Rosiglitazone but Not Metformin Enhances Insulin- and Exercise-Stimulated Skeletal Muscle Glucose Uptake in Patients With Newly Diagnosed Type 2 Diabetes

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Rosiglitazone, a thiazolidinedione, enhances peripheral insulin sensitivity in patients with type 2 diabetes. Because the synergic action of insulin and exercise has been shown to be decreased in insulin resistance, the aim of this study was to compare the effects of rosiglitazone and metformin on muscle insulin responsiveness at rest and during exercise in patients with type 2 diabetes. Therefore, 45 patients with newly diagnosed or diet-treated type 2 diabetes were randomized for treatment with rosiglitazone (4 mg b.i.d.), metformin (1 g b.i.d.), or placebo in a 26-week double-blind trial. Skeletal muscle glucose uptake was measured using fluorine-18–labeled fluoro-deoxy-glucose and positron emission tomography (PET) during euglycemic-hyperinsulinemic clamp and one-legged exercise before and after the treatment period. Rosiglitazone (P < 0.05) and metformin (P < 0.0001) treatment lowered the mean glycosylated hemoglobin. The skeletal muscle glucose uptake was increased by 38% (P < 0.01) and whole-body glucose uptake by 44% in the rosiglitazone group. Furthermore, the exercise-induced increment during insulin stimulation was enhanced by 99% (P < 0.0001). No changes were observed in skeletal muscle or whole-body insulin sensitivity in the metformin group. In conclusion, rosiglitazone but not metformin 1) improves insulin responsiveness in resting skeletal muscle and 2) doubles the insulin-stimulated glucose uptake rate during physical exercise in patients with type 2 diabetes. Our results suggest that rosiglitazone improves synergetic action of insulin and exercise. Diabetes 51:3479–3485, 2002

Impaired glucose utilization and impaired insulin-stimulated glucose uptake and disposal in target tissues constitute two major characteristics of type 2 diabetes (1). In normal subjects, the majority of glucose (70–80%) is taken up by skeletal muscle tissue during insulin stimulation (2,3). Whole-body insulin resistance can be attributed to diminished glucose uptake by skeletal muscles, as shown in obese subjects (4) and patients with type 2 diabetes (5). Although thiazolidinediones (TZDs) are now widely used to treat type 2 diabetes, their mechanism of action remains largely unknown. It is well established that TZDs enhance insulin sensitivity by activating peroxisome proliferator–activated receptor (PPAR)-γ in adipose tissue (6,7). However, the improvement in insulin sensitivity occurs predominantly in skeletal muscle (8,9). One possible explanation for the insulin-sensitizing effects of TZDs is that they may enhance phosphatidylinositol (PI) 3-kinase pathway activation in skeletal muscle of patients with type 2 diabetes (10). It has previously been demonstrated that insulin stimulation of PI 3-kinase activity is defective in skeletal muscle of type 2 diabetic patients (11,12).

The TZD rosiglitazone has been shown to promote adipocyte differentiation by activating PPAR-γ in animal studies (13) and to enhance insulin-stimulated glucose uptake in skeletal muscle in the ob/ob mouse (14). Moreover, the efficacy of rosiglitazone on glycemic control has repeatedly been demonstrated in several clinical trials in patients with poorly controlled type 2 diabetes (7,15). Recently, rosiglitazone has been demonstrated to enhance whole-body insulin sensitivity (16). However, the effects of rosiglitazone on skeletal muscle insulin sensitivity have not previously been measured in human clinical studies.

For many years, oral therapies for patients with type 2 diabetes have largely been based on sulfonylureas and metformin. Metformin is believed to work mainly by inhibiting hepatic glucose production (17–21). In addition, metformin has been demonstrated to increase skeletal muscle glucose uptake in some studies (8,22), but this could be a consequence of improved glycemic control rather than a direct effect (17). Moreover, such an effect does not appear to be a result of enhanced PI 3-kinase pathway activation in skeletal muscle (10).

Both insulin and muscular contractions stimulate glucose uptake, but the cellular mechanism appears to be...
distinct, at least in part. Both stimuli induce a translocalization of GLUT4, but possibly from different intracellular pools (23). Insulin activates the PI 3-kinase pathway, whereas it has been proposed that muscular contraction stimulates glucose transport by an insulin-independent signaling mechanism, via stimulation of AMP-activated protein kinase (24). It has also been demonstrated that the contraction-induced increase in glucose uptake does not involve activation of key insulin-signaling mediators, such as insulin receptor substrate-1 and -2 in skeletal muscle (25). Previous studies addressing the interaction between insulin and exercise on skeletal muscle have demonstrated synergic effects of insulin and muscular contractions on glucose uptake in subjects with either normal or high insulin sensitivity (26). It has also been demonstrated, using positron emission tomography (PET) techniques, that the increment induced by exercise is decreased in insulin-resistant patients with type 1 diabetes compared with nondiabetic subjects (27).


**RESEARCH DESIGN AND METHODS**

**Subjects.** A total of 45 patients with type 2 diabetes, as defined by the new World Health Organization criteria (31), and no diabetes complications were assigned to the protocol. The subjects were recruited by advertisement and among clients of the occupational health service in Turku. Patients were excluded if they had a fasting plasma glucose value < 6.1 mmol/l or > 11.0 mmol/l after the run-in period. Furthermore, patients with cardiovascular disease, blood pressure > 160/100 mmHg, previous or present abnormal hepatic or renal function, antidiabetic medication, anemia, or oral corticosteroid treatment were excluded. Written informed consent was obtained after the purpose and potential risks of the study were explained to the subjects. Two patients in the metformin group withdrew from the study during the treatment period; one of these patients was withdrawn due to symptoms of ischemic heart disease. Furthermore, follow-up data were not received from one patient in the metformin group and one patient in the rosiglitazone group due to technical problems during the second PET day. Characteristics of the study subjects are shown in Table 1. The study protocol was approved by the local ethical committee.

**Study design.** The first part of the study consisted of a 4-week run-in period with written diet instructions. In the second part, patients were randomized for treatment with rosiglitazone (2 mg b.i.d. for 2 weeks, thereafter 4 mg b.i.d.), metformin (500 mg b.i.d. for 2 weeks, thereafter 1 g b.i.d.), or placebo for a 26-week double-blinded trial (Fig. 1). PET studies were performed before the treatment and at week 26, using the same protocol. The rates of whole-body and skeletal muscle glucose uptake, blood flow, and oxygen consumption were determined by combining the euglycemic-hyperinsulinemic clamp technique with [18F]FDG, [15O]H2O, [15O]O2, and PET. The effect of exercise on glucose uptake was quantified through simultaneous glucose measurements from both legs combined with a one-legged exercise using 10% of maximal force.

**PET study protocol.** The PET study was performed after an overnight fast. Alcohol was prohibited for 48 h before the study, and the subjects were instructed to avoid strenuous physical activity for 1 day before the study. Two catheters were inserted, one in an antecubital vein for infusion of glucose and insulin and for injection of [15O]H2O and [18F]FDG and one in the opposite radial artery for blood sampling. The subjects were lying in a supine position during the study, resting between 0 and 45 min, and performing intermittent isometric exercise with one leg between 45 and 110 min, as described in detail below. At 0 min, an intravenous infusion of insulin (1 mU·kg⁻¹·min⁻¹) was started. The study of skeletal muscle for each subject consisted of a 140-min normoglycemic-hyperinsulinemic period. During hyperinsulinemia, normoglycemia was maintained, infusing a variable rate of 20% glucose. Muscle blood flow and muscle oxygen consumption were measured at 60 and 75 min, respectively, in both femoral regions using [15O]H2O infusion and [15O]O2 inhalation techniques. Thereafter, at 90 min, a bolus of [18F]FDG was injected for quantification of muscle glucose uptake (Fig. 2).

**Production of PET tracers.** The [15O]isoole (half-life t½ = 123 s) was produced with Cyclone 3 (IBA sa, Louvain-la-Neuve, Belgium) by the 14N(d,n)15O reaction on natural nitrogen gas (32). [15O]H2O was produced in a water module using diffusion membrane technique (33). [18F]FDG (t½ = 110 min) was synthesized with a computer-controlled apparatus according to a modified method of Hamacher et al. (34).

**Imaging acquisition and processing.** An eight-ring ECAT 931/SPECT tomograph was used for image acquisition (Siemens/CTI, Knoxville, TN). A 5-min transmission scan for the correction of photon attenuation with a removable ring source containing 68Ge was performed before the emission scan. For image processing, we used a recently developed Bayesian iterative reconstruction algorithm, using median root prior with iterations and applying a Bayesian coefficient of 0.3 (30,35).

**Measurement of muscle blood flow and oxygen consumption.** Muscle blood flow was measured as previously described (28,29). [15O]H2O was injected intravenously, and a dynamic scan was performed for 6 min, using 6 × 5, 6 × 15, and 8 × 30-s frames. The autoradiographic method and a 250-s integration time were applied to calculate blood flow pixel by pixel. For the measurement of muscle oxygen consumption, we used a [15O]O2 bolus inhalation technique validated against Fick’s principle. Oxygen consumption was quantitated with nonlinear fitting (26).

**Measurement of muscle glucose uptake.** [18F]FDG was injected intravenously and a dynamic scan was performed for 20 min, using 2 × 30, 4 × 60, and 3 × 300-s frames. An arterial blood sample was drawn once during each time frame for measurement of plasma radioactivity. Plasma radioactivity was measured with an automatic gamma counter (Wizard 1400; Wallac, Turku, Finland). The three-compartment model of [18F]FDG kinetics was used (36). Plasma and tissue time-activity curves were analyzed graphically (37) to quantify the fractional rate of tracer uptake (Kt) (38). The rate of glucose uptake is obtained by multiplying Kt by the plasma glucose concentration divided by a lumped constant. The lumped constant accounts for differences in the transport and phosphorylation of [18F]FDG and glucose. A lumped constant value of 1.2 for skeletal muscle was used as previously validated for [18F]FDG (30). For the measurement of the effect of exercise on glucose uptake, both legs were scanned simultaneously during insulin stimulation and

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**TABLE 1**

Subject characteristics at baseline

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo</th>
<th>Metformin</th>
<th>Rosiglitazone</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>14</td>
<td>13</td>
<td>14</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>10/4</td>
<td>8/5</td>
<td>10/4</td>
</tr>
<tr>
<td>Smokers</td>
<td>4</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Age (years)</td>
<td>57.7 ± 1.9</td>
<td>57.8 ± 2.2</td>
<td>58.6 ± 2.0</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>30.3 ± 1.2</td>
<td>32.9 ± 1.1</td>
<td>39.3 ± 1.0</td>
</tr>
<tr>
<td>Body fat (%)</td>
<td>30.7 ± 2.4</td>
<td>31.8 ± 2.7</td>
<td>31.2 ± 2.3</td>
</tr>
<tr>
<td>VO2max (ml·kg⁻¹·min⁻¹)</td>
<td>25.3 ± 1.6</td>
<td>28.4 ± 1.9</td>
<td>28.2 ± 2.2</td>
</tr>
<tr>
<td>Maximal isometric force (N)</td>
<td>464 ± 41</td>
<td>448 ± 36</td>
<td>478 ± 38</td>
</tr>
</tbody>
</table>

Results are expressed as means ± SE.
the increment induced by exercise was calculated by subtracting the rate of glucose uptake in the resting leg (the effect of insulin) from the rate of glucose uptake in the exercising leg (the effect of insulin and exercise).

**Regions of interest.** Muscle blood flow and metabolism was measured by drawing regions of interest in the anteromedial muscular compartments of the quadriceps femoris muscle in four slices in both legs, as previously described (26).

**Measurement of whole-body glucose uptake.** For determination of the rate of whole-body glucose uptake, the euglycemic insulin clamp technique was used (39). Serum insulin was increased for 120 min using a primed-continuous (1 mU·kg⁻¹·min⁻¹) infusion of insulin (Actrapid; Novo Nordisk A/S, Bagsvaerd, Denmark). Normoglycemia was based on plasma glucose measurements performed every 5 min from arterial blood, and whole-body glucose uptake was calculated from the glucose infusion rate during the period of PET scanning. Hepatic glucose output was assumed to be suppressed (40).

**Design of isometric knee extension during PET study.** The subjects performed one-legged isometric intermittent exercise during the scanning, as previously described (26). The subjects were lying in the PET scanner with the quadriceps femoris muscle in four slices in both legs, as previously described (26).

**Measurement of maximal oxygen uptake and body composition.** $V_{\text{O2max}}$ was determined using cycle ergometer. The criteria used to establish the $V_{\text{O2max}}$ were a plateau in $V_{\text{O2}}$ with increasing exercise intensity and an RQ $>1.10$. Body fat content was estimated with the impedance method (Body Impedance Analyser; Akern, RJL Systems, Florence, Italy).

**Biochemical analyses.** Arterial and plasma glucose was determined in duplicate by the glucose oxidase method (Analog GM9 Analyzer; Analog Instruments, London). Glycosylated hemoglobin was measured by fast protein liquid chromatography (MonoS; Pharmacia, Uppsala, Sweden). Serum C-peptide concentrations were measured basally and serum free insulin basally and at 60-min intervals during insulin infusion using a double-antibody fluorimunnoassay (Autodetlla; Wallac, Turku, Finland). Plasma lactate was measured using standard enzymatic methods (Boehringer Mannheim, Mannheim, Germany) with a fully automated analyzer (Hitachi 704; Hitachi, Tokyo). Serum free fatty acids (FFAs) were determined by an enzymatic method (Boehringer Mannheim, Mannheim, Germany). Glycosylated hemoglobin was measured by fast protein liquid chromatography (MonoS; Pharmacia, Uppsala, Sweden). Serum C-peptide concentrations were measured basally and serum free insulin basally and at 60-min intervals during insulin infusion using a double-antibody fluorimunnoassay (Autodetlla; Wallac, Turku, Finland). Plasma lactate was measured using standard enzymatic methods (Boehringer Mannheim, Mannheim, Germany) with a fully automated analyzer (Hitachi 704; Hitachi, Tokyo). Serum free fatty acids (FFAs) were determined by an enzymatic method (Boehringer Mannheim, Mannheim, Germany).

**Statistical methods.** The results are expressed as means ± SE. Statistical analyses were performed with SAS software, version 8.2. The effect of treatment was assessed with repeated-measures ANOVA. For pairwise comparisons, Tukey’s adjustment method was used. For correlation analysis, Pearson correlation coefficients were calculated.

**RESULTS**

**Dosage and symptoms.** The patients included after 26 weeks of treatment were highly motivated, and compliance, as determined by regular capsule counts, exceeded 95%. Initially, most patients assigned to receive metformin and some assigned to receive rosiglitazone had some slight abdominal discomfort, but none of the subjects withdrew from the study due to side effects of the medication.

**Fasting plasma glucose, insulin, and glycosylated hemoglobin values.** By week 26, the mean glycosylated hemoglobin values were decreased in the metformin ($P < 0.0001$) and rosiglitazone ($P < 0.05$) groups, while the value was unchanged in the placebo group (Fig. 3). The fasting plasma glucose concentration decreased ($P < 0.001$) in the metformin group. The decrease in the rosiglitazone group was not statistically significant (Table 2). There was no significant difference in the change of glycemic control between the metformin and rosiglitazone groups.

**Metabolic characteristics during the PET studies.** During insulin clamps, serum insulin concentrations were similar between the groups before treatment initiation, but significantly decreased after treatment in the rosiglitazone and metformin groups (Table 2). The plasma glucose concentrations during hyperinsulinemia were similar before and after treatments. Fasting serum FFA concentrations were similar in all three groups both at baseline and after treatment (Table 2). However, during hyperinsulinemia, the FFA levels were 50% suppressed in the rosiglitazone group ($P < 0.01$) after treatment, as compared with baseline values. Furthermore, the serum FFA levels correlated inversely with glucose uptake in both resting and exercising muscles. This relationship was present in the pooled data ($n = 41$) both before (in resting: $r = -0.58$, $P < 0.0001$ and in exercising leg: $r = -0.57$, $P < 0.0001$) and after treatment (in resting: $r = -0.45$, $P < 0.01$ and in exercising leg: $r = -0.53$, $P < 0.001$). Plasma lactate
concentrations were expressed as means ± SE. *P < 0.05 vs. baseline.

**Femoral muscle perfusion and oxygen consumption.** Blood flow rates in resting quadriceps femoris muscles were similar at week 26 compared with baseline in all three groups. The effect of exercise on femoral muscle perfusion significantly increased in the metformin group, and a tendency toward an increase was observed in the rosiglitazone group (Fig. 4). No significant effect was found in the placebo group. The muscle blood flow did not correlate with glucose uptake, neither at baseline nor after 26 weeks, in any of the groups.

Before the treatment period, the oxygen consumption rate of the resting muscle was 1.6 ± 0.2, 2.1 ± 0.4, and 1.8 ± 0.2 ml · kg⁻¹ muscle · min⁻¹ in the rosiglitazone, metformin, and placebo groups, respectively (NS among the groups), and 16 ± 1, 12 ± 2, and 15 ± 2 ml · kg⁻¹ muscle · min⁻¹, respectively, in the exercising muscle (NS among the groups). No changes in oxygen consumption were observed between groups or treatments at week 26, when the PET study was repeated with identical design and isometric exercise forces.

**Femoral muscle glucose uptake and glucose extraction.** Femoral muscle insulin-stimulated glucose uptake was similar between the groups at baseline in both resting and exercising muscles (Fig. 5). At week 26, the skeletal muscle glucose uptake had increased by 38% (from 26.6 ± 3.4 to 38.8 ± 3.9 μmol · kg⁻¹ muscle · min⁻¹, P < 0.01) in the rosiglitazone group but was unchanged in the metformin and the placebo groups. The skeletal muscle glucose uptake correlated with the whole-body glucose uptake in all three groups at both baseline and week 26. The exercise-induced increment in glucose uptake was enhanced by 99% in the rosiglitazone group (from 55.2 ± 10.7 to 109.7 ± 14.8 μmol · kg⁻¹ muscle · min⁻¹, P < 0.0001) but not in the metformin or placebo groups (Fig. 5). The muscle glucose extraction was increased by 56% during exercise in the rosiglitazone group (P < 0.05), calculated by dividing glucose uptake with perfusion. No change was observed in the metformin or placebo groups.

**Whole-body glucose uptake.** The whole-body glucose uptake was similar in the rosiglitazone, metformin, and placebo groups at baseline (Table 2). There was a significant (44%) increase in insulin sensitivity compared with baseline after 26 weeks (P < 0.01) in the rosiglitazone group (Table 2). In contrast, no significant change was seen in the metformin or placebo groups.

**Body weight and blood pressure.** The average loss of body weight was 2 kg in the metformin group (P < 0.05), while no significant changes were observed in the rosiglitazone or placebo groups (Table 3). The mean blood

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**TABLE 2**
Subject metabolic characteristics and whole-body insulin sensitivity at fast before and after 26 weeks’ treatment

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo</th>
<th>Metformin</th>
<th>Rosiglitazone</th>
<th>Placebo</th>
<th>Metformin</th>
<th>Rosiglitazone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HbA₁c (% units)</td>
<td>6.3 ± 0.1</td>
<td>6.9 ± 0.2</td>
<td>6.8 ± 0.2</td>
<td>6.1 ± 0.1</td>
<td>6.2 ± 0.2*</td>
<td>6.5 ± 0.2*</td>
</tr>
<tr>
<td>Plasma glucose (nmol/l)</td>
<td>7.2 ± 0.3</td>
<td>8.0 ± 0.5</td>
<td>7.2 ± 0.3</td>
<td>7.2 ± 0.3</td>
<td>6.8 ± 0.3*</td>
<td>6.8 ± 0.3</td>
</tr>
<tr>
<td>Serum insulin (mU/l)</td>
<td>10.1 ± 1.3</td>
<td>11.7 ± 2.1</td>
<td>8.6 ± 1.5</td>
<td>9.6 ± 0.9</td>
<td>8.8 ± 1.1</td>
<td>6.6 ± 0.4</td>
</tr>
<tr>
<td>Serum C-peptide (nmol/l)</td>
<td>0.86 ± 0.07</td>
<td>0.89 ± 0.10</td>
<td>0.78 ± 0.07</td>
<td>0.71 ± 0.04</td>
<td>0.65 ± 0.07*</td>
<td>0.58 ± 0.04*</td>
</tr>
<tr>
<td>Serum FFAs (μmol/l)</td>
<td>607 ± 56</td>
<td>511 ± 63</td>
<td>596 ± 46</td>
<td>519 ± 45</td>
<td>510 ± 47</td>
<td>512 ± 61</td>
</tr>
</tbody>
</table>

During hyperinsulinemia

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo</th>
<th>Metformin</th>
<th>Rosiglitazone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma glucose (nmol/l)</td>
<td>5.1 ± 0.1</td>
<td>5.3 ± 0.1</td>
<td>5.2 ± 0.1</td>
</tr>
<tr>
<td>Serum insulin (mU/l)</td>
<td>83 ± 3</td>
<td>88 ± 4</td>
<td>86 ± 5</td>
</tr>
<tr>
<td>Whole-body glucose uptake (μmol · kg⁻¹ · min⁻¹)</td>
<td>16.4 ± 2.9</td>
<td>15.0 ± 2.0</td>
<td>16.2 ± 2.3</td>
</tr>
<tr>
<td>Serum FFAs (μmol/l)</td>
<td>143 ± 23</td>
<td>162 ± 25</td>
<td>145 ± 14</td>
</tr>
</tbody>
</table>

Results are expressed as means ± SE. *P < 0.05 vs. baseline.
exercise-induced increments in patients with type 2 diabetes (8,9,42). The result of the DIABETES, VOL. 51, DECEMBER 2002 3483

Results are expressed as means ± SE. *P < 0.05 vs. baseline.

**FIG. 5. Rates of skeletal muscle glucose uptake during hyperinsulinemia at baseline (■) and after 26 weeks of treatment with rosiglitazone, metformin, or placebo (■). , exercise-induced increments in glucose uptake. ***P < 0.001, **P < 0.01 compared with baseline.**

pressure was similar in all groups at both baseline and 26 weeks (Table 3).

DISCUSSION

In the present study, rosiglitazone treatment for 26 weeks enhanced skeletal muscle insulin sensitivity by 38% in patients with newly diagnosed type 2 diabetes. Surprisingly, an even more pronounced increment in insulin-stimulated glucose uptake was observed during moderate exercise. Rosiglitazone has previously been shown to increase muscle glucose uptake in diabetic animals under euglycemic clamp conditions (41). However, until now, no human data regarding the effects of TZDs on skeletal muscle insulin sensitivity in vivo have been reported.

In the present data, whole-body insulin sensitivity was improved by 20%. Troglitazone has been shown to enhance skeletal muscle insulin sensitivity by 38% in poorly controlled patients with type 2 diabetes. Metformin has been demonstrated to act primarily by suppressing hepatic glucose output in several studies (19–21). Therefore, the improvement in hyperglycemia could explain the effect on insulin sensitivity demonstrated in poorly controlled patients.

In this placebo-controlled study, the type 2 diabetic patients included were either newly diagnosed or diet treated. All three groups were matched for BMI, age, smoking habits, and sex. Skeletal muscle oxygen consumption was quantified using a bolus inhalation of [18O]O₂ (26). Measurement of oxygen consumption was considered important, because fuel utilization can only be reliably compared between different groups if the rates of oxygen consumption are similar. V′O₂max, maximal isometric contraction forces, and work load were similar in all three groups. Therefore, the differences in skeletal muscle insulin responsiveness cannot be explained by different work levels or by the differences in the phenotype among the groups.

The use of PET combined with radioactive tracers for quantification of skeletal muscle metabolism offers some advantages compared with other methods. All parameters that are being studied can be measured directly in skeletal muscle, thus avoiding any confounding effects caused by intra-arterial catheters. The [18O]FDG method used for the measurement of femoral glucose uptake (38), applying a lumped constant of 1.2, has been validated repeatedly for human skeletal muscle (30,47,48). Hepatic glucose output was assumed to be suppressed during hyperinsulinemia (40). Since hepatic glucose output was not measured in this study, the rates of whole-body glucose uptake could have been underestimated.

The present data show that the improvement in insulin-stimulated glucose uptake in subjects treated with rosiglitazone was more enhanced during physical exercise. It has previously been demonstrated that insulin and exercise act synergistically to enhance glucose uptake (49). Hevener

**TABLE 3**

Effect of treatment on body weight and blood pressure in patients with type 2 diabetes

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Baseline</th>
<th>Rosiglitazone</th>
<th>Placebo</th>
<th>Metformin</th>
<th>Rosiglitazone</th>
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</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>88.3 ± 2.5</td>
<td>83.7 ± 2.1</td>
<td>88.4 ± 2.5</td>
<td>86.8 ± 2.9*</td>
<td>84.3 ± 2.4</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>147.2 ± 3.2</td>
<td>152.0 ± 5.0</td>
<td>144.4 ± 3.8</td>
<td>141.8 ± 4.0</td>
<td>149.0 ± 4.5</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>85.1 ± 2.3</td>
<td>90.5 ± 2.1</td>
<td>85.4 ± 2.7</td>
<td>85.5 ± 2.6</td>
<td>84.2 ± 2.4</td>
</tr>
</tbody>
</table>

Results are expressed as means ± SE. *P < 0.05 vs. baseline.
et al. (50) have demonstrated that TZD therapy combined with chronic exercise normalizes insulin action in obese Zucker fatty rats. This is the first time the effects of rosiglitazone on insulin- and exercise-stimulated skeletal muscle glucose uptake were measured in human clinical studies. Since muscle glucose uptake was not measured without insulin stimulation, we can only speculate about the mode of action. The drug-induced increment in glucose uptake during acute exercise (−110 μmol·kg⁻¹·min⁻¹) was higher than the sum of the exercise-induced increment (−55 μmol·kg⁻¹·min⁻¹) and the treatment-induced increment in resting leg (−10 μmol·kg⁻¹·min⁻¹, P < 0.01, paired t test). Therefore, it seems that the synergy between insulin and exercise on muscle glucose uptake is improved by rosiglitazone. However, the intracellular mechanisms underlying the effects of rosiglitazone on insulin and exercise action in humans requires further investigation.

It has previously been demonstrated that when lipolysis is suppressed in humans, glucose uptake increases in skeletal muscle (3). The TZD-induced alterations in lipid metabolism have a significant impact on insulin sensitivity in animal models (51). Exogenous infusion of Intralipid has been shown to reverse drug-induced improvement in glucose uptake (51). Racette et al. (52) have demonstrated that TZDs increase insulin-mediated suppression of fatty acid release into plasma in patients with type 2 diabetes. In the present data, rosiglitazone lowered serum FFA concentrations during hyperinsulinemia. The suppression of FFA mobilization could be the underlying mechanism explaining why rosiglitazone increases skeletal muscle glucose uptake in humans, although in this study, we were only able to demonstrate an association between femoral muscle glucose uptake and FFA concentrations during hyperinsulinemia, and only in the pooled data.

In the present study, the effect of exercise on femoral blood flow increased significantly with metformin treatment. A slight increase was also observed in the rosiglitazone group. This was a novel finding of this study. Chronic hyperglycemia is known to impair endothelium-dependent vasodilatation in patients with type 1 diabetes (53). Leg blood flow response to insulin is blunted in obesity and type 2 diabetes (54,55). In a study by Vehkavaara et al. (56), insulin therapy for 6 months improved the glycosylated hemoglobin concentrations and increased the forearm blood flow in type 2 diabetes. In this study, glycemic control similarly improved with active treatment in both groups. The improvement in glycemic control could therefore possibly explain the perfusion effects in skeletal muscle.

In conclusion, we found that rosiglitazone enhances skeletal muscle glucose uptake as well as the effect of exercise during hyperinsulinemia in patients with newly diagnosed or diet-treated type 2 diabetes. No such effects were seen in the metformin-treated group despite a similar improvement in blood glucose control.

ACKNOWLEDGMENTS
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