Osteoprotegerin, Thiazolidinediones Treatment, and Silent Myocardial Ischemia in Type 2 Diabetic Patients

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Thiazolidinediones (TZDs) are widely prescribed for the treatment of type 2 diabetes. They were reported to have vasculoprotective properties like a reduction in carotid artery intima-media thickness progression (1) but may also reduce bone formation and favor bone loss (2,3). The decoy receptor osteoprotegerin, a member of the receptor activator of nuclear factor-κB ligand/osteoprotegerin system, involved in osteoclast development and function (4), might also be a regulator of vascular calcification and an indicator of vascular disease (5). In diabetic patients, this latter point is supported by our previous data showing a positive association between silent myocardial ischemia (SMI) and osteoprotegerin levels (6,7). We tested, in a case-control study, the a priori hypothesis that TZDs might be associated with decreased osteoprotegerin levels and lower prevalence of SMI in patients treated with TZDs.

RESEARCH DESIGN AND METHODS

— A total of 198 consecutive asymptomatic non–insulin-treated type 2 diabetes patients (age 60.1 ± 9.1, 68% male, A1C 8.1 ± 1.7%, BMI 30.7 ± 4.6 kg/m^2) with one or more additional risk factor underwent SMI screening, using dipyridamole combined with exercise myocardial perfusion imaging (MPI) as previously described (6,7). SMI was defined as positive MPI (mean activity <70% of the maximal myocardium activity in ≥3 of 20 segments) and/or positive exercise electrocardiogram (ECG) (horizontal or descending ST segment depression >1 mm).

The 46 type 2 diabetic patients receiving TZDs were compared with 152 type 2 diabetic patients treated with other oral antidiabetes drugs. Diabetic nephropathy was defined as an albumin excretion rate >30 mg/day. Peripheral arterial disease was diagnosed when one or more peripheral arterial pulse was abolished and/or when intermittent claudication and/or past history of revascularization of the lower limbs were present. Osteoprotegerin plasma levels were determined by ELISA (Biovendor Laboratory Medicine, Brno, Czech Republic).

Differences between groups were compared using a two-sample Student's *t* test, Mann-Whitney *U* test, or Pearson's χ^2 test when appropriate. Independent associates of osteoprotegerin levels and of SMI were determined using multiple logistic regression analyses. Plasma osteoprotegerin was dichotomized according to a plasma value of 8 pmol/l for the regression models (7). *P* values were considered significant when ≤0.05.

RESULTS

— Age, sex ratio, A1C, BMI, diabetes duration, peripheral arterial disease, serum creatinine, diabetic nephropathy, HDL cholesterol, LDL cholesterol, and diastolic blood pressure were similar between the two groups. TZDs group was characterized by lower systolic blood pressure (125 ± 16 vs. 131 ± 16 mmHg, $P = 0.04$), lower triglycerides (182 ± 134 vs. 165 ± 182, $P = 0.02$) and more frequent lipid lowering (67 vs. 48%, $P = 0.02$) and anti-hypertensive (80 vs. 63%, $P = 0.03$) treatment. In univariate analysis, TZDs use was associated with lower osteoprotegerin levels, without any difference between pioglitazone or rosiglitazone treatment (Figure 1). After adjustment for age, sex, BMI, systolic blood pressure, triglycerides, and antidiabetes, lipid-lowering, and diuretic treatments, TZDs were independently associated with plasma osteoprotegerin values (8 pmol/l; odds ratio [OR] 6.4 [95% CI 1.5–26.3], $P \leq 0.01$).

Fifty-one patients (26%) had SMI, including 35 with abnormal MPI. SMI was present in 8 of 46 patients in the TZDs group and 43 of 152 patients in the no TZDs group (NS). When considering abnormal MPI, the difference between the two groups became significant, with 2 of 46 patients (4%) in the TZDs group having abnormal MPI in comparison with 33 of 152 patients (22%) in the no TZDs group ($P < 0.01$). In the no TZDs group, 8 of the 16 patients with abnormal MPI and normal stress ECG who underwent coronary angiography had no significant coronary stenosis; this proportion could not be evaluated in the TZDs group since only 1 patient underwent coronary angiography.

The 35 patients with abnormal MPI had higher mean levels of osteoprotegerin compared with patients with normal MPI (Fig. 1). When corrected for age, sex, and BMI, TZDs treatment was negatively associated with abnormal MPI (OR 0.15 [95% CI 0.03–0.70], $P \leq 0.01$). When osteoprotegerin was entered into the model, osteoprotegerin >8 pmol/l was indepen-

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Abbreviations: ECG, electrocardiogram; MPI, myocardial perfusion imaging; SMI, silent myocardial infarction; TZD, thiazolidinedione.

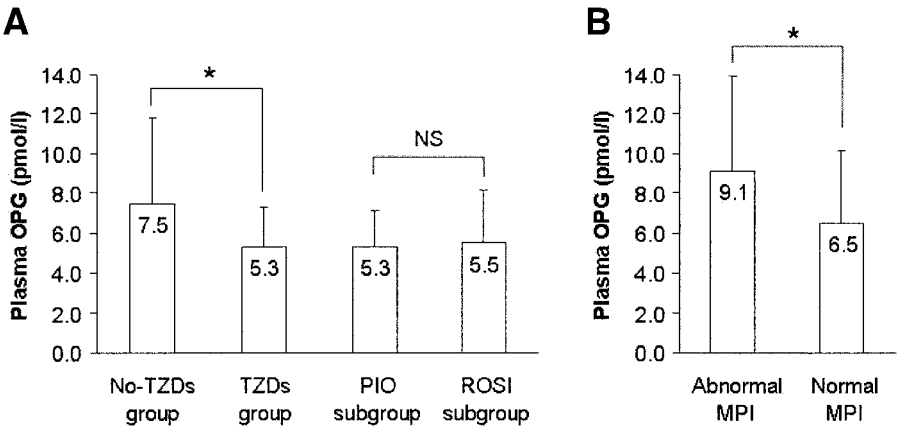

Figure 1—*Plasma osteoprotegerin values* (A) *in the No-TZDs and TZDs groups and in the pioglitazone (PIO) and rosiglitazone (ROSI) subgroups* (B) *in patients with abnormal and normal MPI.* *P < *0.001.*

dently associated with MPI defects (4.2 [1.7–10.2] $P < 0.01$), whereas the association with TZD treatment became insignificant (0.23 [0.05–1.07], $P = 0.06$).

CONCLUSIONS — The present data support our hypothesis that TZD treatment is associated with a decrease in circulating osteoprotegerin levels and a reduced occurrence of abnormal MPI that might be mediated through osteoprotegerin. Potential confounders include the fact that TZDs treatment duration was not available and that systolic blood pressure, triglycerides, and lipid-lowering drug and diuretic use differed between groups (although a statistical adjustment was performed).

Serum osteoprotegerin levels often rise in vascular calcification and are associated with cardiovascular disease and mortality (6–11). Whether circulating osteoprotegerin is directly involved in promoting vascular calcification reflects biological attempts to correct an overmineralization process or provides an indicator of vascular pathology remains controversial (5).

Peroxisome proliferator–activated receptor-γ activation could prevent both osteoprotegerin expression in human aortic smooth muscle cells (12) and differentiation of mesangial precursors into osteoblastic cells (13). Together, these data suggest that TZDs could prevent diabetes-induced osteoblast differentiation in arterial walls and medial calcification, possibly via a reduction of osteoprotegerin plasma levels.

Finally, 50% of the patients of the no TZDs group with abnormal MPIs but normal stress ECG who underwent coronary angiography had no significant coronary stenosis, which is in agreement with previous works (14–17). Endothelial dysfunction, a common feature in diabetes (18), can be causative of abnormal MPI in the absence of significant coronary stenosis. Several studies (19–21) indicate that TZDs can improve endothelial dysfunction, an effect that might explain the lower prevalence of abnormal MPI observed in our TZDs group. Since increased circulating osteoprotegerin levels have been reported to be associated with endothelial dysfunction, the beneficial effect of TZDs could be linked to the decrease in plasma osteoprotegerin (22,23).

Osteoprotegerin is produced by different cell types including osteoblasts and functions as a decoy receptor for receptor activator of nuclear factor-κB ligand, thus inhibiting osteoclastogenesis (24). Therefore, the decreased level of osteoprotegerin observed in patients receiving TZDs could be involved in the bone weakening associated with this treatment (25). To conclude, our data support the hypothesis that osteoprotegerin may mediate the effects of TZDs both on vascular integrity and bone metabolism.

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