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Effects of rosiglitazone on serum paraoxonase activity and metabolic parameters in patients with type 2 diabetes mellitus

Y. Atamer[1], A. Atamer[2], A.S. Can[3], A. Hekimoğlu[4], N. İlhan[5], N. Yenice[6] and Y. Koçyiğit[7]

[1]Department of Medical Biochemistry, Faculty of Medicine, Dicle University, Diyarbakır, Turkey
[2]Division of Gastroenterology, Department of Internal Medicine, Ministry of Health Haydarpaşa Numune Training and Research Hospital, Istanbul, Turkey
[3]Termal Professional School, Yalova University, Yalova, Turkey
[4]Department of Pharmacology, Faculty of Medicine, Dicle University, Diyarbakır, Turkey
[5]Department of Medical Biochemistry, Faculty of Medicine, Fırat University, Elazığ, Turkey
[6]Division of Gastroenterology, Department of Internal Medicine, Faculty of Medicine, Harran University, Urfa, Turkey
[7]Department of Physiology, Faculty of Medicine, Dicle University, Diyarbakır, Turkey

Abstract

Human serum paraoxonase contributes to the anti-atherogenic effect of high-density lipoprotein cholesterol (HDL-C) and has been shown to protect both low-density lipoprotein cholesterol (LDL-C) and HDL-C against lipid peroxidation. We investigated the effects of rosiglitazone on paraoxonase activity and metabolic parameters in patients with type 2 diabetes mellitus [50 patients (30 males, 20 females); mean ± SD age: 58.7 ± 9.2 years, body mass index: 28.2 ± 4.1 kg/m^2], in whom glucose control could not be achieved despite treatment with metformin, sulphonylurea, and/or insulin. The patients were given 4 mg/day rosiglitazone for 3 months in addition to their usual treatment. Serum paraoxonase activity, malondialdehyde, homocysteine, and lipid profile were measured at the time of initiation and at the end of therapy with rosiglitazone. After rosiglitazone therapy, serum levels of HDL-C, apolipoprotein A-1, and paraoxonase activity increased significantly ($P<0.05$) and malondialdehyde, homocysteine, lipoprotein(a), and glucose levels decreased significantly ($P<0.05$), but no significant changes in levels of total cholesterol and apolipoprotein B were observed. Triglyceride levels also increased significantly ($P<0.05$). Rosiglitazone treatment led to an improvement in glycemic control and to an increase in paraoxonase activity and HDL-C levels. Although rosiglitazone showed favorable effects on oxidant/antioxidant balance and lipid profile, further studies are needed to determine the effect of rosiglitazone on cardiovascular risk factors and cardiovascular morbidity and mortality.

Key words: Rosiglitazone; Diabetes mellitus type 2; Paraoxonase; Lipoproteins; Homocysteine; Lipid peroxidation

Introduction

Paraoxonase (PON1; E.C.3.1.8.1), a 43-kDa protein, catalyzes the hydrolysis of organophosphate esters, aromatic carboxylic acid esters, and carbamates in a calcium-dependent manner. High-density lipoprotein cholesterol (HDL-C)-related PON1 hydrolyzes hydrogen peroxide (H_2O_2) and plays a pivotal role in the prevention and/or elimination of the atherosclerotic process (1-3). It is considered that the HDL-C protective effect on low-density lipoprotein cholesterol (LDL-C) oxidation is primarily from PON1 activity (1,2).

It has been reported that PON1 activity is reduced in patients with type 2 diabetes mellitus (DM) (3). Rosiglitazone, a thiazolidinedione group drug, which is a peroxisome proliferator-activated receptor gamma (PPAR-gamma) agonist, is a treatment option for type 2 DM. Rosiglitazone decreases insulin resistance, effectively reduces plasma glucose and hemoglobin A_{1C} (HbA_{1C}) levels, causes a meaningful decrease in toxic free radicals, and has positive effects on the lipid profile and endothelial function.

Oxidative stress is implicated in the pathogenesis of several diseases, such as DM, polycystic ovary syndrome, gastric injury, and atherosclerosis (4-6). It has been shown that paraoxonase reduces H_2O_2, a major

Correspondence: A. Atamer, Division of Gastroenterology, Department of Internal Medicine, Ministry of Health Haydarpaşa Numune Training and Research Hospital, Tıbbiye Caddesi, 40, Üsküdar, 34668 Istanbul, Turkey. Fax: +90-216-336-0565. E-mail: aytacatamer1@gmail.com

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reactive species produced during oxidative stress (2). Reactive oxygen species degrade polyunsaturated lipids, forming malondialdehyde (MDA). This compound is a reactive aldehyde and is one of the many reactive electrophile species that cause toxic stress in cells and forms covalent protein adducts and has been referred to as advanced lipoxidation end-products, analogous to advanced glycation end-products. The production of this aldehyde is used as a biomarker to measure the level of oxidative stress in an organism (7).

Recent studies have demonstrated that serum homocysteine (Hcy) is elevated in patients with type 2 DM who have coexistent cardiovascular disease (1,8-10). Paraoxonase hydrolyzes Hcy-thiolactone to Hcy (10). Rosiglitazone is indicated to improve insulin resistance and glycemic control in patients with type 2 DM (11). The decisions to ban rosiglitazone in Europe and restrict its prescription in the United States were based on a meta-analysis that showed a 43% increase in myocardial infarction and a 64% increase in death from cardiovascular causes (12). In contrast, Rosiglitazone Evaluated for Cardiovascular Outcomes in Oral Agent Combination Therapy for type 2 DM (RECORD), a multicenter, randomized, open-label trial (registered with ClinicalTrials.gov, number NCT00379769), showed no significant increase in cardiovascular mortality, myocardial infarction, or stroke with rosiglitazone administration (13). Heart failure causing admission to the hospital or death was 110% more common in the rosiglitazone group. Despite the RECORD trial results, the sanctions on rosiglitazone were not lifted by the regulatory agencies, but more research was encouraged. In view of the results of the recent *in vitro* and animal studies (14-17) favoring rosiglitazone and the results of the RECORD trial (13), more clinical studies of rosiglitazone are justified.

The aim of this study was to investigate the effects of rosiglitazone treatment on anti-atherogenic PON1 activity and metabolic parameters in subjects with poorly controlled type 2 DM who are on treatment with metformin and sulphonylurea and/or insulin.

Material and Methods

Fifty type 2 DM patients (30 males and 20 females) with poor metabolic control (HbA_{1C} levels between 8.1 and 10.4%) who were already taking oral anti-diabetic agents (metformin and sulphonylurea) and/or insulin for metabolic control were enrolled in the study. Type 2 DM was diagnosed according to the criteria of the American Diabetes Association (11), if the subjects had a history of type 2 diabetes for at least 6 months, or if $HbA_{1C} \geqslant 7.0\%$. Subjects received the same therapy regimen for metabolic control for at least 3 months. In addition to the treatment regimen, patients were given 4 mg/day of rosiglitazone at breakfast for 3 months (Avandia, GlaxoSmithKline Beecham®, USA). It was ensured that the patients did not receive any lipid-reducing medicine affecting their serum PON1 level. Five patients not adherent to the study drug were excluded from the study. Fasting blood samples (fasting blood glucose, HbA_{1C}, lipoproteins, and liver function tests), a physical examination, and a complete medical history were performed at the beginning and at the end of the treatment. Liver enzymes were measured monthly during the study. Subjects with type 2 DM who were on anti-hyperlipidemics and subjects with malignant disease, liver disease, coronary heart disease, renal failure, or anemia were not included in the study. Overall, treatment with rosiglitazone was well tolerated. The Research Ethics Committee of Fırat University, Faculty of Medicine, approved the study protocol, and all individuals gave written informed consent prior to participation in the study. The study was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Blood samples were collected from patients between 8:00 and 9:00 am, following a 12-h fast. Samples were centrifuged, the serum separated, and the metabolic parameters measured without delay. For PON1 activity, serum was kept at -70°C until the study day. Paraoxonase activity depends on the measurement of absorbance of a color product produced as a result of the transformation of paraoxon used as substrata. PON1 activity was determined by measuring the rate of substrate hydrolysis to p-nitrophenol, which absorbance was monitored at 412 nm in a Jasco V530 spectrophotometer (Japan) (18). Metabolic parameters were measured by standard clinical laboratory methods. Results were compared by the paired Student *t*-test or the Mann-Whitney U-test using the SPSS version 10.0 software (USA) for Windows. Statistical significance was set at $P<0.05$. All data were reported as means ± SD.

Results

Clinical and biochemical parameters before and after the rosiglitazone treatment period are shown in Table 1. Blood glucose, insulin, and HbA_{1C} levels decreased significantly ($P<0.05$), and HDL-C, apolipoprotein A-1 (ApoA-1), and triglyceride levels increased significantly ($P<0.05$) after 3 months of rosiglitazone treatment compared to baseline levels. There were no significant changes in total cholesterol and ApoB ($P>0.05$). There was a statistically significant increase in PON1 activity ($P<0.001$). Rosiglitazone use was associated with decreases in lipoprotein(a), Hcy, and MDA concentrations. There were no instances of myocardial infarction, heart failure, cardiovascular mortality or total mortality during the study period.

Discussion

Rosiglitazone treatment led to an improvement in glycemic control and an increase in serum PON1 activity.

Table 1. Clinical and biochemical parameters before and after 3 months of rosiglitazone treatment in subjects with poorly controlled type 2 diabetes mellitus.

	Baseline	Three months after rosiglitazone
Gender (male/female)	30/20	
Age (years)	58.7 ± 9.2	
Glucose (mg/dL)	154 ± 35	136 ± 26*
Insulin (μU/mL)	17.86 ± 10.26	11.26 ± 3.89*
HbA_{1C} (%)	9.3 ± 3.7	7.4 ± 4.4*
BMI (kg/m^2)	28.2 ± 4.1	29.0 ± 4.6
Total cholesterol (mg/dL)	256 ± 38	249 ± 35
HDL-C (mg/dL)	34 ± 10	45 ± 9*
Triglyceride (mg/dL)	180 ± 78	195 ± 72*
ALT (U/L)	30 ± 11	28 ± 9
AST (U/L)	25 ± 10	26 ± 8
Total protein (g/dL)	6.0 ± 0.8	6.4 ± 0.4
Albumin (g/dL)	3.4 ± 0.2	4.0 ± 0.3
Creatinine (mg/dL)	0.9 ± 0.3	0.9 ± 0.4
Uric acid (mg/dL)	4.2 ± 1.2	4.1 ± 1.6
PON1 (IU/L)	359.6 ± 42.1	441.8 ± 44.6*
MDA (nmol/ml)	5.1 ± 1.8	3.2 ± 1.6*
Homocysteine (μM)	11.62 ± 2.01	7.01 ± 1.23*
Lp(a) (mg/dL)	28.20 ± 6.47	19.32 ± 3.74*
ApoA-1 (mg/dL)	73.5 ± 6.4	90.3 ± 15.2*
ApoB (mg/dL)	101.4 ± 21.8	100.1 ± 26.6

Data are reported as means ± SD. To convert to SI units, multiply glucose by 0.0556 for nM, insulin by 6.945 for pM, cholesterol by 0.0259 for nM, triglyceride by 0.0113 for nM, total protein and albumin by 10 for g/dL, creatinine by 88.4 for μM, uric acid by 59.48 for μM, lipoprotein(a) [Lp(a)] by 0.0483 for μM, apolipoprotein A-1 (ApoA-1) by 0.01 for g/L, ApoB by 0.01 for g/L. HbA_{1C}: hemoglobin A_{1C}; BMI: body mass index; HDL-C: high-density lipoprotein cholesterol; ALT: alanine transaminase; AST: aspartate transaminase; PON1: paraoxonase-1; MDA: malondialdehyde; ApoB: apolipoprotein B. *$P<0.05$ (paired Student *t*-test or Mann Whitney U-test, as appropriate).

This increased PON1 activity suggests increased protection from oxidation. These potentially beneficial effects may be the result of improved insulin sensitivity. Rosiglitazone improves peripheral insulin sensitivity through transcriptional mechanisms (19). Rosiglitazone may affect the insulin signal cascade and cause changes in muscle and liver glucose metabolism after binding to PPAR-gamma. Rosiglitazone stimulates PPAR-gamma in fat tissue. This is followed by adipocyte differentiation. Thus, newly formed adipocytes are greater in number but smaller in size, and these cells have higher insulin sensitivity. Small dense LDL-C decreases with rosiglitazone treatment, but there is an increase in LDL-C. However, despite increasing in quantity, LDL-C is transformed into less atherogenic, but bigger particles. It has been shown that rosiglitazone decreases free fatty acids and toxic free radicals, but increases triglyceride levels. It has also been shown that rosiglitazone causes an increase in body weight, but this effect was seen in stored fat tissue, not in visceral fat. Rosiglitazone has been shown to reduce liver fat accumulation (19-21). Several *in vitro* and *in vivo* studies show overall beneficial effects of rosiglitazone on classical and non-classical cardiovascular risk factors.

In an *in vitro* study, rosiglitazone treatment markedly and significantly reduced vascular smooth muscle calcification induced by hyperglycemia. The rosiglitazone-induced reduction in calcification was inhibited by a PPAR-gamma antagonist, confirming the salutary effect of activation of the PPAR-gamma agonist pathway (14). Kim and coworkers (15) suggested that rosiglitazone has a protective effect on oxidatively stressed cardiomyocytes via the thioredoxin system. H_2O_2-induced apoptosis was prevented by rosiglitazone via thioredoxin overexpression and other PPAR-gamma-dependent mechanisms, such as increased superoxide dismutase, pAkt/Akt, pERK/ERK, survivin, Bcl-2/Bax-α, and decreased caspase-3 and p53 (15).

Hussein and coworkers (22) showed that PON1 activity was decreased in male Sprague-Dawley rats with non-alcoholic fatty liver disease, and treatment with rosiglitazone increased PON1 activity and reduced oxidative stress in both serum and liver. In rats with metabolic syndrome, rosiglitazone decreased blood pressure (-17%), plasma triglycerides (-62%), hepatic total lipids (-19%), hepatic triglycerides (-61%), hepatic MDA levels (-88%), and glutathione reductase activity (-84%), and increased adiponectin (+329%), hepatic phospholipids (+46%), hepatic alpha-tocopherol levels (+24%), and hepatic paraoxonase activity (+68%) (23). Another study in rabbits showed that rosiglitazone stimulated the ApoA-1 production rate, the synthesis of smaller HDL particles, and PON1 activity. A study in mice suggested that the antioxidant effects of rosiglitazone are independent of its PPAR-gamma metabolizing properties (24). Kaur et al. (25) reported that rosiglitazone reversed sodium arsenite-induced vascular endothelial dysfunction in rats, because rosiglitazone enhanced acetylcholine-induced endothelium-dependent relaxation, improved the integrity of vascular endothelium, increased nitrite/nitrate concentration, and decreased oxidative stress. The administration of nitric oxide synthase inhibitor *N*-omega-nitro-L-arginine methyl ester prevented the vascular protective effect of rosiglitazone, an observation that suggests rosiglitazone has salutary effects via the endothelial nitric oxide synthase pathway (25). Gao and coworkers (16) studied the effect of rosiglitazone on myocardial ischemia reperfusion injury in male Japanese white big-eared rabbits. All rabbits were subjected to myocardial ischemia reperfusion injury in the study. Rabbits pretreated with either low or high doses of rosiglitazone had a smaller myocardial infarction area and lower arrhythmia rate. These effects were associated

with reduced concentrations of plasma or serum creatinine kinase-MB, high-sensitivity C-reactive protein, MDA, nitric oxide, and endothelin. Antioxidant enzymes, superoxide dismutase, and lactic acid glutathione skin peroxidase were significantly increased in rabbits pretreated with rosiglitazone. All of these levels were measured 1 h after ischemia reperfusion (16). Another study of ischemia reperfusion performed in rats confirmed the beneficial effect of rosiglitazone on infarct size that was thought to be mediated by the extrinsic anti-apoptotic pathway and anti-inflammatory action of rosiglitazone. The rat study suggested that the increased mortality rate observed with rosiglitazone might be due to arrhythmia (17). Rosiglitazone-treated rats had decreased connexin43 phosphorylation and prolonged calcium ion decay rates and decreased time to ventricular fibrillation onset, which may explain the increased fatal arrhythmia rate with rosiglitazone (17).

All of the above mentioned *in vitro* and *in vivo* animal studies showed positive effects of rosiglitazone on lipids and oxidative stress markers. Clinical rosiglitazone studies also showed positive effects of rosiglitazone on oxidative stress markers. Van Wijk and coworkers (26) reported that rosiglitazone increased PON1 activity in type 2 DM patients and decreased fasting plasma peroxides compared with placebo. The expected decrease in postprandial PON1 activity after a 6-h oral fat-loading test was also blunted by rosiglitazone. They concluded that rosiglitazone treatment confers protection against oxidative stress associated with postprandial lipemia. A decrease in insulin resistance, improvement in first and second phases of insulin secretion, a decrease in oxidative stress, and a decrease in markers of inflammation and gamma-glutamyltransferase have also been observed with rosiglitazone administration to overweight non-diabetic individuals (27).

In vitro and *in vivo* animal and short-term clinical studies suggest that, by improving blood pressure, lipid profile, Hcy, and oxidant/antioxidant balance, rosiglitazone seems to improve cardiovascular risk factors (28). Despite improving cardiovascular risk factors, rosiglitazone does not improve cardiovascular morbidity and mortality (13). Rosiglitazone has been associated with increased risk of congestive heart failure, myocardial infarction, and death relative to pioglitazone in a meta-analysis and has been banned from the European market and restricted in the US market (29).

Paraoxonase is an ester hydrolase that has both arylesterase and paraoxonase activity. It has been reported that PON1 protects both LDL-C and HDL-C from oxidation (3). HDL-PON1 has the ability to hydrolyze long-chain oxidized phospholipids (3,30). It has also been reported that PON1 increased cholesterol exit from macrophages (3,30). Recent studies show that PON1 activity is decreased in diabetic patients. Our results are in accordance with studies suggesting that rosiglitazone reduces toxic free oxygen radicals (3,30).

In conclusion, we showed that rosiglitazone had positive effects on anti-atherogenic paraoxonase activity in patients with poorly controlled type 2 DM and that it ensured better glucose control. Its use with other treatment alternatives provided important benefits. We conclude that rosiglitazone reduces levels of Hcy and MDA and increases PON1, ApoA-1, and HDL-C in patients with type 2 DM. Although rosiglitazone showed favorable effects on elements of oxidant/antioxidant balance studied and some aspects of lipid profile, further studies are needed to determine the role of rosiglitazone on cardiovascular risk and cardiovascular morbidity and mortality.

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