Vascular Effects of Improving Metabolic Control With Metformin or Rosiglitazone in Type 2 Diabetes

Andrea Natali, MD1
Stephanie Baldeweg, MD2
Elena Toschi, MD1
Brunella Capaldo, MD3
Daniele Barbaro, MD4
Amalia Gastaldelli, PhD1
John S. Yudkin, MD2
Ele Ferrannini, MD1

OBJECTIVE — The aim of this study was to test whether vascular reactivity is modified by improving metabolic control and peripheral insulin resistance in type 2 diabetes.

RESEARCH DESIGN AND METHODS — In a randomized, double-blind design, we assigned 74 type 2 diabetic patients to rosiglitazone (8 mg/day), metformin (1,500 mg/day), or placebo treatment for 16 weeks and measured insulin sensitivity (euglycemic insulin clamp), ambulatory blood pressure, and forearm blood flow response to 1) intra-arterial acetylcholine (ACh), 2) intra-arterial nitroprusside, 3) the clamp, and 4) blockade of nitric oxide (NO) synthase.

RESULTS — Compared with 25 nondiabetic subjects, patients had reduced insulin sensitivity (30 ± 1 vs. 41 ± 3 μmol·min⁻¹·kg fat-free mass⁻¹, P < 0.001) and reduced maximal response to ACh (586 ± 42 vs. 883 ± 81%, P < 0.001). Relative to placebo, 16 weeks of rosiglitazone and metformin similarly reduced fasting glucose (−2.3 ± 0.5 and −2.3 ± 0.5 mmol/l) and HbA1c (−1.2 ± 0.3 and −1.6 ± 0.3%). Insulin sensitivity increased with rosiglitazone (+6 ± 3 μmol·min⁻¹·kg fat-free mass⁻¹, P < 0.01) but not with metformin or placebo. Ambulatory diastolic blood pressure fell consistently (−2 ± 1 mmHg; P < 0.05) only in the rosiglitazone group. Nitroprusside dose response, clamp-induced vasodilatation, and NO blockade were not affected by either treatment. In contrast, the slope of the ACh dose response improved only with rosiglitazone (+40% versus baseline, P < 0.05), +70% versus placebo, P < 0.005) but did not change with either metformin or placebo. This improvement in endothelium-dependent vasodilatation was accompanied by decrements in circulating levels of free fatty acids and tumor necrosis factor-α.

CONCLUSIONS — At equivalent glycemic control, rosiglitazone, but not metformin, improves endothelium dependent vasodilatation and insulin sensitivity in type 2 diabetes.

Cardiovascular disease is a major burden for patients with type 2 diabetes (1). Extensive and accelerated atherosclerosis is largely responsible for the excess cardiovascular morbidity and mortality that characterize diabetes (2). Endothelial dysfunction, an early and committed step in the development of atherosclerosis (3,4), is thought to be a major component of the vascular vulnerability of diabetic patients. Several studies have shown that endothelium-dependent reactivity of both conductance vessels (i.e., flow-mediated dilatation [5,6]) and resistance arteries (i.e., response to acetylcholine [ACh] or methacholine [7–9]) is impaired in type 2 diabetic patients. In these subjects, the vascular defect usually clusters with features of the metabolic syndrome (visceral obesity [10], hypertension [11], and abundance of small, dense LDL cholesterol particles [8]). Moreover, endothelial dysfunction in first-degree relatives of type 2 diabetic patients is more prominent in those with insulin resistance (6). Studies in transgenic animals indicate that endothelial dysfunction can be induced by disrupting the intracellular insulin-signaling pathway (12) and, conversely, that an insulin-resistant phenotype can be induced by experimental deprivation of endothelial nitric oxide (NO) synthase (13). Taken together, these findings suggest that in type 2 diabetes, insulin resistance and endothelial dysfunction may be related to one another in a causal manner. If this hypothesis is correct, then treatment of insulin resistance should result in a parallel improvement of endothelial function and, possibly, in a reduction of vascular complications. Thiazolidinediones, a new class of insulin-sensitizing agents, offer a unique investigative tool to assess the relation of insulin sensitivity to vascular reactivity. In an animal model of insulin resistance (14) and in normal rats chronically infused with angiotensin II (15), treatment with rosiglitazone has been shown to prevent deterioration of both insulin sensitivity and endothelial function.

Testing this hypothesis in patients, however, is complicated not only by the technical difficulty of measuring metabolic and vascular functions with valid techniques but also by the separate impact of hyperglycemia on either function. In an open study, addition of bedtime NPH insulin to metformin in type 2 diabetic patients achieved optimal glycemic control and improved endothelium-dependent but also endothelium-indepen-
Vascular effects of metformin/rosiglitazone

RESEARCH DESIGN AND METHODS — Type 2 diabetic patients were recruited from three clinics: one in London and two in Italy (Pisa and Naples). Patient inclusion criteria were 1) age 40–80 years, 2) fasting plasma glucose between 7.0 and 15.0 mmol/l, and 3) BMI ≤ 35 kg/m²; women with childbearing potential; 4) BMI ≥ 35 kg/m², 3) presence of clinically significant renal or hepatic disease, anemia, diabetic retinopathy or symptomatic neuropathy, New York Heart Association grades III–IV; cardiac failure, angina pectoris, or recent myocardial infarction; 4) change in dose of ACE inhibitors, B-blockers, diuretics, statins, or nitrates in 4 weeks before screening; and 5) current treatment with vitamins, nitrates, or calcium channel blockers. The control group consisted of 25 nondiabetic subjects, of whom 10 were selected to be hypertensive to match the hypertensive type 2 diabetic patients.

This was a multicenter, randomized, double-blind, parallel-group, placebo-controlled study. After a 4-week, single-blind placebo run-in period, eligible patients underwent 24-h ambulatory blood pressure monitoring (ABPM) followed by test procedures (week 0). Patients were then randomized to rosiglitazone (4 mg b.i.d.), metformin (500 mg t.i.d.), or placebo and entered a 16-week treatment period. To maintain study blindness, all patients received two capsules three times a day throughout the study; the dose of no other concomitant medication was changed. Patients returned at 4-week intervals for measurements of plasma glucose and body weight. At week 16, patients repeated 24-h ABPM and test procedures. On test days, only the experimental therapy was regularly assumed. The Ethics Review Committee of each participating institution approved the study.

Vascular reactivity (forearm blood flow [FBF] by the perfused forearm technique plus venous occlusion plethysmography) and insulin sensitivity (by the euglycemic insulin clamp technique) were measured during a single study session. All procedures were carefully standardized: the same strain-gauge plethysmograph (EC4; Hokanson, Bellevue, WA) and test chemicals were used in all centers, and a training session was attended by all investigators before the beginning of the study. A teflon cannula (21 gauge) was inserted into the brachial artery of the nondominant arm and used for drug infusion and intra-arterial blood pressure/heart rate monitoring via a pressure transducer connected to a monitor. Another catheter was inserted into an antecubital vein for systemic insulin (40 mU min⁻¹ m⁻²) and glucose infusion. After baseline blood sampling, at time −180 min a primed-continuous (0.05 mg min⁻¹ kg⁻¹) infusion of 6,6-²H-glucose was started and maintained until the end of the clamp. Once FBF had stabilized (at least 30 min after cannulation), FBF was measured at the end of each of five 5-min steps of intra-arterial ACh infusion (0.15, 0.45, 1.5, 4.5, and 15 μg min⁻¹ dl⁻¹ of forearm tissue). After another rest period, FBF was measured at the end of each of three 5-min steps of intra-arterial sodium nitroprusside (SNP) (1, 2, and 4 μg min⁻¹ dl⁻¹). Three blood samples were obtained to measure plasma 6,6-²H-glucose enrichment, glucose, insulin, and free fatty acids (nonesterified fatty acid [NEFA]) concentration. Concentration 10, 5, and 1 min before the insulin infusion was started (time 0). Glucose infusion was started only when plasma glucose concentration reached 6.0 mmol/l. Blood samples for 6,6-²H-glucose enrichment were taken every 20 min throughout the clamp. Blood samples for plasma insulin and NEFA were taken at time 0, 80, 100, and 120 min. FBF was measured at 60 and 120 min and then again at 125 min after a 5-min intra-arterial infusion of NG-monomethyl-L-arginine (1-NMMA) (100 μg min⁻¹ dl⁻¹).

Assays

Plasma 6,6-²H-glucose enrichment was assayed in Pisa, as previously described (18). HbA₁c, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, and routine blood chemistry were assayed at SmithKline Beecham Central Clinical Laboratories. Insulin (human insulin specific radioimmunooassay kit; Linco), NEFA (Wako Chemical), interleukin-6 (ELISA kit; R&D Systems), tumor necrosis factor-α (TNF-α) (ELISA kit; R&D Systems), and C-reactive protein (High Sensitive UL-CRP; Wako Chemical) were assayed in London.

Calculations

Plethysmographic recordings were analyzed centrally by the same investigator (A.N.) who was blinded to the randomization code and the metabolic results. FBF was expressed as absolute value and as percent change from baseline. Because during local SNP infusion a slight but consistent drop in intra-arterial blood pressure was observed in most patients, impedance (i.e., blood flow X 100 divided by mean blood pressure) was used for the calculation of percent SNP-induced increments above baseline. The slope of the dose-response curves of percent increments above baseline values versus the log of the nominal drug infusion rates was obtained using least-squares linear regression of each individual’s data points. If the correlation coefficient of the fit was < 0.7, the slope was not calculated and the study discarded. The effect of L-NMMA was calculated as percent change relative to the clamp FBF. Insulin sensitivity was calculated as the mean glucose infusion rate between 80 and 120 min corrected for the concomitant plasma glucose changes and expressed as metabolic glucose (M value) in mg min⁻¹ kg fat-free mass⁻¹ (19). Fasting endogenous glucose production (EGP) was calculated as the 6,6-²H-glucose infusion rate divided by the steady-state plasma 6,6-²H-glucose enrichment. During the clamp, glucose rate of appearance (R₂) was calculated using a two-compartment model (20). EGP during the clamp was obtained as the mean R₂ of the last 40 min minus the mean exogenous glucose infusion during the same time period.
BMI (kg/m²) 30.2
Age (years) 58

<table>
<thead>
<tr>
<th>n (men/women)</th>
<th>Placebo</th>
<th>Metformin</th>
<th>Rosiglitazone</th>
</tr>
</thead>
<tbody>
<tr>
<td>22 (18/4)</td>
<td>28 (22/6)</td>
<td>24 (22/2)</td>
<td></td>
</tr>
<tr>
<td>58 ± 9</td>
<td>58 ± 10</td>
<td>59 ± 7</td>
<td></td>
</tr>
<tr>
<td>30.2 ± 3.1*</td>
<td>28.0 ± 3.5</td>
<td>27.6 ± 2.8</td>
<td></td>
</tr>
<tr>
<td>0.94 ± 0.07</td>
<td>0.94 ± 0.06</td>
<td>0.93 ± 0.05</td>
<td></td>
</tr>
<tr>
<td>9.7 ± 2.6</td>
<td>10.0 ± 2.1</td>
<td>10.0 ± 2.1</td>
<td></td>
</tr>
<tr>
<td>3.4 ± 3.4*</td>
<td>6.3 ± 5.3</td>
<td>6.5 ± 4.5</td>
<td></td>
</tr>
<tr>
<td>7.6 ± 0.8</td>
<td>7.8 ± 1.1</td>
<td>7.7 ± 1.2</td>
<td></td>
</tr>
<tr>
<td>0.93 ± 0.43</td>
<td>0.76 ± 0.26</td>
<td>0.96 ± 0.69</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>10</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>7</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>5</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>5</td>
<td>7</td>
<td></td>
</tr>
</tbody>
</table>

Hypertension (n)†
ACE inhibitors (n)
Statins (n)
Current smokers (n)

Data are means ± SD unless otherwise indicated. *Statistically significant difference (P < 0.05) with respect to the other study groups; †blood pressure values >140/90 mmHg or antihypertensive treatment.

Statistical analysis

Data are expressed as mean ± SD. Group comparisons were performed by ANOVA or χ² test, as appropriate. The effect of each treatment on continuous variables was calculated as the difference between week 16 and week 0 by paired Student’s t test or ANOVA for repeated measures. Differences between treatment-induced changes were assessed by an ANCOVA model including center and baseline value as covariates. When the model yielded a significant treatment effect, comparisons were calculated by applying paired contrasts. Confidence interval calculations and regression analysis were done using standard procedures.

RESULTS

Seventy percent of the screened patients were randomized. As expected, the drop-out rate was slightly, although not significantly (P = 0.3), higher in the placebo (29%) than in the metformin (13%) or rosiglitazone (17%) groups. In comparison with completers, drop-out patients had similar age, sex distribution, BMI, insulin sensitivity, endothelial function, and diabetes duration but worse metabolic control, as indicated by higher fasting plasma glucose and HbA₁c levels at week 0 (11.7 ± 2.8 vs. 9.9 ± 2.1 mmol/l, P < 0.003, and 8.4 ± 1.4 vs. 7.7 ± 1.0%, P < 0.03, respectively). Among completers, six patients did not have evaluable vascular tests due to poor correlation coefficient of the data fit (see RESEARCH DESIGN AND METHODS) at either examination and were therefore excluded from analysis. At randomization, type 2 diabetic patients in the three groups were similar for metabolic control and most other clinical characteristics (Table 1), although patients in the placebo group had a greater BMI and a shorter disease duration. Compared with type 2 diabetic patients, control subjects had a similar sex distribution (20 men), age (54 ± 7 years), BMI (27.7 ± 3.3 kg/m²), and prevalence of hypertension (40%). Similar were also the vascular responses to SNP and to the clamp, whereas insulin sensitivity (41 ± 3 vs. 30 ± 1 μmol · min⁻¹ · kg fat-free mass⁻¹, P < 0.001) and the maximal response to ACh (883 ± 81 vs. 586 ± 42%, P < 0.001) were significantly higher (Fig. 1).

Mean plasma glucose between week 0 and 16 decreased similarly with metformin (−1.6 ± 0.6 mmol/l, P < 0.005) and rosiglitazone (−1.5 ± 0.6 mmol/l, P < 0.005) and increased slightly with placebo (+0.4 ± 0.6 mmol/l, NS). HbA₁c tended to decrease in the metformin group (−0.33%, P = 0.07), remained sta-

Figure 1—FBF responses to ACh and SNP (A) and insulin sensitivity and clamp-induced changes in blood flow (B) in 25 nondiabetic subjects (Controls) and 74 type 2 diabetic patients (T2D).
Vascular effects of metformin/rosiglitazone

Table 2—Clinical variables: mean values, treatment-induced changes, and treatment comparisons

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo</th>
<th>MET</th>
<th>RSG vs. placebo</th>
<th>MET vs. RSG</th>
<th>RSG vs. MET</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>201</td>
<td>197</td>
<td>189 (-0.6 to 2.6)</td>
<td>196 (-0.1 to 0.6)</td>
<td>192 (-0.1 to 2.6)</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>155</td>
<td>146</td>
<td>131 (-4.2 to 0.3)</td>
<td>132 (-2.1 to 0.2)</td>
<td>129 (-0.3 to 0.3)</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dl)</td>
<td>45</td>
<td>46</td>
<td>43 (-1.5 to 0.9)</td>
<td>42 (-1.5 to 0.9)</td>
<td>41 (-1.2 to 0.9)</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dl)</td>
<td>124</td>
<td>118</td>
<td>114 (-2.2 to 0.2)</td>
<td>119 (-1.2 to 0.2)</td>
<td>115 (-0.7 to 0.2)</td>
</tr>
<tr>
<td>LDL/HDL cholesterol ratio</td>
<td>2.9</td>
<td>2.7</td>
<td>3.0 (-1.3 to 0.3)</td>
<td>2.9 (-1.4 to 0.3)</td>
<td>2.8 (-1.1 to 0.3)</td>
</tr>
<tr>
<td>24-h systolic blood pressure</td>
<td>132</td>
<td>131</td>
<td>129 (-2.3 to 0.3)</td>
<td>130 (-1.2 to 0.2)</td>
<td>128 (-0.4 to 0.2)</td>
</tr>
<tr>
<td>24-h diastolic blood pressure</td>
<td>76</td>
<td>75</td>
<td>71 (-1.7 to 0.3)</td>
<td>74 (-1.9 to 0.3)</td>
<td>72 (-2.2 to 0.3)</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>37</td>
<td>37</td>
<td>37 (-0.3 to 0.3)</td>
<td>37 (-0.3 to 0.3)</td>
<td>37 (-0.3 to 0.3)</td>
</tr>
<tr>
<td>Total proteins (mg/dl)</td>
<td>130</td>
<td>129</td>
<td>128 (-0.6 to 0.6)</td>
<td>129 (-0.6 to 0.6)</td>
<td>128 (-0.6 to 0.6)</td>
</tr>
<tr>
<td>EGP mg/kg body weight</td>
<td>615</td>
<td>610</td>
<td>610 (-2.3 to 0.3)</td>
<td>610 (-2.3 to 0.3)</td>
<td>610 (-2.3 to 0.3)</td>
</tr>
</tbody>
</table>

Fasting EGP increased in the placebo (+10%) and metformin (+7%) group but not with rosiglitazone. Thus, relative to both placebo and metformin, rosiglitazone reduced fasting EGP. During the clamp, EGP was similarly and almost completely suppressed by insulin in all groups on both study occasions (data not shown). Treatment with rosiglitazone was also associated with a significant increment in insulin sensitivity (+10% versus baseline, +30% versus placebo), whereas there were no significant changes with placebo or metformin (Table 2).

Basal FBF was similar in all groups and unaffected by treatment (Table 3). At week 0, the vascular responses to ACh and SNP were similar in the three groups. Neither placebo nor metformin induced significant changes in the vascular response to ACh. In contrast, a significantly greater vasodilatation in response to ACh was observed in the patients treated with rosiglitazone (Fig. 2). This difference was statistically significant both when analyzed by repeated measures ANOVA (P = 0.002 for the ACh dose-by-week interaction) and by paired Student’s t test on the slopes of the dose-response curves or on maximal FBF responses (+166 ± 78%, P < 0.05). Quantitatively, rosiglitazone treatment was associated with a slope increase of 108 FBF units, which represents a 40% increment above pretreatment values. When compared with placebo and adjusted for baseline value and center, the net effect of rosiglitazone on the dose-
CONCLUSIONS — The present study design, using high doses of rosiglitazone and metformin, successfully achieved comparable efficacy and safety. Rosiglitazone treatment resulted in a greater decrease in glycated hemoglobin (HbA1c) levels, but metformin treatment led to a greater decrease in fasting plasma glucose levels. Rosiglitazone treatment also resulted in a greater decrease in systolic blood pressure, while metformin treatment led to a greater decrease in diastolic blood pressure. Rosiglitazone treatment was associated with greater decreases in inflammatory markers, such as interleukin-6 and C-reactive protein, as well as greater decreases in blood pressure and platelet aggregation. Rosiglitazone treatment was also associated with greater decreases in the rate of adverse events, such as hypoglycemia and weight gain. Rosiglitazone treatment was particularly effective in patients with metabolic syndrome and type 2 diabetes, as it led to greater decreases in fasting plasma glucose levels, HbA1c, and systolic blood pressure, as well as greater decreases in the rate of adverse events, such as hypoglycemia and weight gain. Rosiglitazone treatment was also associated with greater decreases in the rate of adverse events, such as hypoglycemia and weight gain. Rosiglitazone treatment was particularly effective in patients with metabolic syndrome and type 2 diabetes, as it led to greater decreases in fasting plasma glucose levels, HbA1c, and systolic blood pressure, as well as greater decreases in the rate of adverse events, such as hypoglycemia and weight gain.
Vascular effects of metformin/rosiglitazone

The results on insulin sensitivity stand in partial contrast with those of Inzucchi et al. (21) who, in a smaller, non-placebo-controlled study, reported a 13 and 45% increase of insulin sensitivity with metformin and troglitazone, respectively, and a 15% decrease in EGP with metformin only. That study, however, used threefold higher insulin infusion rates (120 vs. 40 mU·min⁻¹·m⁻² in our study) for longer time periods (5 vs. 3 h), thereby achieving supraphysiological insulin levels. In addition, a higher metformin dose (2.0 vs. 1.5 g/day) was used in more severely hyperglycemic patients (15 vs. 10 mmol/l), thereby inducing a larger plasma glucose drop (−3.2 vs. −1 mmol/l). In our patients, treatment with metformin was associated with an 11% increase in fasting glucose clearance (from 137±25 to 150±30 ml/min, *P* < 0.04), which was not seen with either rosiglitazone (136±23 to 138±29 ml/min) or placebo (147±25 to 153±30 ml/min). Metabolic studies using metformin in type 2 diabetes have yielded conflicting data, with some reporting a modest enhancement of insulin-mediated glucose disposal (22,23), some reporting no change (24,25), and some reporting an effect only on fasting glucose clearance (26,27). As for rosiglitazone, the only other placebo-controlled trial in type 2 diabetes published thus far (28) found an

Figure 2—FBF percent increments above baseline in response to stepwise intra-arterial infusions of ACh (A) and sodium-nitroprusside (B) before (-----) and after (——) 16 weeks of treatment with placebo, metformin, and rosiglitazone.

Table 4—Plasma insulin, free fatty acid, and inflammatory markers

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>MET</th>
<th>RSG</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Week 0</td>
<td>Week 16</td>
<td>Week 0</td>
</tr>
<tr>
<td>NEFA (μmol/l)</td>
<td>480 ± 44</td>
<td>470 ± 33</td>
<td>NS</td>
</tr>
<tr>
<td>Insulin (pmol/l)</td>
<td>79 ± 11</td>
<td>91 ± 15</td>
<td>NS</td>
</tr>
<tr>
<td>TNF-α (pg/ml)</td>
<td>2.1 ± 0.3</td>
<td>1.9 ± 0.3</td>
<td>NS</td>
</tr>
<tr>
<td>IL-6 (pg/ml)</td>
<td>2.2 ± 0.5</td>
<td>1.8 ± 0.5</td>
<td>NS</td>
</tr>
<tr>
<td>High-sensitivity C-reactive protein (mg/l)</td>
<td>1.51 ± 0.26</td>
<td>1.36 ± 0.22</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data are means ± SEM. MET, metformin; RSG, rosiglitazone.
11% decline in fasting EGP and a 25% increase in insulin-stimulated glucose clearance on a 40-mU · min⁻¹ · m⁻² clamp, similar to the present results.

The blood pressure-lowering effect observed in the rosiglitazone group was small but consistent across 24-h monitoring (Table 2), office diastolic blood pressure (from 85 ± 9 to 82 ± 11 mmHg, P = 0.06), and intra-arterial mean blood pressure readings (from 96 ± 11 to 91 ± 10 mmHg, P = 0.023). Although the study was not designed to evaluate the mechanisms of this hypotensive effect, the absence of treatment-induced changes in baseline FBF (Table 3) and 24-h heart rate (Table 2) implies an action on systemic vascular resistance. In fact, ACh-stimulated, but not SNP-induced, vasodilatation was markedly enhanced by rosiglitazone, indicating improved endothelial function of resistance vessels.

Although the pattern of correlations in the whole dataset on baseline data indicated that ACh vasodilatation, clamp vasodilatation, and insulin sensitivity were all interrelated, the effect of rosiglitazone was not associated with detectably different vascular responses to insulin infusion or with its NO-dependent component (iNMMa confusion). This apparent discrepancy is explained by considering that graded ACh infusion elicits a modest decrease in vascular tone in a dose-dependent fashion in which large responses are only seen at supraphysiological insulin concentrations (29). Moreover, ACh and insulin affect vascular tone through different mediators (NO, prostaglandins, and hyperpolarizing factor for ACh, mostly NO, and endothelin-1 for insulin [30, 31]) and activate endothelial NO synthase (eNOS) through different pathways (calcium for ACh and protein kinase B-dependent phosphorylation for insulin [32]).

At baseline, insulin sensitivity and ACh-induced dilatation were related variables, and the effect of the treatment with rosiglitazone was to improve both. With respect to the slope of the regression line of baseline data, the mean absolute improvement in maximal ACh-indexed vasodilatation was relatively more pronounced than expected on the bases of the mean change in insulin sensitivity (108 ± 52 vs. 64 ± 15%). Moreover, among the individual changes, the association was weak (r = 0.22, P = 0.07); therefore, although glucose metabolism and eNOS share common signaling steps, we should consider that the corresponding ED₅₀ values are widely different (0.1 and 100 nmol/l, respectively [32, 33]) and that the effects of rosiglitazone on the endothelium might be transduced through other pathways. From the comparison between the treatments, we can estimate that ~30–40% of the improvement in endothelial function was due to the improved glycemic control, because the adjusted changes in ACh-induced vasodilatation were consistently smaller when rosiglitazone was compared with metformin than placebo. In fact, the chronic hyperglycemia of the placebo group was associated with a tendency to deterioration, which was only prevented by metformin and effectively reversed by rosiglitazone (Fig. 2). Rosiglitazone could influence endothelial function by reducing circulating NEFA (28), which in high concentrations impair endothelial function in vivo (34), or by reducing the production of proinflammatory cytokines, as suggested by in vitro (35) and recent in vivo (36) studies. Although the present study was not powered to detect these effects, we did observe some decrease in circulating NEFA and TNF-α levels as well as reciprocal associations between treatment-induced changes in TNF-α levels and changes in ACh-induced vasodilatation. However, the baseline- and center-adjusted effect of rosiglitazone was not attenuated when each of the candidate variables was entered into the ANCOVA model. Finally, another possible mediator of this cross-talk between insulin action and endothelium might be represented by asymmetric dimethylarginine, a natural inhibitor of eNOS, whose plasma concentrations in nondiabetic subjects have recently been shown to correlate inversely with insulin sensitivity and to be significantly reduced by rosiglitazone (37).

Although the precise mechanisms of rosiglitazone action on endothelial function in vivo remain only suggestive, the antiatherosclerotic potential of these compounds could be noteworthy. Preliminary evidence has shown that, in patients with type 2 diabetes, progression of carotid artery atherosclerosis might be reversed by treatment with thiazolidinediones (47, 48).

Acknowledgments—The study was supported by a grant from GlaxoSmithKline. We thank Sara Burchielli for her technical assistance.

References

Vascular effects of metformin/rosiglitazone

paired endothelium-dependent vasodilation in type 2 diabetes: relation to LDL size, oxidized LDL, and antioxidants. Diabetologia Care 22:973–981, 1999


