Rosiglitazone Improves Insulin Sensitivity and Lowers Blood Pressure in Hypertensive Patients

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OBJECTIVE — To examine the effect of rosiglitazone on insulin resistance and blood pressure in patients with essential hypertension, classified based on abnormalities of their renin-angiotensin system.

RESEARCH DESIGN AND METHODS — A total of 24 hypertensive nondiabetic patients (age 58 ± 6 years, BMI 30 ± 5 kg/m²) were studied before and after rosiglitazone treatment. After 2 weeks off antihypertensive medication, subjects received a euglycemic-hyperinsulinemic clamp (40 mU·m⁻²·min⁻¹) with 6,6-[³H]glucose infusion, ambulatory blood pressure monitoring, and blood tests for cardiovascular risk factors. Subjects were then placed on rosiglitazone (4 mg orally b.i.d.) and their usual antihypertensive medications (but not ACE inhibitors) for 16 weeks, and baseline tests were repeated.

RESULTS — There was no change in fasting plasma glucose (83 ± 2 vs. 82 ± 2 mg/dl, P = 0.60), but fasting insulin decreased (161 ± 14 vs. 125 ± 9 µU/ml, P < 0.01). Total glucose disposal during the clamp increased (5.0 ± 0.4 vs. 5.9 ± 0.5 mg·kg⁻¹·min⁻¹, P < 0.001), with no change in suppression of hepatic glucose output. There were significant decreases in mean 24-h systolic (138 ± 2 vs. 134 ± 2 mmHg, P < 0.02) and diastolic (85 ± 2 vs. 80 ± 2 mmHg, P < 0.0001) blood pressure, and the decline in systolic blood pressure was correlated with the improvement in insulin sensitivity (r = 0.59, P < 0.005). Triglycerides (135 ± 16 vs. 89 ± 8 mg/dl, P < 0.01), LDL cholesterol (129 ± 6 vs. 122 ± 8 mg/dl, P = 0.18), and HDL cholesterol (51 ± 3 vs. 46 ± 3 mg/dl, P < 0.02) all decreased, with no change in the LDL-to-HDL ratio. Plasminogen activator inhibitor-1 and C-reactive protein also declined significantly.

CONCLUSIONS — Rosiglitazone treatment of nondiabetic hypertensive patients improves insulin sensitivity, reduces systolic and diastolic blood pressure, and induces favorable changes in markers of cardiovascular risk. Insulin sensitizers may provide cardiovascular benefits when used in the treatment of patients with hypertension.

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The insulin resistance syndrome is a heterogeneous disorder characterized by the presence of hyperinsulinemia, impaired glucose tolerance or type 2 diabetes, essential hypertension, dyslipidemia, visceral adiposity, and/or hypercoagulability (1–3). This clustering of cardiovascular risk factors leads to a high rate of coronary events and increased mortality in this population (4,5). Thiazolidinediones (TZDs) are insulin sensitizers that reduce insulin resistance in muscle and adipose tissue by modifying key pathophysiological defects in type 2 diabetes. TZDs may provide therapeutic benefits for the insulin resistance syndrome beyond improving glycemic control and have been shown in smaller studies to have beneficial effects on blood pressure and dyslipidemia in vivo and to exhibit vasorelaxant activity in vitro (6–9).

Hyperinsulinemia and insulin resistance occur in both obese and nonobese patients with essential hypertension, although the pathophysiological basis for this association is poorly understood (10,11). Potential mechanisms include sodium retention, increased sympathetic activity, or impaired vasorelaxation (12,13). It is not well established whether insulin resistance is present in all patients with essential hypertension or whether it is more characteristic of certain identifiable subgroups of patients.

Previous studies by our group have demonstrated that a particular subset of salt-sensitive essential hypertensive patients is more insulin resistant than individuals with low-renin (LR) hypertension (14,15). This subset comprises ~30% of the hypertensive population and has been termed “nonmodulators” (NMs) because of an inability to appropriately regulate their blood pressure, renal plasma flow, and responsiveness to angiotensin II during transition from a high-salt to a low-salt diet (16,17).

The primary purpose of this study was to determine whether treatment of nondiabetic hypertensive patients with the TZD rosiglitazone would improve insulin sensitivity and reduce blood pressure. On the basis of our previous findings, we hypothesized that the NM subgroup would experience a greater improvement in insulin sensitivity and a greater reduction in blood pressure than the LR group. A secondary goal of the study was to evaluate the effect of rosiglitazone on cardiovascular risk factors.

RESEARCH DESIGN AND METHODS

Subjects

Twelve NM and 12 LR hypertensive patients were studied. Subjects had previ-
ously been classified into normal/high-renin and LR groups based on a plasma renin activity >2.4 ng·mL⁻¹·h⁻¹ after 90–120 min of upright posture after 5 days on a low-sodium diet (10 mEq/day). The normal/high-renin group was further classified into two subsets termed “modulators” and “nonmodulators” based on the adrenal response to a 3 ng·kg⁻¹·min⁻¹ angiotensin II infusion for 30 min on a 10 mEq/day sodium intake. Nonmodulators (NM) were defined as those subjects who had an increase in aldosterone of <15 ng/dl, with basal aldosterone levels of <30 ng/dl (16,17). The subjects who responded normally to the angiotensin II infusion (>15 ng/dl increment in aldosterone) were classified as modulators. All 24 subjects had normal fasting plasma glucose levels, although 8 had a family history of type 2 diabetes. The study was approved by the institutional review board at Brigham and Women’s Hospital, and voluntary informed written consent was obtained from each subject.

### Study protocol

Subjects initially were seen at the outpatient General Clinic Research Center (GCRC) for a screening physical exam and blood tests including fasting glucose and insulin, lipid profile, blood urea nitrogen, creatinine, serum electrolytes, and liver function. Subjects were excluded if they had diabetes, coronary artery disease, congestive heart failure, renal disease, or liver disease. Because ACE inhibitors can change the nonmodulator phenotype (18) and decrease insulin resistance (19,20), the 12 subjects who had been on ACE inhibitors were switched to a calcium-channel blocker (5–10 mg/day amlodipine and, in one patient, 180 mg/day diltiazem, as per patient’s request), plus a diuretic if necessary, for 10 weeks.

Two weeks before the inpatient physiological evaluation described below, all antihypertensive medications were discontinued. During the last 5 days of this period, subjects were placed on a low-salt diet (10 mEq sodium/day), and during the last 3 days, subjects were also placed on a 200- to 300-g carbohydrate diet to prepare for the insulin clamp study. The 24-h ambulatory blood pressure (described below) was recorded during the final day before admission.

Patients were admitted to the GCRC and, after an overnight fast, had insulin sensitivity determined by the euglycemic-hyperinsulinemic clamp technique, as described below. During this admission, subjects had their waist-to-hip ratio measured and body composition estimated by bioelectric impedance (21). Fasting blood samples were drawn for plasminogen activator inhibitor 1 (PAI-1) and C-reactive protein (CRP).

After completion of these tests, subjects were placed on rosiglitazone (4 mg orally per day titrated to 4 mg orally b.i.d. after 2 weeks) for 16 weeks. Baseline antihyperglycemic medications were resumed for 14 weeks and were discontinued for the last 2 weeks, after which all of the baseline tests were repeated. Liver function tests were monitored at baseline and at 4-week intervals during the study period, and subjects were asked to report any untoward side effects, including leg edema or shortness of breath.

### Procedures

#### Ambulatory blood pressure monitoring.

Ambulatory blood pressure monitors (Spacelabs 90207, Redmond, WA) were used to measure blood pressure before each euglycemic-hyperinsulinemic clamp. The ambulatory blood pressure monitors were preprogrammed to record the blood pressure every 30 min during the day (0600–2300) and once hourly at night (2300–0600). Each subject was asked to record activities throughout the day. If >30% of the measurements were artifacts or missing, readings were not used for analysis. Mean blood pressures were calculated for daytime, nighttime, and the overall 24-h period to determine whether the normal nocturnal fall in blood pressure (>10 mmHg) was present at baseline and whether it changed after rosiglitazone treatment. As part of a post hoc analysis, we subdivided the patients into “dippers” and “nondippers” based on the blood pressure fall from daytime to nighttime. Patients with a ≥10 mmHg drop in systolic blood pressure during the first ambulatory blood pressure monitoring (ABPM) were classified as dippers, and the rest were classified as nondippers.

#### Euglycemic-hyperinsulinemic clamp technique.

Insulin sensitivity was measured as previously described (22,23). After an overnight fast, intravenous lines were placed into an antecubital vein for administration of test substances and into a heated (70°C) hand vein of the same arm for blood sampling (24). After basal samples were obtained, a primed-continuous infusion of insulin was administered at 40 mU·m⁻²·min⁻¹ for 2 h. The plasma glucose concentration was measured at 5-min intervals and maintained at the basal level by a variable infusion of 20% dextrose.

To determine the site of insulin resistance, endogenous glucose production was measured using stable tracer methods as previously described (23). A primed-continuous infusion of 6,6-[²H₂]glucose was administered at 0.03 mg·kg⁻¹·min⁻¹ starting 2 h before the insulin infusion and continued until the completion of the study (total of 4 h). Blood samples for 6,6-[²H₂]glucose atoms percent excess were taken at times −15, −10, −5, and 0 min to determine baseline enrichment and at 105, 110, 115, and 120 min to measure enrichment during steady-state hyperinsulinemia. To minimize the fluctuation of plasma 6,6-[²H₂]glucose enrichment during the clamp, the glucose tracer was added to the exogenous glucose infusion at a concentration of 2.73 mg/ml (25).

Basal hepatic glucose production was calculated by dividing the baseline tracer infusion rate by the baseline steady-state plasma enrichment. The rate of whole-body glucose metabolism during the clamp was calculated by dividing the total tracer infusion rate (the sum of the ongoing primed-continuous infusion plus the tracer contained in the 20% dextrose infusion) by the plasma enrichment during the final 20 min of the study. The known rate of exogenous glucose infusion was subtracted from the calculated total rate of glucose appearance to determine residual hepatic glucose production.

#### Biochemical analyses.

Plasma glucose was measured using a glucose reflectometer (LifeScan, Mountain View, CA). Plasma insulin levels were determined by radioimmunoassay (Linco Research, St. Louis, MO). Plasma samples were assayed for PAI-1 antigen using a two-site enzyme-linked immunosorbent assay (Biopool AB, Umea, Sweden; normal range 4–43 ng/ml) and for CRP using a latex-based immunoassay (Dade Behring, Newark, DE). Lipid levels were measured at the Brigham and Women’s Hospital laboratory. Deuterated glucose analysis was done using a Hewlett Packard gas chromatograph mass spectrometer (Metabolic Solutions, Nashua, NH) (26).
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Table 1—Patient demographic characteristics

<table>
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<td>24</td>
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<td>Age (years)</td>
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Data are means ± SD.

Statistical analysis. Power was determined using change in insulin sensitivity and change in blood pressure as primary end points. Baseline demographic data are expressed as means ± SD, whereas all other summary data comparing the two groups are expressed as means ± SE. All statistical analyses were performed using the STATA statistical software version 7.0 (Stata Corporation, College Station, TX). Standard statistical tests used to compare the two groups included t tests for means, Wilcoxon’s rank-sum test where ranks were appropriate, and standard regression methods. Paired t test or appropriate nonparametric tests were used to estimate the effects of rosiglitazone on all the primary and secondary variables. All tests were conducted using an α level of 0.05.

RESULTS — Baseline demographic data are presented in Table 1. There was no statistically significant difference between the LR and NM group in terms of age, race, BMI, body composition, or baseline systolic and diastolic blood pressures, but there were more women in the LR group than in the NM group. One subject in the NM group was unable to undergo the second insulin clamp because of difficulty with intravenous access, and one subject in the LR group failed to complete the second ABPM.

At the end of 16 weeks, rosiglitazone treatment produced significant decreases in the 24-h mean, nighttime, and daytime systolic and diastolic blood pressure in the entire group (Table 2). There were no significant differences in the blood pressure responses between the LR and NM subsets (mean systolic blood pressure change -5 ± 2 vs. -2 ± 2 mmHg, P = 0.2; mean diastolic blood pressure change -6 ± 1 vs. -4 ± 1 mmHg, P = 0.1).

There was no change in fasting plasma glucose (83 ± 2 vs. 82 ± 2 mg/dl), but there was a significant decline in fasting plasma insulin levels (16.1 ± 1.4 vs. 12.5 ± 0.9 μU/ml, P < 0.01). There was no change in body composition (67 ± 3 vs. 67 ± 3% fat-free mass), but there was a small but statistically significant increase in weight after rosiglitazone treatment (88 ± 3 vs. 89 ± 3 kg, P < 0.05).

Basal hepatic glucose production was normal at baseline and remained unchanged after 16 weeks of rosiglitazone treatment (1.8 ± 0.1 vs. 1.8 ± 0.1 mg·kg⁻¹·min⁻¹). During the hyperinsulinemic clamp, whole-body glucose metabolism improved from 5.0 ± 0.4 mg·kg⁻¹·min⁻¹ at baseline to 5.9 ± 0.5 mg·kg⁻¹·min⁻¹ after rosiglitazone treatment (P < 0.001). The improvement in insulin sensitivity was almost entirely accounted for by an increase in peripheral glucose disposal with no change in residual hepatic glucose production (Table 2). Although the LR group exhibited a slightly greater improvement in insulin sensitivity than the NM group (1.2 ± 0.3 vs. 0.5 ± 0.3 mg·kg⁻¹·min⁻¹), the difference was not statistically significant (P = 0.09).

There was a highly significant correlation between the improvement in insulin sensitivity and the decline in mean 24-h systolic blood pressure (r = 0.59, P < 0.005), and a trend toward significance in the mean 24-h diastolic blood pressure (r = 0.36, P < 0.10). The correlation was maintained in both hypertensive groups as shown in Fig. 1.

Markers of cardiovascular risk including triglycerides, PAI-1, and CRP declined significantly in both groups after rosiglitazone treatment (Table 2). Both LDL and HDL cholesterol declined, resulting in no change in the LDL-to-HDL ratio.

Circadian disturbance in blood press-
Elevations have been reported with diabetes and other insulin-resistant states, and the loss of circadian variation has been associated with increased mortality rate in both type 1 and type 2 diabetic patients (27). In our patient sample, the 11 nondippers showed a significant improvement in their nocturnal blood pressure drop after rosiglitazone treatment (−3 ± 1 vs. −8 ± 1 mmHg, P < 0.0009), whereas the 12 dippers had no significant change (−16 ± 1 vs. −14 ± 2 mmHg, P = 0.4).

None of the subjects had significant elevations (defined as twice their baseline) in liver function tests nor had any hypoglycemia. Two subjects complained of leg edema but continued to be compliant with the medication. Both of these subjects had been switched from ACE inhibitors to calcium channel blockers for the study period. The edema resolved with discontinuation of rosiglitazone and resumption of their original antihypertensive medications.

**CONCLUSIONS** — Many previous studies have determined that essential hypertension is accompanied by insulin resistance, dyslipidemia, diabetes, and other cardiovascular risk factors (1–3). However, it is not well established whether certain identifiable subgroups of hypertensive patients are more insulin resistant than others or whether treatment with an insulin sensitizer might effectively lower blood pressure in those patients who are most insulin resistant. Our group previously demonstrated that a subset of hypertensive patients termed “nonmodulators” is more insulin resistant than the LR group (15). The current study was designed to determine whether the insulin sensitizer rosiglitazone would improve insulin sensitivity, lower blood pressure, and improve other cardiovascular risk factors, particularly in the NM subset of patients.

Our results indicate that rosiglitazone significantly improves insulin sensitivity and lowers blood pressure in patients with essential hypertension and that these two physiological changes are closely correlated. Rosiglitazone also restored the normal nocturnal decline in blood pressure and produced improvements in several cardiovascular risk factors, including triglycerides, total cholesterol, PAI-1, and CRP. However, we found no substantive differences in the magnitude of these responses between the subsets of hypertensive patients as we had originally hypothesized.

TZDs have proven to be effective oral medications in the treatment of insulin resistance and type 2 diabetes (28). They improve insulin sensitivity by interacting with a family of nuclear receptors known as peroxisome proliferator–activated receptors (PPARs), particularly PPAR-γ. TZDs are thought to enhance the actions of insulin by increasing insulin-dependent glucose disposal in muscle and fat, to a lesser extent, which reduces hepatic glucose production (29). The results of the current study demonstrate that patients with essential hypertension are insulin resistant and that significant improvements in insulin action occur after rosiglitazone treatment. As has been shown in other insulin-resistant states, the physiological site of this improvement is predominantly in peripheral tissues such as muscle and adipose tissue.

Small studies have suggested that the TZDs may have therapeutic potential beyond glycemic control in diabetes (30). Both troglitazone and rosiglitazone have been reported to produce small, but often statistically significant, reductions in blood pressure in diabetic patients and nondiabetic insulin-resistant patients (7,9,31). All three TZDs also have been shown to have a favorable effect on dyslipidemia and hypercoagulability in diabetes (30). Recent in vivo and in vitro studies also suggest that TZDs enhance vasorelaxation in vascular smooth muscle (32–34). However, their potential clinical application in nondiabetic insulin-resistant states has not been widely studied.

In this study, we found a substantial and statistically significant reduction in blood pressure of 4/5 mmHg after rosiglitazone treatment. Our ability to reliably detect this effect is likely due to the use of 24-h ABPM, which generates a more reproducible and clinically meaningful measurement than the single random cuff pressures that were used in most previous studies (35). Also, by studying nondiabetic individuals, we removed any potential confounding effects of changes in blood glucose on sodium and water homeostasis. Finally, we performed the study on a low-salt diet that would tend to enhance the antihypertensive effect. It is not known whether a similarly large effect would be seen on a more typical high-salt diet.

The use of 24-h ABPM also enabled us to examine changes in nocturnal and diurnal blood pressure. It is known that many patients with essential hypertension or diabetes do not exhibit the normal nighttime reduction in blood pressure.

**Figure 1** — Effect of rosiglitazone on the change in insulin sensitivity versus change in systolic blood pressure in LR (circles) and NM (triangles) hypertensive patients (r = −0.59; P < 0.005).
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These individuals, often called “nondippers,” tend to have greater end-organ damage and increased mortality than normal “dippers” (27,36). In the present study, we found that 11 of the 12 nondippers exhibited restoration of the normal circadian pattern after treatment with rosiglitazone. This may be another mechanism by which the thiazolidinediones help reduce cardiovascular morbidity or mortality.

It is not clear why we did not observe our hypothesized difference in response between the NM and LR groups, but there are several potential explanations. First, in our previous studies demonstrating differences in insulin sensitivity among the subgroups, the differences were greater on a high-salt diet (37). Because the current study was performed on a low-salt diet to more effectively assess the antihypertensive effect of rosiglitazone, the differences in insulin sensitivity between the subsets tended to be minimized. Also, studies by other investigators have suggested that all forms of salt-sensitive hypertension (including NM and LR groups) are more insulin resistant than other forms of hypertension (38,39). Finally, the subjects were moderately overweight, which may explain the increase in insulin resistance seen in both groups. Further studies comparing the effects on high- and low-salt diet in nonobese individuals should help clarify these questions. It should be noted, however, that the relationship between the improvement in insulin sensitivity and reduction in blood pressure was similar in the two groups, suggesting that the physiological mechanisms underlying this relationship are consistent across different types of hypertensive patients. Thus, to the degree that insulin resistance is contributing to an elevation of blood pressure, a given improvement in insulin sensitivity will produce a certain reduction in blood pressure, independent of other factors.

In addition to reducing blood pressure, rosiglitazone had salutary effects on other cardiovascular risk factors. Triglyceride and total cholesterol levels both decreased, although the decrease in cholesterol was the result of reductions in both LDL and HDL, with no change in the ratio (40,41). High PAI-1 levels are associated with an increased cardiovascular risk, including impaired fibrinolysis, that often is observed in insulin-resistant states such as obesity, impaired glucose tolerance, and type 2 diabetes (42,43). Treatment of obese and type 2 diabetic patients with troglitazone can reverse these abnormalities (44,45). In our present study of nondiabetic hypertensive subjects, treatment with rosiglitazone also produced a significant fall in PAI-1. C-reactive protein, a marker of inflammation, also has been identified as a cardiovascular disease risk factor in obesity, type 2 diabetes, and other diseases associated with insulin resistance (46–48). Rosiglitazone produced a small but significant decrease in CRP in our study, consistent with its beneficial effects on other cardiovascular risk factors.

The patients in this study tolerated the medication well with minimal adverse effects. There was a small but statistically significant weight gain of ~1 kg. Weight gain is known to occur with all of the TZDs and often is much larger in diabetic patients because of reduced glycosuria, sodium retention, and the positive anabolic effects associated with improved glucose control. Two patients developed trace pedal edema, which resolved when the drug was discontinued at the end of the study, and none of the patients experienced any significant increase in liver function tests.

Several limitations of our study must be acknowledged. First, only salt-sensitive hypertensive subjects were studied. It is not known if other groups of hypertensive patients may have the same result. Second, our patients were mildly obese, which would tend to make both subgroups of patients more insulin resistant. Whether a more lean insulin-sensitive group would have responded similarly is unknown. Thus, the relation between rosiglitazone’s effect on insulin sensitivity and blood pressure needs to be interpreted cautiously. Accepting the limitations of patient selection, the significant blood pressure decrease in subjects with essential hypertension, even on a low-salt diet, points to the potential of treating selected high-risk insulin-resistant hypertensive subjects with insulin sensitizers.

In summary, in nondiabetic hypertensive patients, rosiglitazone treatment leads to a significant increase in insulin sensitivity, reduced blood pressure, and improvements in several cardiovascular disease risk factors. Although the mechanism is not fully understood, the close relationship between change in insulin sensitivity and change in blood pressure across different subgroups of hypertensive patients indicates that there may be a common physiological mechanism relating these two effects. Because our patients were not diabetic and had no change in fasting plasma glucose levels after treatment, it appears that changes in glucose level per se are not required to observe the antihypertensive and other metabolic effects. The data also suggest that further studies are indicated to pursue potential clinical applications of the thiazolidinediones in cardiovascular risk reduction.

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References


