The Effect of Rosiglitazone on Serum Lipoprotein(a) Levels in Korean Patients With Type 2 Diabetes Mellitus

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The aim of the study was to determine if rosiglitazone increases serum levels of lipoprotein(a) [Lp(a)] in Korean patients with type 2 diabetes mellitus. A total of 118 patients were divided into 2 groups: those with rosiglitazone (rosiglitazone group, n = 49) and those without rosiglitazone (control group, n = 69). The rosiglitazone group was given rosiglitazone (4 mg/d) with previous treatment, insulin, or sulfonylurea, for 12 weeks, whereas the control group continued previous treatment with some dose modification for glycemic control. The patients had their blood glucose, lipid levels, as well as Lp(a) levels assessed to obtain a baseline, which were remeasured 12 weeks later. The fasting blood glucose and glycosylated hemoglobin (HbA_{1c}) levels decreased significantly in both groups as compared with the baseline. The fasting glucose and HbA_{1c} levels in both groups were similar at 12 weeks. The total cholesterol levels increased significantly in the rosiglitazone group (190.6 ± 32.4 to 212.2 ± 47.2 mg/dL, $P = .002$), while they were unchanged in the control group (185.4 ± 36.8 to 188.0 ± 35.8 mg/dL, $P = .615$). The triglyceride levels did not change in either group. Significant increases in high-density lipoprotein (HDL) cholesterol levels were observed in the rosiglitazone group as compared with the baseline (41.7 ± 10.6 to 45.9 ± 11.4 mg/dL, $P = .004$). The low-density lipoprotein (LDL) cholesterol levels increased significantly in the rosiglitazone group (120.5 ± 29.9 to 136.3 ± 40.0 mg/dL, $P = .012$), while they did not change in the control group (113.0 ± 29.1 to 118.3 ± 31.7 mg/dL, $P = .234$). Significant increases in Lp(a) levels were observed in the rosiglitazone group as compared with the baseline (22.4 ± 17.4 to 25.7 ± 20.5 mg/dL, $P = .015$), approximately a 15% increase in average values. In contrast, there was no change in Lp(a) levels in the control group. There was no correlation between the changes in Lp(a) and changes in fasting blood glucose or HbA_{1c} levels in all study subjects. In summary, rosiglitazone increased serum total cholesterol, LDL cholesterol, as well as Lp(a) levels in patients with type 2 diabetes mellitus. Considering that patients with type 2 diabetes mellitus have increased risks for cardiovascular disease, caution should be taken when prescribing rosiglitazone to patients who already have other risk factors, such as hypertension and smoking.

LIPOPROTEIN(a) [Lp(a)] is a low-density lipoprotein (LDL)-like substance with apolipoprotein (a) bound to apolipoprotein B-100 by disulfide bond.[1] Although most studies have reported that Lp(a) levels are not increased in patients with type 2 diabetes mellitus,[2-4] elevated Lp(a) levels are considered an independent risk factor for cardiovascular disease in these patients.[5,6]

Thiazolidinedione (TZD) derivatives, such as troglitazone, rosiglitazone, and pioglitazone are a new class of antidiabetic agents that reduce hyperglycemia through binding to the peroxisome proliferator-activated receptor-γ (PPAR-γ) and altering expression of components that influence insulin signaling and the glucose transport system.[7] In addition, TZDs are known to affect lipid metabolism.[8-13] Recently, troglitazone has been reported to increase serum levels of Lp(a) in patients with type 2 diabetes mellitus,[14,15] which has raised concern that this may increase the well-known risk of cardiovascular disease in these patients.[16] However, the effect of rosiglitazone on Lp(a) has not been evaluated.

Therefore, this prospective study was conducted to determine if rosiglitazone increases serum levels of Lp(a) in Korean patients with type 2 diabetes mellitus.

SUBJECTS AND METHODS

Patients

A total of 136 patients with type 2 diabetes mellitus were recruited from the diabetes clinic at St. Vincent's Hospital in Suwon, Korea. The inclusion criteria for type 2 diabetes mellitus were: use of sulfonylurea, metformin, or insulin for glycemic control; absence of a history of diabetic ketoacidosis; onset of diabetes >40 years old; and fasting C-peptide level >1.0 ng/mL in the insulin-requiring patients.[17] Subjects with serum creatinine >1.2 mg/dL, overt proteinuria, active or chronic liver disease, malignancy, and heart failure were excluded from the study. None were taking estrogen hormone, hypolipidemic drugs, or glucocorticoids.

The patients were divided into 2 groups: those with rosiglitazone (rosiglitazone group) and those without rosiglitazone (control group). The rosiglitazone group was given rosiglitazone (4 mg/d) with previous treatment (insulin or sulfonylurea) for 12 weeks, whereas the control group continued previous treatment (insulin, sulfonylurea or metformin) with some dose modification for glycemic control. Rosiglitazone was not added to patients previously treated with sulfonylurea plus metformin, because its use is not approved in Korea. At baseline, patients gave their blood samples for assessment of glycemic control, lipid levels, as well as Lp(a) levels, which were remeasured 12 weeks after randomization.

Of 136 patients selected for this study, 60 patients received rosiglitazone. Twelve patients were lost to follow-up; 5 in the rosiglitazone group and 7 in the control group. Six patients discontinued rosiglitazone because of edema or weight gain. Therefore, 118 patients completed the study: 69 patients in the control group and 49 patients in the rosiglitazone group. The analysis was performed from the data of these 118 patients.

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Table 1. Clinical Characteristics of Study Subjects at Baseline

	Control Group (n = 69)	Rosiglitazone Group (n = 49)
Age (yr)	60.2 ± 8.8	61.6 ± 8.2
Sex (male/female)	25/44	15/34
Duration of diabetes (yr)	6.3 ± 4.7	9.3 ± 6.1*
Body mass index (kg/m^2)	26.1 ± 3.8	25.3 ± 3.0
Previous treatment (n)		
Sulfonylurea	30	32
Sulfonylurea + metformin	16	0
Insulin	21	17
Insulin + metformin	2	0

NOTE. Data are means ± SD or no.
*$P < .05$.

Laboratory Analysis

After an overnight fast, blood samples were obtained at baseline and after 12 weeks of treatment. The blood glucose level was measured using an automated enzymatic method, and the glycosylated hemoglobin (HbA_{1c}) level was determined by a boronate affinity binding assay (Abbott, North Chicago, IL) with a reference range of 4.4% to 6.4%. The total cholesterol and triglyceride levels were measured enzymatically. The high-density lipoprotein (HDL) cholesterol level was measured enzymatically after precipitation of the other lipoproteins. The LDL cholesterol level was calculated using Friedewald's equation[18] if the serum triglyceride level was <400 mg/dL. Serum Lp(a) was measured by a 1-step sandwich enzyme-linked immunoassay technique (TintElize Lp(a) kit; Biopool AB, Umea, Sweden) on samples stored at 4°C for up to 24 hours. The intra- and interassay coefficients of variation were 4.5% and 6.7%, respectively.

Statistical Analysis

Statistical analyses were performed using the statistical package StatView (Abacus Concepts, Berkeley, CA) for Macintosh version 4.5. Because of their skewed distribution, Lp(a) and triglyceride levels were compared after logarithmic transformations. The paired *t* test was used to compare the changes in the values after treatment. The Pearson's correlation was used to analyze the correlation between changes in the fasting blood glucose or HbA_{1c} levels and the changes in Lp(a) levels. A $P < .05$ was considered significant.

RESULTS

Clinical Characteristics

The clinical characteristics of the study subjects at the baseline are shown in Table 1. There was no difference in age, sex distribution, and body mass index between the control and rosiglitazone groups, although the duration of diabetes was significantly longer in the rosiglitazone group (9.3 ± 6.1 *v* 6.3 ± 4.7 years, $P = .004$).

Changes in Glycemic Control, Lipid Levels, and Lp(a)

The baseline fasting blood glucose and HbA_{1c} levels in the control and rosiglitazone groups were similar. After 12 weeks, those levels decreased significantly in both groups. No difference in the fasting glucose and HbA_{1c} levels was found between both groups after 12 weeks, suggesting similar glycemic control during follow-up (Table 2).

The total cholesterol levels increased significantly in the rosiglitazone group (190.6 ± 32.4 to 212.2 ± 47.2 mg/dL, $P = .002$), while they did not change in the control group (185.4 ± 36.8 to 188.0 ± 35.8 mg/dL, $P = .615$). The triglyceride levels did not change in either group. At baseline, the HDL cholesterol levels were significantly lower in the rosiglitazone group compared with those in the control group (41.7 ± 10.6 *v* 46.7 ± 13.3 mg/dL, $P = .034$). Significant increases in the HDL cholesterol levels were observed in the rosiglitazone group as compared with baseline (41.7 ± 10.6 to 45.9 ± 11.4 mg/dL, $P = .004$). However, in the control group, the HDL cholesterol levels decreased significantly (46.7 ± 13.3 to 43.7 ± 10.7 mg/dL, $P = .017$). The LDL cholesterol levels increased significantly in the rosiglitazone group (120.5 ± 29.9 to 136.3 ± 40.0 mg/dL, $P = .012$), while they did not change in the control group (113.0 ± 29.1 to 118.3 ± 31.7 mg/dL, $P = .234$) (Table 2). The total cholesterol/HDL cholesterol and the LDL cholesterol/HDL cholesterol ratios did not change in the rosiglitazone group (4.8 ± 1.2 to 4.8 ± 1.3, $P = .882$; 3.1 ± 1.1 to 3.1 ± 1.0, $P = .794$).

Significant increases in Lp(a) levels were observed in the rosiglitazone group as compared with the baseline (22.4 ± 17.4, 18.0 to 25.7 ± 20.5, 21.5 mg/dL [mean ± SD, median], $P = .015$). In contrast, there was no change in Lp(a) levels in the control group (Table 2, Fig 1). Although a few reports have shown that metformin may lower Lp(a) levels,[19,20] Lp(a) levels obtained excluding the 18 patients with metformin in the control group also did not change (24.9 ± 17.6 to 22.2 ± 13.3 mg/dL, $P = .493$). There was no correlation between the changes in Lp(a) and changes in the fasting blood glucose ($r = .01$, $P = .924$) or HbA_{1c} levels ($r = .17$, $P = .197$) in all study subjects. In addition, the changes in the LDL cholesterol levels

Table 2. Changes in Glycemic Control, Lipid, and Lp(a) Levels Before and After 12 Weeks of Treatment

	Control Group (n = 69)		Rosiglitazone Group (n = 49)	
	Before	After	Before	After
Fasting glucose (mg/dL)	192.6 ± 90.9	161.9 ± 71.1*	213.8 ± 82.6	167.3 ± 77.8†
HbA_{1c} (%)	9.6 ± 2.6	8.0 ± 1.5*	9.4 ± 1.9	8.6 ± 1.5†
Total cholesterol (mg/dL)	185.4 ± 36.8	188.0 ± 35.8	190.6 ± 32.4	212.2 ± 47.2†
Triglyceridse (mg/dL)	128.4 ± 61.9	129.3 ± 68.9	141.5 ± 61.8	150.1 ± 79.4
HDL cholesterol (mg/dL)	46.7 ± 13.3	43.7 ± 10.7*	41.7 ± 10.6*	45.9 ± 11.4†
LDL cholesterol (mg/dL)	113.0 ± 29.1	118.3 ± 31.7	120.5 ± 29.9	136.3 ± 40.0†
Lp(a) (mg/dL)	24.6 ± 18.6	23.0 ± 15.8	22.4 ± 17.4	25.7 ± 20.5†

NOTE. Variables are mean ± SD.
*$P < .05$ *v* before in the control group.
†$P < .05$ *v* before in the rosiglitazone group.

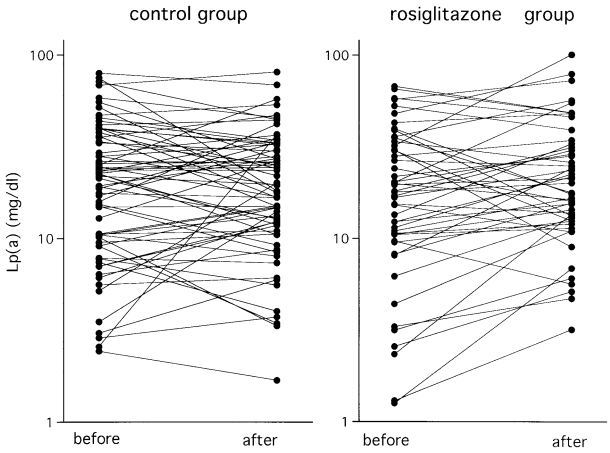

Fig 1. Lp(a) levels before and after 12 weeks of treatment in the control and rosiglitazone groups.

were not correlated with the changes in Lp(a) levels in the rosiglitazone group ($r = -.07$, $P = .624$).

DISCUSSION

This 12 week-prospective study showed that rosiglitazone significantly increased Lp(a) levels, as well as total cholesterol, HDL cholesterol, and LDL cholesterol levels in Korean patients with type 2 diabetes mellitus.

It is well known that increased LDL cholesterol and decreased HDL cholesterol are risk factors for cardiovascular disease in the general population, as well as patients with type 2 diabetes mellitus.[21] In addition, an elevated Lp(a) level is an independent risk factor for cardiovascular disease.[5,6]

PPAR-γ, a nuclear hormone receptor, participates in biologic pathways, such as differentiation, insulin sensitivity, type 2 diabetes, atherosclerosis, and cancer.[22] Rosiglitazone, a member of TZD family, binds to this receptor with a high affinity (kd of approximately 40 nmol/L), whereas troglitazone and pioglitazone are less potent ligands.[23,24]

Rosiglitazone has been reported to be effective in improving glycemic control as either a monotherapy or a combination therapy by increasing insulin sensitivity in patients with type 2 diabetes.[10,11] Its effect on serum lipids has been reported as well.[10-12] Rosiglitazone reduces free fatty acids that may play a role in insulin sensitivity at the tissue level and increases the total cholesterol and LDL cholesterol level. The increases in LDL cholesterol level are counterbalanced by the corresponding increases in the HDL cholesterol level. It does not change triglyceride levels. In this study, 12 weeks of rosiglitazone treatment combined with sulfonylurea or insulin, confirmed these findings.

Recently, Matsumoto et al[14] reported that troglitazone increased serum Lp(a) in patients with type 2 diabetes independently of the apolipoprotein(a) phenotype, raising the concern that TZDs might increase the risk for cardiovascular disease. Increased Lp(a) levels by troglitazone were demonstrated in nondiabetic, obese subjects, as well.[25] On the other hand, it was reported that pioglitazone did not increase Lp(a) levels in type 2 diabetic patients.[26] However, this study included too small a number of patients (n = 8), and therefore more studies with a larger number of patients need to be performed. To our knowledge, the effect of rosiglitazone on Lp(a) has not been reported. In this study, patients treated with rosiglitazone showed approximately 15% increase of average Lp(a) levels, while patients without rosiglitazone showed no significant changes in their Lp(a) levels.

The mechanism by which rosiglitazone or TZDs increases Lp(a) levels is not clear. Glycemic control itself did not affect Lp(a) levels in most studies.[27-29] In fact, glycemic control was achieved to a similar degree in the control and rosiglitazone groups. In addition, the changes in Lp(a) levels did not correlate with the changes in the fasting blood glucose or HbA_{1c} levels. As there was no correlation between the changes in Lp(a) levels and changes in LDL cholesterol levels in the rosiglitazone group, it is not likely that the modification in Lp(a) levels by rosiglitazone is a consequence of an increase in LDL cholesterol levels. Some studies showed that Lp(a) levels are inversely related to insulin resistance despite the fact that nearly 90% of Lp(a) variation is controlled by variation at the locus encoding the apolipoprotein(a) protein.[30,31] Therefore, the improvement in insulin sensitivity by rosiglitazone might be one plausible mechanism of increased Lp(a) levels, although the insulin sensitivity before and after rosiglitazone treatment was not measured in this study. Another possible mechanism is that TZDs might directly increase Lp(a) production by binding to the enhancer elements in the apolipoprotein(a) gene, as suggested in a recent study.[32]

In summary, rosiglitazone increased the serum total cholesterol, the LDL cholesterol, as well as Lp(a) levels in patients with type 2 diabetes mellitus. Considering that patients with type 2 diabetes mellitus have increased risks for cardiovascular disease, caution should be taken when prescribing rosiglitazone to the patients who already have other risk factors, such as hypertension and smoking. However, more long-term studies will be needed to determine the consistent effect of rosiglitazone on Lp(a) levels and the impact of Lp(a) changes on the cardiovascular outcomes.

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