazone group	*P* values*
n	28	26	
Age (years)	67.5 ± 10.3	66.2 ± 8.6	0.674
Male sex (%)	20 (71.4)	19 (73.1)	0.893
BMI (kg/m^2)	24.6 ± 3.5	24.6 ± 3.9	0.996
Follow-up	24.5 ± 2.9	24.7 ± 3.6	0.818
P values	0.57	0.901	
Systolic blood pressure (mmHg)	131.7 ± 16.9	126.9 ± 19.4	0.405
Follow-up	133.2 ± 19.6	125.1 ± 23.4	0.268
P values	0.847	0.937	
Diastolic blood pressure (mmHg)	74.1 ± 11.1	74.3 ± 7.5	0.958
Follow-up	74.6 ± 9.9	73.5 ± 8.8	0.744
P values	0.784	0.762	
Risk factors (%)			
Hypertension (%)	13 (46.4)	10 (38.1)	0.554
Hyperlipidemia (%)	17 (61.9)	20 (76.9)	0.2
Cigarette smoking (%)	9 (32.1)	6 (23.1)	0.457
Acute coronary syndrome			
Unstable angina pectoris (%)	13 (46.4)	8 (30.9)	0.238
AMI (%)	15 (53.6)	18 (69.1)	0.238
Treatments			
β-Blockers	4 (14.3)	5 (19.5)	0.724
ACE inhibitors	5 (17.9)	5 (19.5)	>0.999
Angiotensin receptor blocker	11 (39.3)	14 (53.8)	0.283
Statins	13 (46.4)	16 (61.5)	0.266
α Glucosidase	17 (60.7)	15 (57.7)	0.821
Sulfonylureas	12 (42.9)	15 (57.7)	0.276

Data are means ± SD or *n* (%).

of CK-MB, in the absence of new Q waves on the surface electrocardiogram.

Statistical analysis

Results are expressed as means ± SD or as proportions (%). The Student's *t* test was used for parametric data when normal distribution and equal dispersion were recognized. The Mann-Whitney *U* test and the Wilcoxon's signed-rank test were used when the variance was unequal. Differences in the categorical data were analyzed by χ^2 analysis, and the Fisher's exact test was used when appropriate. Multiple regression analysis was performed with late loss as the dependent variable and other parameters (insulin, eNOS, leptin, and HOMA-IR, which were significantly different at follow-up, compared the control group with the pioglitazone group) as independent variables. Differences were considered to be statistically significant when the *P* values was <0.05.

RESULTS

Clinical characteristics of the patients

Clinical characteristics of patients are shown in Table 1. The two groups were similar to all variables examined. Overall, 72.2% of patients were men, and the mean age was 66.9 years with the prevalences of dyslipidemia, hypertension, and current tobacco use. Stenting was performed because of unstable angina pectoris in 38.9% of patients and AMI in 61.1% of the patients. A total of 60.7% of patients in the control group and 38.5% of patients in the pioglitazone group had been previously treated for diabetes ($P = 0.102$), and the remaining patients had newly diagnosed diabetes. There were no significant differences in the various treatments except for pioglitazone in the two groups.

Laboratory characteristics of patients

Laboratory characteristics of patients are shown in Table 2 and 3. There were no significant differences in glycemic control levels or in lipid levels in the two groups at baseline or at follow-up. FPG, insulin, HbA_{1c}, HOMA-IR, eNOS, and leptin in the pioglitazone group were significantly reduced at follow-up compared with at study entry. Insulin, HOMA-IR, eNOS, and leptin at follow-up were significantly reduced in the pioglitazone group compared with the control group.

Table 2—*Laboratory characteristics of patients*

	Control group	Pioglitazone group	*P* values
n	28	26	
Glucose (mmol/l)	8.9 ± 3.7	9.1 ± 3.5	0.861
Follow-up	7.7 ± 2.1	6.8 ± 1.4	0.119
P values	0.122	0.024	
Insulin (pmol/l)	55.1 ± 25.2	69.7 ± 46.4	0.278
Follow-up	56.0 ± 33.6	35.6 ± 15.1	0.032
P values	0.983	0.033	
HbA_{1c} (%)	6.9 ± 1.6	7.7 ± 2.2	0.143
Follow-up	6.5 ± 1.2	6.0 ± 0.9	0.263
P values	0.356	0.028	
HOMA-IR	4.40 ± 3.33	5.75 ± 4.70	0.315
Follow-up	3.33 ± 2.69	1.95 ± 1.05	0.031
P values	0.345	0.012	
Total cholesterol (mmol/l)	4.75 ± 0.88	5.09 ± 1.20	0.263
Follow-up	4.79 ± 0.86	4.88 ± 1.04	0.791
P values	0.883	0.302	
HDL cholesterol (mmol/l)	1.08 ± 0.28	1.13 ± 0.30	0.513
Follow-up	1.09 ± 0.30	1.09 ± 0.31	0.993
P values	0.456	0.667	
Triglycerides (mmol/l)	1.50 ± 1.25	1.09 ± 0.37	0.667
Follow-up	1.60 ± 0.72	1.70 ± 0.92	0.706
P values	0.101	0.687	
LDL cholesterol (mmol/l)	2.98 ± 0.58	3.16 ± 0.79	0.403
Follow-up	2.97 ± 0.65	3.03 ± 0.96	0.832
P values	0.865	0.352	

Data are means ± SD.

Quantitative angiographic analysis

Angiographic and procedural data are summarized in Table 4. The lesions in the two groups were treated similarly with the use of conventional techniques. The target vessel was the left anterior descending coronary artery in 33.3% of the patients, the right coronary artery in 35.2%, and left circumflex artery in 31.5%. The treated lesion types according to the American College of Cardiology/American Heart Association classification were similar in the two groups. All stents were bare metal, including the PENTA and the ZETA stent (Guidant, Santa Clara, CA), the Express stent (Boston Scientific, ON,

Table 3—*The changes of adipocytokines and eNOS*

	Control group	Pioglitazone group	*P* values
n	28	26	
eNOS (pg/ml)	22.0 ± 11.8	25.7 ± 9.3	0.375
Follow-up	26.6 ± 10.9	14.4 ± 10.6	0.01
P values	0.114	0.014	
Interleukin-6 (pg/ml)	33.1 ± 18.1	27.1 ± 19.7	0.448
Follow-up	16.6 ± 10.2	17.9 ± 11.1	0.76
P values	0.048	0.245	
Tumor necrosis factor α (pg/ml)	9.2 ± 4.4	10.8 ± 4.3	0.349
Follow-up	10.3 ± 4.4	11.9 ± 3.2	0.318
P values	0.967	0.492	
Leptin (ng/ml)	11.0 ± 6.0	15.6 ± 8.9	0.166
Follow-up	10.3 ± 4.4	4.2 ± 3.1	0.002
P values	0.829	0.0005	
Adiponectin (μg/ml)	7.2 ± 4.3	7.6 ± 5.5	0.853
Follow-up	9.2 ± 8.6	13.2 ± 9.2	0.25
P values	0.661	0.132	

Data are means ± SD.

Table 4—*Angiographic and procedural characteristics*

	Control group	Pioglitazone group	*P* value
n	28	26	
Number of narrowed coronary arteries			
One (%)	6 (21.4)	9 (34.6)	0.28
Two (%)	15 (53.6)	11 (42.3)	0.408
Three (%)	7 (25.0)	6 (23.1)	0.869
Lesion-related variables (%)			
LAD	7 (25.0)	11 (42.3)	0.178
LCX	10 (35.7)	7 (26.9)	0.487
RCA	11 (39.3)	8 (30.8)	0.513
Lesion type (%)			
A	4 (14.3)	5 (19.2)	0.724
B1	13 (46.4)	9 (35.3)	0.377
B2	6 (21.4)	5 (19.2)	0.841
C	5 (17.9)	7 (26.9)	0.423
Procedural variables			
Stent length (mm)	16.9 ± 3.1	18.4 ± 2.9	0.159
Stent diameter (mm)	3.0 ± 0.4	3.2 ± 0.4	0.155
Final balloon pressure (atm)	11.8 ± 3.3	11.8 ± 2.2	0.94
Quantitative coronary analysis			
Reference vessel diameter (mm)	2.90 ± 0.48	3.17 ± 0.25	0.1238
Minimal luminal diameter (mm)	0.13 ± 0.20	0.09 ± 0.13	0.1243
Acute gain (mm)	2.77 ± 0.48	3.08 ± 0.30	0.0301
Late loss (mm)	1.43 ± 1.04	0.30 ± 0.66	0.0008
Loss index	0.53 ± 0.39	0.13 ± 0.27	0.0185
Restenosis (%)	16 (57.1)	2 (7.7)	0.0052
Lesion length (mm)	14.2 ± 8.0	14.7 ± 7.2	0.81

Data are means ± SD or *n* (%). LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; RCA, right coronary artery.

Canada), the Duraflex stent (Avantec Vascular, Sunnyvale, CA), and the S670 stent (Medtronic, Minneapolis, MN). The mean reference diameter of the target vessel, the mean minimal luminal diameter, and the mean length of the lesion at baseline were similar in the two groups. The late luminal loss and in-stent restenosis were significantly less in the pioglitazone group than in the control group. Leptin at follow-up independently correlated with late loss at multiple regression analysis ($r = 0.490$, $P = 0.004$ [insulin: $r = -068$, $P = 0.109$; eNOS: $r = 0.006$, $P = 0.474$; leptin: $r = 0.073$, $P = 0.012$; and HOMA-IR: $r = 0.166$, $P = 0.135$]).

Safety of treatment

Pioglitazone was well tolerated in all patients, and no patients in the pioglitazone group had transient elevation of liver enzyme levels two or more times the upper limits, severe congestive heart failure, or edema.

Major adverse cardiac events

One patient in the control group had a Q wave myocardial infarction during a follow-up period. Death or non–Q wave myocardial infarction did not occur in either group. Percutaneous revascularization of the target lesion was performed in 16 patients in the control group and 2 patients in the pioglitazone group. Coronary artery bypass grafting was not performed in either group. There was a lower incidence of major adverse cardiac events at 6 months in the pioglitazone group than in the control group (60.7 vs. 7.7%, $P < 0.0001$).

CONCLUSIONS — This study demonstrated that pioglitazone significantly reduced restenosis 6 months after coronary stenting in the type 2 diabetic patients. These effects were dependent on improving endothelial function and the decreased leptin by the treatment with pioglitazone. This is the first study in which the criterion to treat patients with insulin resistance was considered. The treatment with pioglitazone resulted in a sevenfold reduction in the rate of restenosis in stent compared with the control group.

The European Group for the Study of Insulin Resistance has reported that it is not possible to propose a universal cutoff of insulin for insulin resistance in the comment on the provisional report from the World Health Organization consultation (23). Previously, we have demonstrated as follows (13). One of the previous studies was carried out for 4 months' follow-up with 61 nondiabetic patients with AMI who had undergone coronary stenting. There are the insulin-resistant patients and the patients who were not insulin resistant. Insulin resistance consists of the transient insulin resistance that correlated with thyrotropin, glucagon, and cortisol and the continuous insulin resistance that correlated with leptin in nondiabetic patients with AMI. Continuous insulin resistance affects restenosis after coronary stenting. The cutoff value of HOMA-IR for restenosis after coronary stenting is 2.0. Late loss was significantly higher in the insulin-resistant patients than in the patients who were not insulin resistant. We selected patients with type 2 diabetes and HOMA-IR >2.0 to conduct this study on equal terms. It is very important to consider the efficacy of pioglitazone because not all patients with type 2 diabetes are insulin resistant. It may well be that pioglitazone is not efficacious against patients who are not insulin resistant from the point of view of restenosis. Takagi et al. (10) demonstrated that TZDs reduce neointimal tissue proliferation after coronary intervention using serial intravascular ultrasound scanning and that troglitazone reduces in-stent restenosis with type 2 diabetes. Some reported that TZDs did not reduce the in-stent restenosis despite reducing neointimal tissue proliferation (24,25). The discrepancy in the previous studies may be caused by the existence of the non–insulin-resistant patients.

Pioglitazone is an antidiabetic agent of the TZD class. TZD's cellular actions are mediated by binding to its nuclear receptor, the peroxisome proliferator–activated receptor γ. These agents have been primarily viewed as insulin-sensitizing agents (26). These drugs inhibit growth factor–induced proliferation of vascular smooth muscle cells, inhibit smooth muscle cell migration, and attenuate the development of intimal hyperplasia after balloon-induced vascular injury in animal models (27,28).

Leptin, a hormone related to fat metabolism and insulin resistance, has been recognized as an independent risk factor for coronary heart disease in a large co-

hort of the West of Scotland Coronary Prevention Study (29) and promotes vascular remodeling and neointimal tissue proliferation (30). Several studies (31,32) suggested that insulin regulates leptin production and strong positive correlations between leptin and insulin concentrations. Moreover, recent studies (33) have suggested that leptin enhances the NO system. Endothelial production of NO plays an important role in preventing vascular disease through regulation of thrombosis, inflammation, vasculartone, and remodeling (34). The increase in fasting NO levels, suggesting impairment of endothelial function and cardiovascular disease, has been reported in insulin-resistant patients (35–37). Our data suggested that the endothelium with insulin resistance is hyperactivated by hyperleptinemia, that it causes excess proliferation of the impaired endothelium after coronary stenting, and that the treatment with pioglitazone reduced leptin and improved endothelial function. Leptin independently correlated with late loss at multiple regression analysis but not eNOS or insulin. It suggested that there may be direct action of leptin on the endothelium. Knudson et al. (38) demonstrated that leptin receptor is present in coronary arteries and coupled to NO-dependent vasodilation and that hyperleptinemia produces significant coronary endothelial dysfunction.

Recent studies have demonstrated that pioglitazone increase plasma adiponectin level (39), which is associated with endothelial dysfunction (40) and coronary risk factor (41). In this study, plasma adiponectin level was not statistically increased but tended to increase after pioglitazone treatment. Pioglitazone may affect plasma leptin levels more than plasma adiponectin levels. The treatment for coronary artery disease is revascularization, which means recanalization, endothelialisation, and prevention of restenosis. The treatment with pioglitazone improved endothelial function and prevented restenosis after coronary stenting.

Study limitations

This study had some limitations. First, it was a single-center, nonplacebo-controlled study with small number of patients. Second, intravascular ultrasound cannot be used to measure lumen dimensions. One millimeter was the smallest minimal luminal diameter and 0.8 mm^2 was the smallest cross-sectional lumen area that could be measured by intravascular ultrasound before intervention (42). The mean minimal luminal diameters in this study were <1.0 mm.

Conclusions

The treatment with pioglitazone in type 2 diabetic patients significantly reduced leptin. This decreased leptin improved insulin resistance and endothelial function with the reduction of insulin. The improved endothelial function affected the reduction of in-stent restenosis.

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