

Title:

The effect of rosiglitazone on the expression of thrombogenic markers on leukocytes in type 2 diabetes mellitus

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Short title:

Rosiglitazone and thrombogenic markers in type 2 diabetes

Summary

Background: Diabetes mellitus is associated with a number of prothrombotic abnormalities, and correction of these abnormalities might translate into the reduction of cardiovascular risk. Glitazones improve endothelial function and reduce inflammation, but much less is known about their effect on thrombogenic factors. We have therefore studied the effect of rosiglitazone on leukocyte and soluble thrombogenic markers in patients with type 2 diabetes mellitus.

Material and methods: 33 subjects with type 2 diabetes and 32 normal controls were included; patients were examined at baseline and after 5 months of rosiglitazone treatment (4mg/d). We measured leukocyte-platelet aggregates and leukocyte expression of P-selectin glycoprotein ligand 1 (PSGL-1) and of receptor for urokinase-type plasminogen activator (uPAR) using flow cytometry, and several circulating soluble thrombogenic markers by ELISA method.

Results: Leukocyte expression of uPAR and PSGL-1 was significantly higher in patients than in controls. Leukocyte-platelet aggregates and leukocyte expression of uPAR and PSGL-1 significantly decreased after rosiglitazone. There was also significant decrease in CRP and fibrinogen levels, but there was no effect of diabetes and/or rosiglitazone on other circulating molecules.

Conclusion: We observed substantial improvement in the expression of thrombogenic markers on leukocytes after rosiglitazone treatment, suggesting the novel antithrombotic effects of rosiglitazone.

Key words: diabetes mellitus, rosiglitazone, thrombogenic markers

Introduction

Patients with diabetes mellitus have substantially increased risk of cardiovascular diseases due to premature atherosclerosis. Diabetes is associated with the number of pathological abnormalities of the platelet function and of coagulation factors, which are proinflammatory and prothrombotic in consequence and contribute to premature atherosclerosis in diabetic patients (Bansilal et al. 2007, Dunn and Grant 2005, Moreno and Fuster 2004). These include fibrinogen, various platelet-derived molecules, plasminogen, or tissue factor (TF).

Platelets play a central role in the development of acute atherothrombotic events (Fuster et al. 2005). In addition, they produce numerous molecules, such as P-selectin, platelet factor 4, platelet-derived growth factor, or thromboxane A₂, which modulate leukocyte recruitment into atherosclerotic lesions or angiogenesis (Stratmann and Tschoepe 2005). Activated platelets also interact with circulating leukocytes to form platelet-leukocyte aggregates, which contribute to development of atherosclerotic lesions as well as plaque disruption and thrombosis (Sarma et al. 2002, Furman et al. 1998). Plasminogen with the whole system of activators and inhibitors contributes to the regulation of the vessel wall remodeling and inflammation and influences thus the plaque stability (Salame et al. 2000). Tissue factor (TF) stimulates migration of vascular smooth muscle cells and neointimal growth (Penn and Topol 2001). Through these diverse functions, the thrombotic factors independently contribute to all stages of atherosclerotic plaque development.

Thiazolidindiones (glitazones) have been increasingly used in the treatment of diabetes. Glitazones are agonists of nuclear peroxisome proliferator-activated receptors γ (PPAR- γ); they improve insulin sensitivity, increasing thus glucose utilisation and reducing blood glucose concentration. In addition, glitazones exhibit a number of other effects, which are potentially antiatherogenic and appear largely independent on their metabolic action. These include improved endothelial function, reduction of serum inflammatory markers and decreased leukocyte adhesion and activity (Patel et al. 2006). The effect of glitazones on thrombogenic factors, on the other hand, has been studied to a much lesser extent. Diabetes is associated with a number of abnormalities of the platelets and hemostatic factors, and correction of these abnormalities might translate into the reduction of cardiovascular risk. We therefore studied the effect of the PPAR- γ agonist, rosiglitazone, on leukocyte-platelet aggregates, on the leukocyte expression of P-selectin glycoprotein ligand 1 (PSGL-1) and receptor for urokinase-type plasminogen activator (uPAR), and on the circulating soluble thrombogenic markers in patients with type 2 diabetes mellitus.

Methods

Subjects and study design

We included patients with type 2 diabetes mellitus, which was not properly controlled by monotherapy with metformin (94% of patients) or sulfonylurea derivatives (6% of patients). Patients taking combination of antidiabetic drugs or insulin, as well as those with severe uncontrolled hypertension (BP >160/100 torr), renal insufficiency (serum creatinine >150 $\mu\text{mol/l}$), uncontrolled hypothyroidism or malignancy were excluded. Antihypertensive and lipid-lowering therapy was not changed during the study. The

control group consisted of healthy non-diabetic subjects without manifest vascular disease; baseline characteristics of the study subjects are shown in Table 1.

Patients with diabetes were treated with rosiglitazone 4 mg o.d. for 5 months. Clinical and laboratory examinations were performed at baseline and at the end of the treatment period; in the control group, only baseline examination was performed. Blood for laboratory tests was drawn after an overnight fast. All subjects signed an informed consent; the study protocol was approved by the Local Ethics Committee. The study conforms with the principles outlined in the Declaration of Helsinki.

Measurement of leukocyte surface markers and platelet-leukocyte aggregates

We examined platelet-leukocyte aggregates and leukocyte surface expression of PSGL-1 (CD162) and uPAR (CD87). Measurements were performed within 2 hours of blood sampling; EDTA or heparin-anticoagulated blood was cooled down immediately after collection and kept at 4°C until processing to minimize in-vitro leukocyte and platelet activation.

The expression of leukocyte markers was measured by an immunofluorescence method using single-step staining with monoclonal antibodies. 100 µl of EDTA-anticoagulated whole blood was incubated for 15 minutes with the relevant antibody at room temperature; after that, erythrocytes were lysed with 2 ml of the FACS lysis solution (for 7 min) with subsequent centrifugation and rinsing once with PBS. The fluorescence was quantified by the flow cytometry (FACSCalibur, Becton Dickinson, San Jose, CA, USA); lymphocytes, monocytes and neutrophils were identified according to their light-scattering properties and were analyzed separately. A specific fluorescence was used as a measure of antigen expression, which was calculated as

the difference between the fluorescence of cells labeled with the specific antibody and the non-specific fluorescence of cells labeled with the control antibody. We used the following murine monoclonal antibodies conjugated with phycoerythrin (PE) for antigen detection: anti-CD87 (clone VIM5) and anti-CD162 (clone KPL-1) from BD Biosciences, USA, and non-specific control antibody (clone 679.1Mc7) from Immunotech (Marseille, France). All the antibodies were of the IgG1 isotype. We also intended to measure leukocyte expression of tissue factor (CD142), but it was not detectable and was therefore not measured in the whole study population.

For examination of platelet-leukocyte aggregates, heparin was used as anticoagulant because calcium chelation with EDTA would prevent most of the leukocyte-platelet binding. To identify leukocytes with attached platelets, blood samples were stained with PE-labeled antibody directed against platelet antigen CD42a (clone ALMA.16) from BD Biosciences, USA; staining procedure was the same as described above. Positivity for platelet binding was defined as the PE fluorescence greater than the 99th percentile of the cells stained with the non-specific control antibody. The percentage of platelet-positive lymphocytes, monocytes and neutrophils was then calculated. In addition, the mean specific fluorescence for each leukocyte subpopulation was also calculated to better reflect the average number of platelets per one cell.

Other laboratory measurements

For measurements of soluble markers, serum and EDTA-anticoagulated plasma were collected and kept at -85°C until analysis. We measured serum CD40L and P-selectin and plasma thrombomodulin, tissue factor (TF), tissue factor pathway

inhibitor (TFPI) and platelet factor 4 (PF4) by the ELISA method using commercially available kits. CD40L and P-selectin kits were from Bender MedSystems (Vienna, Austria) and thrombomodulin, PF4, TFPI and TF kits were all from American Diagnostica (Stamford, CT, USA). Serum high-sensitivity C-reactive protein (hsCRP) levels were measured by time-resolved amplified cryptate emission (Mathis 1993) technology (TRACE, Kryptor analyser, Cezanne, France) using the kit from Brahms (Hennigsdorf, Germany). Serum biochemical tests and full blood count were measured using automated analyzer methods and glycated hemoglobin HbA1c (according to IFCC) by HPLC method. LDL-cholesterol concentrations were calculated using the Friedewald formula.

Statistics

The results are expressed as a mean \pm standard deviation (SD). For platelet-leukocyte aggregates, expression of leukocyte markers and concentrations of thrombogenic molecules, the Mann-Whitney U test was used to compare the differences between the controls and patients; Wilcoxon's paired test was used to compare the values before and after treatment. Differences in the remaining variables were tested by the two-sample or paired t test as appropriate. Spearman correlation was used to test for the relationship between variables. All statistical tests are two-sided; $p < 0.05$ was considered significant.

Results

Thirty-two control subjects and 33 patients with type 2 diabetes mellitus were included in the study; all patients completed the entire treatment period. The average follow-up time was 153 ± 25 days. Baseline characteristics of the study groups are shown in *Table 1*. The treatment was well tolerated; neither clinically manifest side effects were noted throughout the study. There was no increase in body weight after the treatment. Serum creatinine was similar in patients and controls, but increased significantly (by 10%) after rosiglitazone; the mechanism for this effect of rosiglitazone remains unclear (Stulc et al. 2005). There were no significant alterations in serum electrolytes, liver tests or blood count.

There was only mild 11% decrease in blood glucose after the treatment, which was not accompanied by any change in glycated hemoglobin. HDL-cholesterol increased by 17%, but there was also increase in triglycerides (by 25%) and in total and LDL-cholesterol (by 13% and 11%, resp.).

The results of platelet-leukocyte aggregates and leukocyte expression of PSGL-1 and uPAR in the study subjects are shown in *Figure 1*. In patients, there was increased expression of PSGL-1 in all leukocyte subpopulations and of uPAR in monocytes compared to controls, which normalised after rosiglitazone treatment. The differences were not significant for uPAR on neutrophils, and uPAR expression was not detectable on lymphocytes. There was no significant difference in platelet-leukocyte aggregates in patients compared to controls; the aggregates were significantly reduced after the treatment (to the values even below those of controls). The treatment effect was more pronounced for total platelet fluorescence ($PLA_{total\ platelets}$) than for the percentage of platelet-positive cells ($PLA_{\%}$), suggesting that

rosiglitazone not only decreased the number of platelet-positive cells, but also the number of platelets per one leukocyte. There were no significant correlations between the expression of leukocyte markers and glucose or lipid levels.

There were no changes in serum or plasma concentrations of P-selectin, tissue factor, tissue factor pathway inhibitor, platelet factor 4 or CD40L in patients with diabetes, and these markers were not influenced by the rosiglitazone treatment. Serum concentrations of CRP were markedly increased in patients and almost normalised after the treatment. Fibrinogen levels were similar in patients and controls, and they decreased after the treatment (*Table 1*).

Discussion

In this study, we observed decrease of leukocyte PSGL-1 and uPAR expression and of leukocyte-platelet aggregates in type 2 diabetes patients after the treatment with the PPAR- γ agonist, rosiglitazone; this is the first report of the effect of PPAR- γ agonists on these thrombogenic markers.

Platelet-leukocyte aggregates are present in normal healthy subjects but increase in conditions that are associated with activation of platelets; these aggregates are mostly considered markers of platelet activation. Their increase was observed in acute coronary syndromes and stable coronary heart disease (Furman et al. 1998), and in smokers (Casey et al. 2004), and enhanced leukocyte-platelet interaction was associated with microangiopathy in type 1 diabetes (Hu et al. 2004). Increase of

platelet-leukocyte aggregates, observed in our study, may therefore adversely influence the progression of microvascular and macrovascular disease in type 2 diabetes, and their decrease after rosiglitazone may contribute to beneficial effects of this drug beyond glucose lowering.

Formation of platelet-leukocyte aggregates is primarily mediated through binding of platelet P-selectin to PSGL-1 on leukocytes, but interactions of other molecules may also be involved in this process (Sarma et al. 2002). In our study, the changes of PSGL-1 expression were less pronounced than the changes of leukocyte-platelet aggregates. These results suggest that both PSGL-dependent and independent interactions contribute to increased leukocyte-platelet binding in patients with diabetes, and that both these mechanisms are influenced by rosiglitazone treatment.

We also observed increase in uPAR expression on monocytes in the diabetic patients, which was reduced after the rosiglitazone treatment. uPAR is a plasma membrane receptor for the urokinase-type plasminogen activator (uPA). Serving as an anchor for uPA, the uPAR localises the cell-surface associated activation of plasmin; that in turn leads to fibrinolysis, activation of matrix metalloproteinases, and degradation of extracellular matrix (Ragno 2006). With respect to atherosclerosis, increased amounts of uPAR were detected in various cell types in human atherosclerotic lesions and on human monocytes (Salame et al. 2000, Steins et al. 2004). uPAR may also contribute to the development of diabetic retinopathy (El-Remessy et al. 2003) and nephropathy (Kenichi et al. 2004), and blockage of uPAR reduced retinal neovascularisation (Le Gat et al. 2003). These data suggest that our observation of increased leukocyte expression of uPAR is clinically relevant and that

the decrease of uPAR expression after rosiglitazone might be beneficial in patients with diabetes.

In contrast to the leukocyte surface markers and platelet-leukocyte aggregates, we observed no changes in concentrations of soluble thrombogenic markers. This may appear surprising because diabetes mellitus is associated with numerous of abnormalities of thrombotic and hemostatic factors (Dunn and Grant 2005). However, production of these factors is typically limited to the sites of their local activation; release of these factors into bloodstream is therefore probably not very sensitive marker of their highly localised activation. Unlike these molecules, serum concentrations of CRP, which is a typical systemic inflammatory marker, were markedly increased in patients and almost normalised after the treatment. We also noted significant decrease in concentrations of fibrinogen - another marker of systemic inflammation. This observation is in agreement with other reports of antiinflammatory effects of PPAR- γ agonists (Lehrke and Lazar 2005, Patel et al. 2006).

The mechanisms whereby rosiglitazone influenced thrombogenic factors remain to be elucidated. One likely mechanism is the effect through correction of hyperglycemia and insulin resistance. However, rosiglitazone may also affect platelet and leukocyte functions directly, through binding to PPAR- γ receptors in vascular smooth muscle cells, endothelial cells and monocytes (Hsueh and Law 2001, Lehrke and Lazar 2005, Patel et al. 2006). However, it is difficult to separate these diverse effects of glitazones in clinical settings. Our study was not designed to elucidate these mechanisms, but may nevertheless suggest some answers. The improvement

in metabolic compensation was only marginal - the moderate improvement in the serum glucose and HDL-cholesterol concentrations was at least partially outweighed by increase in cholesterol and triglycerides. Also, the on-treatment changes in thrombogenic markers did not correlate with changes in blood glucose or lipids. The metabolic effects can therefore hardly explain the beneficial effects of rosiglitazone observed in our study, and some direct mechanisms, independent of its metabolic action, are likely to have contributed to the effect of rosiglitazone on leukocyte and platelet function.

The question that arises is whether these novel effects of rosiglitazone would translate into clinically meaningful benefits. Our study was not designed to address this question, but it was tempting to speculate that reducing leukocyte and platelet activation might decrease the risk of cardiovascular disease. However, the recent meta-analysis of rosiglitazone studies (Nissen and Wolski 2007) suggests that this drug increases rather than decreases cardiovascular risk. This surprising possibility is in contrast with multiple laboratory effects of rosiglitazone, which are all potentially antiatherogenic. It therefore appears likely that rosiglitazone may have some other effects, yet unknown but highly atherogenic, which outweigh the known beneficial effects of PPAR- γ stimulation. Future research is obviously needed to clarify this issue.

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Table 1. Baseline characteristics and serum/plasma laboratory results of the study subjects.

	Control subjects	Patients before treatment	Patients after treatment
Number	32	33	
Sex (male/female)	19 / 13	12 / 21	
Age [years]	56.4 ± 8.6	63.8 ± 10.1 *	
BMI [kgm ⁻²]	25.8 ± 3.1	29.1 ± 3.1 *	
Hypertension	9 (28%)	25 (76%) *	
Smoking	10 (31%)	8 (24%)	
TC [mmol/l]	5.03 ± 0.79	4.40 ± 0.83 *	4.92 ± 0.93 **
LDL-cholesterol [mmol/l]	2.87 ± 0.64	2.50 ± 0.68 *	2.75 ± 0.83 **
HDL-cholesterol [mmol/l]	1.64 ± 0.35	1.22 ± 0.22 *	1.42 ± 0.29 **
TG [mmol/l]	1.15 ± 0.45	1.52 ± 0.57 *	1.79 ± 1.20
Glucose [mmol/l]	5.06 ± 0.47	9.18 ± 2.00 *	8.03 ± 1.93 **
HbA _{1c} [%]	3.79 ± 0.37	5.57 ± 0.98 *	5.69 ± 1.01
Creatinine [μmol/l]	85.16 ± 10.68	83.69 ± 9.23	91.97 ± 10.96 **
Urea [mmol/l]	5.10 ± 1.20	6.06 ± 1.69 *	6.34 ± 1.84
CRP [mg/l]	1.70 ± 1.55	4.52 ± 5.14 *	2.03 ± 3.16 **

Fibrinogen [g/l]	3.01 ± 0.45	3.32 ± 0.85	2.83 ± 0.60 **
P-selectin [mg/l]	292.62 ± 132.70	273.44 ± 138.48	282.59 ± 147.84
CD40L [mg/l]	6.15 ± 4.26	9.10 ± 4.12 *	8.01 ± 4.01
TF [ng/l]	221.58 ± 56.44	226.77 ± 137.89	216.06 ± 66.65
TFPI [mg/l]	73.89 ± 30.78	61.72 ± 19.70	59.39 ± 24.65
PF4 [IU/ml]	137.64 ± 176.09	163.62 ± 167.71	152.39 ± 169.99
Thrombomodulin [mg/l]	1.99 ± 1.35	2.15 ± 0.85	2.42 ± 1.48

BMI - body mass index, TC - total cholesterol, TG - triglycerides, HDL-C - HDL-cholesterol, LD-C - LDL-cholesterol, HbA_{1c} - glycated hemoglobin, CRP - C-reactive protein, TF - tissue factor, TFPI - tissue factor pathway inhibitor, PF4 - platelet factor 4, NA - not available. Hypertension and smoking are presented as the number (percentage) of patients with the condition.

* P<0.05 patients vs. controls

** P<0.05 patients before vs. after treatment

Figure 1. Platelet-leukocyte aggregates and leukocyte expression of PSGL-1 and uPAR in the study subjects.

Platelet-leukocyte aggregates (PLA) and leukocyte expression of PSGL-1 and uPAR in healthy persons (filled circles) and in patients with diabetes before (filled squares) and after 5 months of rosiglitazone treatment (opened circles). The results for lymphocytes (left column), monocytes (middle column) and neutrophils (right column) are shown separately. The results (mean \pm SD) are in the arbitrary fluorescence units; for platelet-leukocyte aggregates, the percentage of platelet-positive cells (PLA%) is also shown, in addition to total platelet fluorescence (PLA_{total platelets}). The expression of uPAR on lymphocytes was essentially not detectable and it is therefore not shown (ND). The significance levels are shown in the figures; NS - not significant.

Rosiglitazone and thrombogenic markers in type 2 diabetes

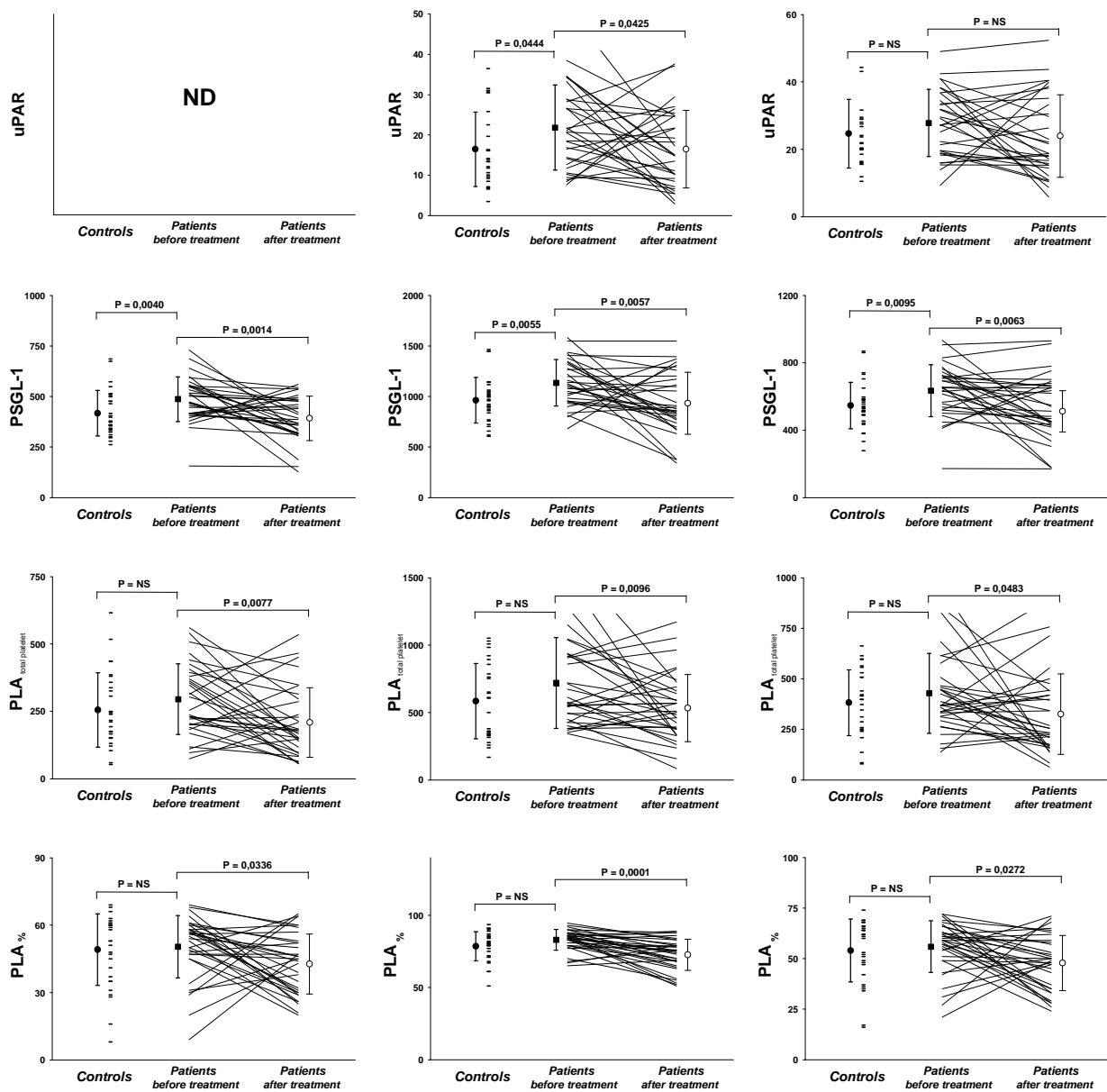


Figure 1