Treatment With Rosiglitazone Reduces Hyperinsulinemia and Improves Arterial Elasticity in Patients With Type 2 Diabetes Mellitus

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Objective: The aim of this study was to determine whether reduction of hyperinsulinemia with rosiglitazone will improve vascular elasticity in patients with non-insulin dependent diabetes mellitus.

Methods: In an open label study 52 patients with non-insulin dependent diabetes mellitus and at least one additional cardiovascular risk factor, were treated for 6 months with 4 mg of rosiglitazone, and uptitrated to 8 mg after 3 months of treatment, if needed. At the beginning of the study and at its end, blood was drawn for insulin, C-peptide, and 24-h urine collected for microalbuminuria/proteinuria. Glucose, chemistry, lipid profile, and hemoglobin A1C were determined at 0, 3, and 6 months. Vascular compliance was measured in monthly intervals.

Results: Treatment increased significantly small artery elasticity from 1.45 to 2.43 mL/mm Hg/100. Large artery elasticity tended to increase toward the end of the study (P not significant). Systolic blood pressure decreased from 144 to 124 mm Hg and diastolic blood pressure decreased from 80 to 68 mm Hg, despite mild weight gain. Heart rate tended to decrease from 76.3 to 74.7 beats/min (P = not significant). Systemic vascular resistance decreased from 1789.8 to 1329.4 dyne sec/cm5. Plasma insulin, in patients not treated with insulin, decreased from 42.45 ± 24.90 to 27.86 ± 14.86 IU/mL (P = .0001).

Conclusions: Treatment with rosiglitazone reduced hyperinsulinemia and improved small artery elasticity with a tendency to improve large artery elasticity, in hypertensive and in normotensive patients. Because rosiglitazone improves insulin receptor sensitivity (IRS), it is logical to assume that the reduction in hyperinsulinemia reflects improvement in IRS. Our data support the hypothesis that hyperinsulinemia and IRS participate in the mechanisms of tissue injury and their improvement induces improvement in arterial elasticity. Am J Hypertens 2003;16:617–622 © 2003 American Journal of Hypertension, Ltd.

Key Words: Rosiglitazone, hyperinsulinemia, insulin resistance, arterial elasticity, diabetes mellitus.
aging and in disease and are induced by hormonal and physical factors, these affect proliferation, growth, and intracellular mechanisms that have influence on growth of vascular smooth muscle cells (VSMC) and myocytes and increase production of collagen. Because these changes develop during years before an event, detection of vascular damage may serve as a predictor for future complications. Estimation of vascular compliance may serve as a surrogate end point for prediction of morbid events and for estimation of success of treatment. Because compliance is considered as a surrogate end point to estimate the probability of morbid events, we studied the effect of prolonged treatment with rosiglitazone on arterial elasticity.

Patients and Methods

In an open label study 65 patients diagnosed as suffering of type 2 diabetes mellitus with at least one additional risk factor were recruited from the outpatient clinic and evaluated for the study. The study included 52 patients who completed the study (24 men, 28 women). We did not have a control group and each patient served as his or her control, all measurements were compared to the baseline measurements on entrance into the study. All patients underwent screening procedures: full examination, full blood chemistry, complete blood count, urine examination, and electrocardiogram performed at the beginning of the study. Patients included in the study were stabilized on their previous medical treatment in the outpatient clinic for up to 3 months, with an effort not to change treatment during the study. Patients suspected of secondary hypertension or with significant disease, with history of major disease or surgery within the 6 months preceding entrance to the study were excluded. Patients with hemodynamic instability, unbalanced endocrine disease, any disease that might affect absorption of rosiglitazone were excluded, as were patients with plasma creatinine of more than 2 mg/dL, elevation of liver enzymes to more than twice the upper normal limit, and electrolyte abnormalities. Concomitant medications were kept stable to prevent possible effects on the study parameters. Treatment for diabetes was allowed including insulin. The patients received 4 mg of rosiglitazone orally for 6 months. If after 3 months of treatment the hemoglobin A1C (HbA1C) levels were >9%, the dose of rosiglitazone was increased to 8 mg.

Arterial compliance was determined and patients were invited for follow-up once a month; additional clinic visits were allowed according to patients’ request.

Arterial Compliance Measurements

The method was described in detail by us and other investigators. The investigations were performed between 8 and 11 AM, in a quiet, temperature-controlled laboratory. Radial arterial waveforms were recorded for 30 sec for each subject in the supine position. The pressure transducer amplifier system was connected to a specially designed device (Model CR-2000, Hypertension Diagnostics Inc., Eagen, MN). The passive transient response of the arterial vasculature to the initial loading conditions was determined by analyzing the diastolic portion of the pressure pulse waveform. This technique, which has been used extensively by us and other researchers, was used with a simple noninvasive radial pulse wave recording and a computer analysis of the diastolic decay. This provides separate assessment of the large artery or capacitive compliance (C1) and small artery reflective or oscillatory compliance (C2). Studies have demonstrated an age-dependent decline in both C1 and C2 parameters, reflecting structural or functional changes in the large conduit arteries as well as in the smaller reflective sites. Systemic vascular resistance (SVR) is calculated as mean arterial pressure (MAP) divided by cardiac output. The MAP is derived from waveform analysis, integrating the area under the curve and calculating the mean area of recordings during 30 sec.

The study was approved by the local Institutional Review Board and the patients signed a full informed consent.

Statistical Methods

The SPSS statistical package (Microsoft Inc., Seattle, WA) was used for statistical analysis. Paired t test was used to compare changes from baseline in monthly intervals for the treatment group. Results are expressed as means with a 95% confidence interval (CI).

Results

Of the 65 patients recruited to the study 52 completed the 6-month treatment period. The reasons for dropout were: 4 patients were excluded because of high glucose levels (above 250 mg% in all 4 patients) exclusion according to the patients’ demand, before rosiglitazone came to its full clinical effect within the first month of treatment and intensive treatment with insulin was started; severe weight gain of more than 6 kg of baseline and pedal edema (3 patients); referral for coronary angiography (1 patient); acute ischemic event (1 patient); pneumonia with prolonged hospitalization (1 patient); increase in liver enzymes (1 patient); abdominal pain (1 patient); and did not return for follow-up (1 patient). In 9 patients the dose of rosiglitazone was increased to 8 mg/d, because of Hba1C
was >9% at month 3 of treatment. In 4 patients the dose of sulfonylurea medication was decreased by 1 to 2 tablets per day. In 4 patients treated with insulin the dose was decreased by up to 15%. The clinical characteristics of the patients included in the study are listed in Table 1.

As previously reported, rosiglitazone can induce weight gain in patients. The mean weight at the beginning of the study was 83.8 ± 14.5 kg. During 6 months of treatment the weight increased significantly to 85.8 ± 15.3 kg ($P < 0.00008$), the mean increase in weight was 2.0 kg. Despite weight gain, the metabolic status of the patients improved, HbA1C decreased significantly from 8.95 ± 1.40% to 7.80 ± 1.27% ($P < 0.0000003$). All patients were hyperinsulinemic and treatment induced a significant decrease in fasting plasma insulin levels from 42.4 ± 24.9 IU/mL to 27.9 ± 14.9 IU/mL ($P < 0.0001$). The C-peptide levels decreased significantly from 4.60 ± 2.21 to 3.1 ± 1.40 mg/dl ($P < 0.00003$). Systolic and diastolic blood pressure (BP) decreased significantly (Table 2). Pulse pressure tended to decline from 62.9 ± 18.6 mm Hg at entrance to the study to 60.2 ± 15.1 mm Hg at the end of the study ($P = \ldots$).

### Table 1. Baseline demographic and metabolic characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Sex</th>
<th>Age, mean (range)</th>
<th>BMI, mean (range)</th>
<th>Duration of diabetes, mean (y)</th>
<th>Additional cardiovascular risk factors:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male (46.2%)</td>
<td>61.3 (43–70)</td>
<td>29.66 ± 4.41</td>
<td>15.8 (5–28)</td>
<td>Dyslipidemia (55.8%)</td>
</tr>
<tr>
<td></td>
<td>Female (53.8%)</td>
<td></td>
<td></td>
<td></td>
<td>Hypertension (57.7%)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Current smokers (15.4%)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Obesity—overweight (25.0%)</td>
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<td></td>
<td></td>
<td></td>
<td>Severe obesity (46.2%)</td>
</tr>
<tr>
<td>Prior therapy</td>
<td>Oral antidiabetic medications (75.0%)</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Oral antidiabetics + insulin (9.6%)</td>
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<tr>
<td></td>
<td>Baseline HbA1C (mean range)</td>
<td>8.97 ± 1.43</td>
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<tr>
<td></td>
<td>Baseline fasting insulin levels, mean</td>
<td>42.35 ± 24.97</td>
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<tr>
<td></td>
<td>Baseline C-peptide levels, mean</td>
<td>4.69 ± 2.09</td>
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<td></td>
<td>Baseline systolic blood pressure (mm Hg)</td>
<td>143.59 ± 18.57</td>
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<tr>
<td></td>
<td>Baseline diastolic blood pressure (mm Hg)</td>
<td>79.65 ± 10.82</td>
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</tr>
</tbody>
</table>

BMI = body mass index; HbA1C = hemoglobin A1C.
Severe obesity: BMI > 30 (%); obesity—overweight: BMI = 27 to 30 (%).

### Table 2. Blood pressure and arterial compliance during the 6-month treatment with rosiglitazone

<table>
<thead>
<tr>
<th>Baseline</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>143.8 ± 2.7</td>
<td>140.4 ± 2.9</td>
<td>137.3 ± 2.7</td>
<td>*</td>
<td>135.6 ± 2.7</td>
<td>134.9 ± 2.7</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>79.7 ± 1.5</td>
<td>76.5 ± 1.5</td>
<td>75.3 ± 1.7</td>
<td>+</td>
<td>73.0 ± 1.7</td>
<td>72.7 ± 1.7</td>
</tr>
<tr>
<td>Systolic arterial pressure (mMol/L)</td>
<td>10.4 ± 0.7</td>
<td>10.6 ± 0.6</td>
<td>10.7 ± 0.6</td>
<td>+</td>
<td>10.5 ± 0.6</td>
<td>10.4 ± 0.6</td>
</tr>
<tr>
<td>DBP arterial pressure (mMol/L)</td>
<td>3.4 ± 0.2</td>
<td>4.1 ± 0.3</td>
<td>4.2 ± 0.3</td>
<td>+</td>
<td>4.7 ± 0.3</td>
<td>4.4 ± 0.3</td>
</tr>
</tbody>
</table>

SBP = systolic blood pressure; DBP = diastolic blood pressure; SAEI = small artery elasticity index.
not significant [ns]). No correlation was found between pulse pressure and arterial compliance ($P = .17$ between visit 1 and visit 7).

Large artery elasticity index tended to increase ($P = ns$) during the 6 months of treatment with rosiglitazone (Table 2, Fig. 1b). Small artery elasticity index increased significantly during the study with a mean increase of up to 50% during monthly follow-up ($P < .001$ at least) in comparison to baseline measurements (Fig. 1b).

Systolic BP decreased significantly, the decrease reaching significance in the second month of treatment ($P < .0004$ and higher). The decrease in systolic BP continued throughout the study and a plateau was not reached after 6 months of treatment at which time the systolic BP decreased by 14% (Table 2, Fig. 1).

Diastolic BP decreased significantly from the first month of treatment ($P < .002$ and higher), the decrease continued throughout the study and did not reach a plateau within 6 months of treatment (Fig. 1). The decrease in diastolic BP at the end of the 6 months of study was 22.82%. Mean BP continued to decrease during the study, as with systolic and diastolic BP; the decrease was also progressive and did not reach a plateau after the 6-month period.

Heart rate during the treatment period tended to decrease (from 76 to 74 beats/min), but the decrease did not reach statistical significance.

Systemic vascular resistance decreased significantly during the treatment period ($P < .001$ and lower). The decrease in SVR was progressive during the study, decreasing by 5% to 10% per month, reaching a decrease of about 25% at completion of 6 months of treatment (Fig. 1c).

**Discussion**

The prominent finding of the present study is that treatment with rosiglitazone improved significantly the small artery elasticity (SAE). These findings comply with the theory that hyperinsulinemia and insulin resistance participate in the development of tissue damage, a progressive decrease in SAE. Because treatment with rosiglitazone has been shown in the present study to reduce hyperinsulinemia and by other investigators14 –16 to improve insulin receptor sensitivity, our findings comply with the concept that improvement of these factors cannot only halt the progression but also improve decreased vascular elasticity, which has been recently accepted as a surrogate marker of vascular disease. The impressive extent of improvement of SAE of up to 50% during a relatively short period of time (6 months) confirms the fact that hyperinsulinemia and reduced insulin sensitivity are powerful factors in the development of vascular disease. It is important to note that SAE continued to improve throughout the study without reaching a plateau, thus it is possible that additional improvement will be seen with continuation of treatment beyond the 6-month period.

It has been questioned whether measurement of compliance reflects merely the BP change, in our study the changes in compliance (SAE and large artery elasticity [LAE]) did not correspond with BP changes. The time course of the changes did not correspond and LAE did not change significantly during the study, despite the change in BP. The SAE improved gradually, but its change was different from the pattern of BP change. Thus, it is clear that changes in C1 and C2 do not reflect BP changes but reflect compliance.

Despite a tendency of pulse pressure to decline ($P = ns$), we did not find a significant correlation between pulse pressure and SAE or LAE.

This new therapeutic approach enables us to correct these powerful metabolic derangements and has great po-
tential to induce regression of development of small vessel disease.

We did not find significant change in LAE. At the end of the 6-month treatment period a clear trend of increase in LAE is seen with borderline statistical significance (Fig. 1b). Lack of change in LAE implies that treatment with rosiglitazone either did not affect the fibrotic component of the large blood vessels like the aorta and its large branches or, more logically, that this process of “tissue repair” in the large arteries is lengthy and may take more than the 6 months of our treatment period. Large arteries have a major component of fixed fibrotic tissue that probably needs more time for repair under conditions of improved insulin receptor sensitivity and amelioration of hyperinsulinemia in patients with type 2 diabetes mellitus. The fact that at the end of 6 months of treatment a clear trend of increase in LAE is seen, implies that LAE may improve after longer periods of treatment. To answer this question studies with longer periods of treatment with rosiglitazone are needed. In contrast, small arteries probably contain a more repairable component regarding arterial elasticity. This includes endothelial dysfunction, which usually changes in a shorter time period. The fact that the large artery compliance increased only slightly and insignificantly makes the increase in small artery compliance more likely to be, at least in part, due to a direct effect on endothelial function of the small arteries.

In our study, treatment with rosiglitazone improved additional cardiovascular risk factors, which also affect vascular properties like BP and plasma glucose levels. We can speculate that endothelial dysfunction might have been improved as SVR decreased significantly when no antihypertensive nor vasodilatatory agent was added.

Systolic, diastolic, and mean BP decreased significantly during the study. During the whole study period there were no changes in the concomitant medications; we did not change the number or dose of antihypertensive medications nor did we change any antidiabetic medications.

The fact that both systolic and diastolic BP continued to decrease throughout the study implies that the change in metabolic/growth factor profile had a continuous beneficiary effect and caused continued regression of damage in the small arteries—a positive vascular remodeling. These changes probably occurred due to improvement in hyperinsulinemia, as shown in our study, and in insulin receptor sensitivity of type 2 diabetes mellitus patients.4–6,14–16 It is possible that further improvement in SAE would have occurred with continuation of treatment during longer periods.

It is important to note that most of our patients were normotensive; however, a decrease in BP levels (although within normal range) was seen. The BP reduction was mediated by a decrease in SVR and it is logical to assume that improvement in endothelial dysfunction plays at least a part in this beneficiary hemodynamic phenomenon.

The tendency of the pulse rate to decrease complies with the assumption that one of the effects of hyperinsulinemia is increased sympathetic nervous system activity. In our study, treatment that lowers hyperinsulinemia and increases insulin receptor sensitivity could have led to a decrease in sympathetic nervous system activity with a resulting tendency to decrease the heart rate.

Systemic vascular resistance decreased significantly during the treatment period. The decrease in SVR was progressive during the study and continued to decrease during the treatment period. It is possible that a further decrease could have occurred with continuation of treatment. In our study each patient served as his or her control and no control group was present; therefore, we cannot conclude that rosiglitazone has also antihypertensive properties.

Because the main effect of treatment is metabolic, the mechanism of the impressive improvement in hemodynamic parameters and in small vessel elasticity is probably induced by metabolic changes, associated with a decrease in the degree of hyperinsulinemia and thus of improvement in insulin receptor sensitivity. However, as BP decreased relatively early in our study we cannot exclude the possibility of a contributory effect of BP decrease as well as of improvement in endothelial dysfunction and metabolic components as contributing factors to improve small vessel elasticity.

In summary, our study showed significant improvement in SAE as well as of decrease in both systolic and diastolic BP with additional beneficiary hemodynamic effects resulting in decreased SVR. Because treatment with rosiglitazone decreases hyperinsulinemia and thus, as proven, improves insulin receptor sensitivity, this is probably the main mechanism that improved the SAE of the patients with type 2 diabetes mellitus in our study. Because one of the early changes seen in our patients was a significant decrease in BP, although most of our patients were not hypertensive, this could have also contributed to the beneficiary results of our study.

It is evident from our study that rosiglitazone as a representative of a new group of medications that improve insulin receptor sensitivity and decrease hyperinsulinemia has additional beneficiary effects in tissue protection of which we are not aware yet. Our results also support the hypothesis that a decrease in hyperinsulinemia and improvement of insulin receptor sensitivity plays a significant role in the repair of tissue damage and their improvement has great potential in future therapeutic approach of prevention of end-organ damage.

References