Effect of Rosiglitazone on Endothelial Function and Inflammatory Markers in Patients With the Metabolic Syndrome

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OBJECTIVE — The aim of this study was to assess the effect of rosiglitazone on endothelial function and inflammatory markers in patients with the metabolic syndrome.

RESEARCH DESIGN AND METHODS — This was a randomized, double-blind, controlled clinical trial. One hundred subjects (54 men and 46 women) with the metabolic syndrome, as defined by the Adult Treatment Panel III, were followed for 12 months after random assignment to rosiglitazone (4 mg/day) or placebo. Primary end points were flow-mediated dilation and high-sensitivity C-reactive protein (hs-CRP) levels; secondary end points were lipid and glucose parameters, homeostasis model assessment (HOMA) of insulin sensitivity, endothelial function score, and circulating levels of interleukin (IL)-6, IL-18, and adiponectin.

RESULTS — Compared with 60 control subjects matched for age and sex, patients with the metabolic syndrome had decreased endothelial function, raised concentrations of inflammatory markers, and reduced insulin sensitivity. After 12 months, subjects with the metabolic syndrome receiving rosiglitazone showed improved flow-mediated vasodilation (4.2%, $P < 0.001$) and reduced hs-CRP levels (−0.7 mg/dl, $P = 0.04$), compared with the placebo group. Moreover, HOMA (−0.8, $P = 0.01$) and serum concentrations of IL-6 (−0.5 pg/ml, $P = 0.045$) and IL-18 (−31 pg/ml, $P = 0.036$) were significantly reduced in subjects receiving rosiglitazone, whereas adiponectin levels showed a significant increment (2.3 μg/ml, $P = 0.02$). High-density lipoprotein-cholesterol levels increased more and triglyceride levels decreased more in the rosiglitazone group compared with the placebo group. At 1 year of follow-up, 30 subjects receiving rosiglitazone still had features of the metabolic syndrome, compared with 45 subjects receiving placebo ($P < 0.001$).

CONCLUSIONS — Rosiglitazone might be effective in reducing the prevalence of the metabolic syndrome.

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The metabolic syndrome represents a cluster of several risk factors for atherosclerosis, including visceral obesity, atherogenic dyslipidemia, hyperglycemia, and hypertension (1). Patients with the metabolic syndrome are at increased risk of future cardiovascular events (2,3). Recent data indicated that inflammation is strongly associated with the features of the metabolic syndrome (4–7). The prevalence of the metabolic syndrome was reduced by approximately one-half in patients after a 2-year diet intervention program (8), whereas the incidence of new cases of the metabolic syndrome in the participants in the Diabetes Prevention Program was reduced by 41% after intensive lifestyle intervention (9).

Thiazolidinediones are a class of insulin-sensitizing agents currently used in the treatment of diabetic hyperglycemia (10). These compounds may have direct beneficial effects on cardiovascular risk independent of their hypoglycemic action (11). In particular, in patients with type 2 diabetes rosiglitazone has a positive impact on a number of nontraditional cardiovascular risk factors and markers of endothelial dysfunction, including the sensitive marker of vascular inflammation, C-reactive protein (CRP) (12).

The aim of the present study was to assess the effects of rosiglitazone on vascular inflammation and endothelial function in patients with the metabolic syndrome. We first compared patients with the syndrome with matched subjects without the syndrome; then we conducted a double-blind, randomized, placebo-controlled trial with rosiglitazone of 12-month duration in nondiabetic patients with the metabolic syndrome.

RESEARCH DESIGN AND METHODS

— Men and women from those attending the outpatient department of the Division of Metabolic Diseases at the University SUN of Naples, Italy, were recruited from January 2003 to January 2005. The subjects were sedentary (<1 h/week of physical activity) with no evidence of participation in diet reduction programs and with a stable weight (±1 kg) within the last 6 months and were asked to complete a personal health and medical history questionnaire, which served as a screening tool.

To be enrolled in the study, subjects had to have three or more of the criteria for diagnosis of the metabolic syndrome recommended by the Adult Treatment Panel III (13). Subjects were excluded if they had diabetes, cardiovascular disease,

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Abbreviations: CRP, C-reactive protein; FMD, flow-mediated vasodilation; HOMA, homeostasis model assessment; hs-CRP, high-sensitivity CRP; IL, interleukin.

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

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Table 1—*Characteristics of the study participants*

Characteristics	Patients with the metabolic syndrome	Control subjects	*P* value
n	100	60	
Sex (male/female)	54/46	30/30	0.75
Age (years)	46 ± 4.5 (32–59)	44 ± 4.9 (30–61)	0.57
Components of the syndrome			
High waist circumference (%)	74	10	
Low HDL cholesterol (%)	88	8.3	
High triglycerides (%)	76	10	
High fasting glucose (%)	54	7.6	
High blood pressure (%)	69	5	
Smoking (%)	35	32	0.78
BMI (kg/m^2)	28.3 ± 3.6 (23.4–34.2)	27.9 ± 2.9 (23.9–32.7)	0.43
Body weight (kg)	82.9 ± 9.3 (68–104)	82.3 ± 8.5 (67–102)	0.75
Waist circumference (cm)	93 ± 6 (85–108)	90 ± 5 (80–105)	0.01
Components of the syndrome (%)			
Plasma glucose (mg/dl)	108 ± 14 (86–25)	102 ± 10 (78–109)	0.046
Serum insulin (μU/ml)	13 ± 5 (6–21)	10 ± 4 (5–20)	0.02
HOMA score	3.5 ± 1.0 (1.9–6.2)	2.5 ± 0.8 (1.5–5.2)	0.01
Serum lipids (mg/dl)			
Total cholesterol	212 ± 27 (175–256)	206 ± 25 (153–238)	0.16
HDL cholesterol	38 ± 7 (22–52)	41 ± 8 (28–60)	0.01
Triglycerides	184 ± 76 (98–309)	136 ± 59 (56–298)	0.01
Blood pressure (mmHg)			
Systolic	137 ± 9 (115–159)	133 ± 10 (112–161)	0.012
Diastolic	86 ± 6 (75–103)	84 ± 7 (73–101)	0.16
hs-CRP (mg/dl)	2.0 (0.7–4.1)	0.7 (0.3–2.1)	0.01
IL-6 (pg/ml)	2.4 (0.8–4.8)	1.5 (0.5–3.4)	0.02
IL-18 (pg/ml)	180 (102–232)	136 (85–190)	0.02
Adiponectin (μg/ml)	5.3 (3.9–7.2)	8.7 (4.6–11.5)	0.01
Endothelial function score	6.1 ± 1.1 (4.2–8.9)	9.1 ± 0.4 (8.5–10)	<0.001
Vessel size (mm)	4.2 ± 0.3 (3.8–4.6)	4.3 ± 0.3 (3.8–4.3)	0.13
FMD (%)	6.7 (4.2–9.3)	12.1 (9.1–14.9)	<0.001

Data are means ± SD (range) or median (interquartile range) unless otherwise indicated.

psychiatric problems, a history of alcohol abuse (at least 500 g alcohol/week in the last year), or if they took any medication. Also excluded were those with overt liver or renal disease and hypothyroidism. Thus, 140 patients were assessed for eligibility and 100 were randomly assigned; 40 patients were determined to be ineligible (15 were unwilling to participate and 25 did not meet inclusion/exclusion criteria).

The study was approved by the institutional committee of ethical practice of our institution, and all the study subjects gave informed written consent. Men and women without the metabolic syndrome were recruited from the medical and paramedical staff of our institution, were matched for sex and age (± 2 years) with those with the metabolic syndrome, and served as a control group.

Patients were instructed to follow a weight-maintaining diet consisting of 50% carbohydrate, 30% lipid (<10% saturated fat), and 20% protein throughout the study and underwent a 6-week run-in period, after which they were randomly assigned to receive either rosiglitazone (4 mg/day, $n = 50$) or matching placebo ($n = 50$) for the 12-month double-blind phase. Patients were seen at the screening visit (before the run-in), 1 week before randomization for baseline determinations, at randomization, and at 1 month intervals for physical examination. Laboratory assessments and vascular studies were repeated at 12 months.

Endothelial function assessment

Endothelial function was assessed with the L-arginine test, as previously described (14,15). We developed a score (8) in which responses of blood pressure and platelet aggregation to L-arginine were summed up, with a maximal score of 10 indicating normal endothelial function.

Endothelium-dependent flow-mediated vasodilation (FMD) was evaluated in the right brachial artery with a high-resolution ultrasound machine (Aloka 5500) and in a temperature-controlled room (21–24°C). Reactive hyperemia was induced by inflation of a pneumatic cuff on the upper arm to suprasystolic pressure, followed by cuff deflation after 4.5 min. The maximum vessel diameter was defined as the average of the three consecutive maximum diameter measurements after hyperemia. Vasodilation was calculated as the percent change in diameter compared with baseline. The same experienced operator performed all the studies with an intraobserver variation <5%.

Laboratory analysis

Insulin sensitivity in the fasting state was assessed with homeostasis model assessment (HOMA) and calculated using the formula: fasting plasma glucose (millimoles per liter) × fasting serum insulin (microunits per milliliter)/22.5, as origi-

Table 2—*Changes in assessed variables at the end of the study*

Variable	Baseline	Rosiglitazone change	*P* value	Baseline	Placebo change	*P* value	Corrected difference (95% CI)*	*P* value at 1 year
n		50			50			
BMI (kg/m^2)	28.2 ± 3.7	+0.8 ± 0.6	0.15	28.3 ± 3.5	+0.1 ± 0.2	0.3	+0.7 (−0.1 to 1.4)	0.13
Weight (kg)	83 ± 9.2	+1.6 ± 1.1	0.24	82.9	+0.4 ± 0.3	0.7	+1.2 (−0.3 to 2.7)	0.11
Waist circumference (cm)	93 ± 6	+1 ± 1	0.4	93 ± 7	0 ± 0.5	0.5	+1 (−1 to 2)	0.24
Plasma glucose (mg/dl)	107 ± 9	−4 ± 3	0.14	109 ± 10	−2 ± 3	0.26	−2 (−4 to 1)	0.10
Serum insulin (μU/ml)	13 ± 4	−4 ± 2	0.045	14 ± 4	+1 ± 1	0.57	−5 (−9 to −1)	0.04
HOMA	3.4 ± 0.7	−0.9 ± 0.3	0.04	3.5 ± 0.8	−0.1 ± 0.2	0.65	−0.8 (−2 to −0.3)	0.03
Serum lipids (mg/dl)								
Total cholesterol	213 ± 30	+15 ± 13	0.15	210 ± 27	+4 ± 5	0.78	+11 (−5 to 18)	0.26
HDL cholesterol	38 ± 7	+4 ± 2	0.04	38 ± 8	0 ± 1	0.46	+4 (1–9)	0.039
Triglycerides	190 ± 77	−37 ± 17	0.03	183 ± 63	−5 ± 10	0.67	−32 (−54 to −6)	0.01
Blood pressure (mmHg)	137 ± 9	−5 ± 2	0.03	136 ± 8	−1 ± 1	0.67	−4 (−7 to −2)	0.01
Systolic								
Diastolic	88 ± 6	−4 ± 1	0.02	89 ± 5	0 ± 0.5	0.18	−4 (−6 to −2)	0.01
hs-CRP (mg/dl)	2.1 (0.7–4.0)	−0.8 ± 0.3	0.04	2.0 (0.8–4.0)	+0.1 ± 0.1	0.32	−0.7 (−1.3 to −0.2)	0.04
IL-6 (pg/ml)	2.4 (0.8–5.0)	−0.7 ± 0.3	0.04	2.3 (0.7–5.0)	−0.2 ± 0.3	0.19	−0.5 (−1 to −0.1)	0.045
IL-18 (pg/ml)	179 (99–240)	−25 ± 10	0.038	164 (95–235)	+6 ± 8	0.46	−31 (−55 to −4)	0.036
Adiponectin (μg/ml)	5.4 (3.7–7.1)	+2.5 ± 0.9	0.01	5.2 (3.5–6.9)	+0.2 ± 0.2	0.35	+2.3 (0.3 to 4.2)	0.02
Endothelial function score	6.0 ± 1.3	+1.5 ± 0.5	0.02	6.1 ± 1.3	+0.1 ± 0.2	0.29	1.4 (0.9 to 1.9)	<0.001
Vessel size (mm)	4.2 ± 0.3	−0.1 ± 0.1	0.46	4.2 ± 0.3	0 ± 0.1	0.54	−0.1 (−0.1 to 0.1)	0.50
FMD (%)	7.2 (4.2–9.3)	4.4 ± 1.0	0.01	7.3 (4.3–9.2)	0.2 ± 0.2	0.1	4.2 (2.2 to 6.3)	<0.001

Data are means ± SD or median (interquartile range). *P* values relate to comparisons between baseline and follow-up in each of the two arms; *P* values at 1 year are based on comparisons of changes between baseline and follow-up in both arms.

nally described by Matthews et al. (16). Assays for serum total and HDL cholesterol, triglyceride, and glucose levels were performed in the hospital's chemistry laboratory. Plasma insulin levels were assayed by radioimmunoassay (Ares; Serono). Serum samples for cytokine and high-sensitivity (hs)-CRP levels were stored at −80°C until assay. Serum concentrations of interleukin (IL)-6 and IL-18 were determined in duplicate using a high-sensitivity quantitative sandwich enzyme assay (Quantikine HS; R&D Systems, Minneapolis, MN); plasma adiponectin was assessed using a commercially available radioimmunoassay kit (HADP-61HK; Linco Research, St. Charles, MO). hs-CRP was assayed by immunonephelometry on a Behring Nephelometer 2 (Dade Behring, Marburg, Germany).

Statistical analysis

Data are presented as means ± SD for continuous variables or median (interquartile range) and were analyzed using the intention-to-treat principle. Comparisons between groups were made using the Mann-Whitney *U* statistic test. The effects of treatment on laboratory parameters, endothelial function, and cytokine levels were tested by means of paired *t* tests and a Wilcoxon matched test, as appropriate. Mann-Whitney analysis was used for comparing changes between baseline and posttreatment values in patients receiving rosiglitazone versus those receiving placebo. Spearman rank correlation coefficients were used to quantify the relations between metabolic variables and cytokine levels. The χ^2 test was used for comparing proportions of subjects in the two groups with the metabolic syndrome after treatment. $P < 0.05$ was considered statistically significant. All analysis was conducted using SPSS version 9.0 (SPSS, Chicago, IL).

RESULTS — The baseline clinical and metabolic characteristics of participants in the study are shown in Table 1. Compared with control subjects, patients with the metabolic syndrome had greater waist circumference, higher systolic pressure values, and higher fasting glucose and insulin concentrations indicating reduced insulin sensitivity (higher HOMA values), higher triglyceride levels, and lower HDL cholesterol levels. Levels of IL-6, IL-18, and hs-CRP were significantly higher in patients with the metabolic syndrome than in subjects without, whereas fasting adiponectin concentrations were significantly lower. Endothelial function score and FMD were lower in patients with the metabolic syndrome compared with control subjects. Endothelial function score and FMD were strictly related in the whole population ($n = 160$, $r = 0.81$, $P < 0.001$).

The two groups of patients with the metabolic syndrome assigned to either rosiglitazone or placebo had similar baseline characteristics (Table 2). Although fasting glucose concentrations did not change significantly with either treatment, plasma insulin concentrations decreased more in the rosiglitazone group (−4 μU/ml, $P = 0.045$) with a significant difference for the HOMA index. Total and HDL cholesterol levels increased more in the rosiglitazone group compared with the placebo group, whereas triglyceride levels decreased more in the rosiglitazone group. Systolic and diastolic blood pressure showed significant reductions after rosiglitazone treatment; on the other hand, both endothelial function score and FMD improved significantly after active treatment. There was a linear relation between increases in FMD and endothelial function score after rosiglitazone ($r = 0.74$, $P < 0.001$).

Compared with placebo, rosiglitazone resulted in significant reductions of circulating hs-CRP, IL-6, and IL-18 con-

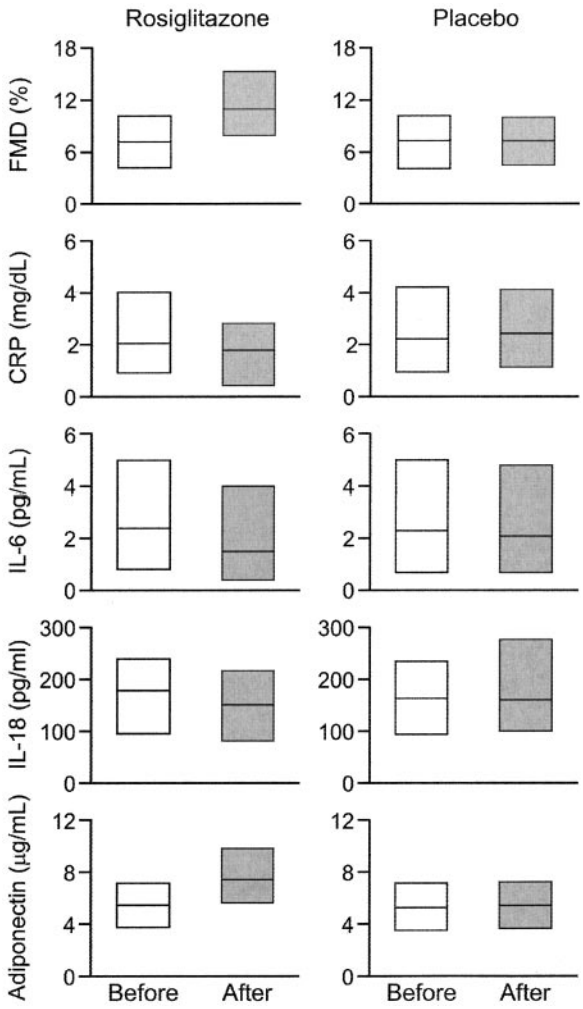

Figure 1—*Effect of rosiglitazone or placebo treatment on FMD, CRP, IL-6, IL-18, and adiponectin in patients with the metabolic syndrome. The values were adjusted for age and sex and for changes in BMI, waist circumference, and HOMA.* P *values (rosiglitazone vs. placebo) were 0.001, 0.045, 0.05, 0.042, and 0.039, respectively. Data are presented as median (interquartile range).*

centrations and in significant increments of adiponectin levels (Fig. 1). Changes in IL-6 and adiponectin after treatment were related to reductions in HOMA index ($r = 0.27$, $P = 0.04$; $r = -0.32$, $P = 0.03$, respectively).

At 12 months of follow-up, there were 20 subjects receiving rosiglitazone who had their number of components of the metabolic syndrome reduced, so that only 30 subjects (60%) could be classified as having the metabolic syndrome. This figure was significantly different from that seen in the placebo group, in which 45 subjects (90%) fit the attributes of the metabolic syndrome ($P < 0.001$). Thus, there was a 30% reduction in the prevalence of the metabolic syndrome in the intervention group compared with that in the placebo group. In particular, rosiglitazone decreased the prevalence of low levels of HDL cholesterol (from 88 to 67%) and that of high triglyceride levels (from 76 to 55%) and blood pressure (from 69 to 47%) levels.

There were three dropouts in the rosiglitazone group and two dropouts in the placebo group, all because they declined follow-up. Results of safety screening biochemical tests, which included liver transaminases and creatine phosphokinase, did not change significantly during the study.

CONCLUSIONS — This study shows that the prevalence of the metabolic syndrome can be reduced by treatment with rosiglitazone over 1 year. In particular, at the same glucose level, rosiglitazone was significantly better than placebo in reducing circulating markers of inflammation and ameliorating endothelial function in patients with the metabolic syndrome.

Although the original driving force leading to the association of vascular inflammation, endothelial dysfunction, and insulin resistance in the metabolic syndrome is still unclear, each factor may affect the other two with the development of vicious circles. For instance, CRP may directly cause endothelial dysfunction (17) and is predictive of future type 2 diabetes (18). Alternatively, insulin resistance may be responsible for the higher production of cytokines as a consequence of a reduced anti-inflammatory effect of insulin in insulin-resistant states (4). Finally, endothelial dysfunction may lead to insulin resistance by inhibiting the ability of insulin to recruit new capillaries and reach its target organ to produce its metabolic effects (19). Regardless of the mechanisms, the proinflammatory state that accompanies the metabolic syndrome is associated with both insulin resistance and endothelial dysfunction, providing a connection between inflammation and metabolic processes that is highly deleterious for vascular functions.

Peroxisome proliferator–activated receptor activation by thiazolidinediones is a promising treatment for diabetes; it reduces insulin resistance and leads to improved glycemic control in patients with type 2 diabetes (20). Peroxisome proliferator–activated receptor agonists have displayed unique characteristics in both animal and clinical studies, indicating that they have antiatherogenic effects. They inhibit the production of inflammatory cytokines in monocytes (21), induce apoptosis in macrophages (22), and reduce the expression of adhesion molecules (23) and receptors for advanced glycation end products (24) in endothelial cells. These effects have been seen in both diabetic (25) and nondiabetic atherosclerosis-prone animal models (26,27). An antiatherogenic effect also exists in humans. Two pilot studies with troglitazone (28) and pioglitazone (29) have shown reduced carotid intima-media thickness in patients with type 2 diabetes. Moreover, a placebo-controlled study showed reduced progression of intima-media thickness of the common carotid artery in nondiabetic patients who were treated with rosiglitazone (30).

Although there is evidence that rosiglitazone may reduce hs-CRP levels in patients with type 2 diabetes (12), our study showed an effect of the drug on many markers of vascular inflammation, including IL-6, IL-18, hs-CRP, and adiponectin in nondiabetic patients with the

metabolic syndrome. Both IL-6 and PCR have been prospectively associated with thrombotic cardiovascular events (31), and IL-18 has been suggested to be involved in plaque destabilization (32), whereas low adiponectin levels are associated with both future development of type 2 diabetes (33) and coronary events (34). Treatment with rosiglitazone was associated with a reduction of the proinflammatory milieu, which may also explain the significant decrease in the prevalence of the syndrome after treatment. This effect has recently been reported with pioglitazone in nondiabetic patients with the metabolic syndrome (35). Moreover, a short-term (12-week) treatment with 8 mg/day rosiglitazone in patients with a low HDL cholesterol level and the metabolic syndrome has been shown to reduce inflammatory markers including CRP, IL-6, and tumor necrosis factor-α (36). Endothelial function also improved after rosiglitazone, as indicated by the increase in the endothelial function score and the improved FMD in the brachial artery.

The effects we found on lipid levels are in line with those reported in the current literature (37) and include the slight increase in HDL and total cholesterol levels, associated with a decrease in triglyceride concentrations. Moreover, we also found no significant trend for a slight increase in body weight after rosiglitazone. We found no evidence for idiosyncratic liver toxicity during treatment.

This is the largest and longest study of rosiglitazone in nondiabetic patients to date. We found that rosiglitazone was effective in improving several of the metabolic derangements seen in patients with the metabolic syndrome (Adult Treatment Panel III criteria). As a consequence, the prevalence of the metabolic syndrome was reduced by 30% at the end of the study. Whether this reduction could translate into clinical benefits awaits further investigation. Diet and weight loss remain the cornerstone of therapy for the metabolic syndrome (8,9). However, in patients who do not lose weight or in those not adhering to dietetic regimens, an insulin-sensitizing drug such as rosiglitazone may be effective. The results of the Diabetes Prevention Program show that troglitazone prevented the incidence of new cases of diabetes in high-risk people, such as those with impaired glucose tolerance (38).

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