

Rosiglitazone Improves Myocardial Glucose Uptake in Patients With Type 2 Diabetes and Coronary Artery Disease

A 16-Week Randomized, Double-Blind, Placebo-Controlled Study

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Rosiglitazone therapy improves insulin sensitivity and glucose uptake in patients with uncomplicated type 2 diabetes. In coronary artery disease (CAD), glucose is an important source of energy and preserved myocardial glucose uptake is essential for the viability of jeopardized myocardium. The aim was to test whether rosiglitazone changes myocardial metabolism in type 2 diabetic patients with CAD. We studied 54 patients (38 men and 16 women) with type 2 diabetes (HbA_{1c} 7.2 ± 0.9%) and CAD. Myocardial glucose uptake was measured with [¹⁸F]fluoro-2-deoxy-D-glucose positron emission tomography in ischemic (evaluated by single-photon emission tomography and coronary angiography) and nonischemic regions during euglycemic-hyperinsulinemic clamp before and after a 16-week intervention period with rosiglitazone (*n* = 27) or placebo (*n* = 27). Rosiglitazone significantly improved glycemic control (*P* < 0.0001) and whole-body insulin sensitivity (*P* < 0.0001). Rosiglitazone increased myocardial glucose uptake from 20.6 ± 11.8 to 25.5 ± 12.4 μmol · 100 g⁻¹ · min⁻¹ (*P* = 0.038 vs. baseline, *P* = 0.023 vs. placebo) in ischemic regions and from 21.7 ± 12.1 to 28.0 ± 12.7 μmol · 100 g⁻¹ · min⁻¹ (*P* = 0.014 vs. baseline, *P* = 0.003 vs. placebo) in nonischemic regions. The increase in myocardial glucose uptake was partly explained by the suppression of free fatty acid levels during clamp. Rosiglitazone therapy significantly increased insulin sensi-

tivity and improved myocardial glucose uptake in type 2 diabetic patients with CAD. These results suggest that rosiglitazone therapy may facilitate myocardial glucose storage and utilization in these patients. *Diabetes* 54: 2787–2794, 2005

The risk of myocardial infarction is increased in diabetes (1), and the outcome is poor with these patients. It has been suggested that one reason might be abnormal myocardial substrate metabolism (2). Myocardium is able to use free fatty acids (FFAs), glucose, lactate, pyruvate, and ketone bodies as energy sources. In healthy subjects, the primary sources of energy are FFAs at fast and glucose in the fed state (3). In patients with ischemic heart disease, glucose becomes an important energy source, and glucose uptake can be stimulated by insulin in dysfunctional myocardium (4). Currently, the degree of myocardial insulin sensitivity in patients with whole-body insulin resistance remains under investigation. It has been suggested that myocardial glucose uptake in type 2 diabetic and nondiabetic patients with and without coronary artery disease (CAD) is similar to that of healthy subjects (5,6). In some studies, myocardial glucose uptake has been noted to differ between groups (7–10).

Rosiglitazone is a member of the peroxisome proliferator-activated receptor-γ (PPARγ)-agonists, which are widely used as antidiabetic agents. In addition to the effects on glucose metabolism, rosiglitazone has effects on lipid metabolism, inflammatory responses, and cellular proliferation (11–13). In animal studies, rosiglitazone reduces infarct size and improves ischemia/reperfusion-induced myocardial contractile dysfunction (14). Furthermore, rosiglitazone treatment restores myocardial glucose uptake during ischemia and thus protects myocardium from ischemic injury (15). In humans, rosiglitazone reduces whole-body insulin resistance by its insulin-sensitizing effect on muscle, adipose tissue, and liver (16–18). Previously, we

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CAD, coronary artery disease; FDG, fluoro-2-deoxy-D-glucose; FFA, free fatty acid; PET, positron emission tomography; PPARγ, peroxisome proliferator-activated receptor-γ; SPECT, single-photon emission tomography.

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TABLE 1
The characteristics of the study subjects ($n = 54$) at randomization

Characteristics	Placebo	Rosiglitazone
Sex (M/F)	19/8	19/8
Age (year)	63.2 ± 7.4	64.1 ± 7.8
Body weight (kg)	89.1 ± 14.3	85.3 ± 17.4
BMI (kg/m ²)	29.6 ± 3.4	29.6 ± 4.7
Blood pressure (mmHg)	147/78 ± 25/8	141/76 ± 20/7
Fasting plasma glucose (mmol/l)	7.7 ± 1.7	7.3 ± 2.0
A1C (%)	7.1 ± 0.9	7.3 ± 0.9
Total cholesterol (mmol/l)	4.7 ± 0.8	4.2 ± 0.7*
LDL cholesterol (mmol/l)	2.7 ± 0.7	2.3 ± 0.8
HDL cholesterol (mmol/l)	1.2 ± 0.3	1.1 ± 0.2
Triglycerides (mmol/l)	1.9 ± 1.0	1.7 ± 0.8
Medications		
β-Blockers	78 (21/27)	70 (19/27)
Statins	56 (15/27)	44 (12/27)
ACE inhibitors	41 (11/27)	44 (12/27)
Ca blockers	15 (4/27)	26 (7/27)
ASA	78 (21/27)	85 (23/27)
Long-acting nitrates	22 (6/27)	26 (7/27)

Data are means ±SD or % (n). * $P = 0.02$. ASA, acetylsalicylic acid.

have shown that rosiglitazone improves myocardial glucose uptake in patients with uncomplicated type 2 diabetes (19). To our knowledge, the effect of rosiglitazone on myocardial metabolism in patients with type 2 diabetes and CAD has not been previously evaluated.

The purpose of this study was to determine whether rosiglitazone therapy improves myocardial glucose uptake in the regions of abnormal myocardial perfusion in patients with type 2 diabetes and CAD. Exercise-rest single-photon emission tomography (SPECT) perfusion imaging and coronary angiography were performed to locate the region with exercise-induced ischemia and coronary artery stenosis. Myocardial glucose uptake was measured during euglycemic-hyperinsulinemic clamp with positron emission tomography (PET) and [¹⁸F]fluoro-2-deoxy-D-glucose (FDG) at baseline and after a 16-week rosiglitazone or placebo intervention period.

RESEARCH DESIGN AND METHODS

Patients were recruited with an advertisement in a local newspaper from outpatient clinics in the Turku area and from the clinic of cardiology in the Turku University Hospital. Inclusion criteria were past or current angina pectoris symptoms under stress, type 2 diabetes treated with diet or with metformin and/or sulfonylurea, and good or moderate glycemic control (HbA_{1c} [A1C] <8.5%). Criteria for exclusion were unstable angina pectoris, symptomatic tachy- or bradyarrhythmias, history of percutaneous transluminal coronary angioplasty during the preceding 6 months, asthma, chronic use of insulin, or the clinical signs of the heart failure. All patients gave written informed consent before participation. The study was conducted according to the guidelines of the Declaration of Helsinki, and the study protocol was approved by the Ethics Committee of the Hospital District of Southwest Finland.

A total of 62 patients were enrolled in the intervention study, and 58 completed the study. One patient was withdrawn because of hepatopathy, one because of a kidney tumor diagnosed during the intervention period, one because of suspected sick sinus syndrome, and one patient withdrew consent. Of the 58 patients who completed the study, 54 were included in the analysis (Table 1). Three patients were excluded because of discrepancies in the

medication breaks before the PET studies, and one patient was excluded because of unstable angina pectoris during the PET study.

All patients were on stable medical therapy before entering the study (Table 1). In most patients, the medications remained the same during the intervention. During intervention, statin therapy was started in two patients (one in each group) and stopped in one patient (placebo). Metformin dosage was altered in two patients during the intervention. These patients were included in the final analysis after evaluating that their exclusion did not affect the net results. A total of 36 patients had angina pectoris during stress, and 18 had silent ischemia. Nine patients had a history of previous myocardial infarction, five with a Q-wave infarction. In addition to macrovascular disease, four patients had microalbuminuria. The mean duration of diabetes was 6.7 ± 6.4 years in the rosiglitazone group and 6.8 ± 5.9 years in the placebo group ($P = NS$).

Study design. All subjects underwent a screening visit and SPECT exercise-rest perfusion imaging. Patients who met the inclusion and exclusion criteria and showed a completely or partially reversible perfusion defect in SPECT study entered a 4-week run-in period with placebo, after which the patients were randomized for treatment either with rosiglitazone (4–8 mg per day) or placebo for a 16-week double-blinded trial. PET studies were performed at baseline and at week 16 ± 7 days. Rest echocardiography was performed after each PET study. Coronary angiography was performed, and the SPECT study was repeated after the second PET study.

Exercise SPECT perfusion imaging. ^{99m}Myoview-tetrofosmin (Amersham, Buckinghamshire, U.K.) was used in SPECT. Patients refrained from β-blockers, Ca blockers, and long-acting nitrates for 48 h before the SPECT study. Rest and stress studies were performed with an injection of 250 MBq (1.5 mSv) and 900 MBq (5.36 mSv), respectively. Acquisition was performed with VertexPlus EPIC gamma camera (ADAC Laboratories, Milpitas, CA) 15–30 min after the injection. Patients were placed in a supine position with their arms lifted above their head, and the gamma camera was placed at an angle of 90° near the thoracic region with an acquisition time of 40 s for at rest imaging and 20 s for exercise imaging. The exercise test was performed with a bicycle ergometer with steps of 15 W. ^{99m}Myoview was injected at the level of maximum stress, and patient continued pedaling for 2 min. The rest and the stress images were scored, and the summed difference score (ischemic score) was calculated based on a 20-segment model, as earlier described (20). The ischemic region was defined as a completely or partially reversible perfusion defect (change in segment grade by ≥1). Normal regions had normal perfusion both at rest and during stress.

Coronary angiography. Coronary angiography was performed via femoral artery with Judkins technique after an intravenous injection of 3,750 IU heparin and 0.5 mg sublingual nitroglycerin. Angiography was performed with 5-Fr catheters (Cordis, Johnson & Johnson, Miami Lakes, FL). Coronary artery diameters were analyzed with QCA software (Quantcor stenosis evaluation software; Siemens, Munich).

Echocardiographic examination. Rest echocardiographic examination was performed during insulin stimulation after completion of PET imaging, using the same ultrasound scanner (Acuson 128XP/10; Acuson, Mountain View, CA). Standard echocardiographic views of the left ventricle were obtained, and resting cardiac dimensions were measured. Left ventricular mass and wall stress were calculated as previously described (21,22). Myocardial workload was calculated as follows: systolic blood pressure × stroke volume × heart rate. Myocardial workload per gram of tissue was calculated as myocardial workload divided by left ventricular mass. Myocardial workload-corrected myocardial glucose uptake was calculated as myocardial glucose uptake divided by myocardial workload.

PET study. Patients refrained from caffeine-containing drinks, smoking, and all medications with the exception of short-acting nitrates for 12 h before the PET scan. One catheter was inserted in each antecubital vein, one for [¹⁸F]FDG injection, insulin, and glucose infusions and the other for blood sampling. Insulin (Actrapid, Novo Nordisk, Copenhagen) was infused with a primed continuous infusion of 1 mU · kg⁻¹ · min⁻¹. Normoglycemia was adjusted with 20% glucose infusion. The arm for blood sampling was warmed with a heating pillow to arterialize the venous blood. Plasma glucose concentration was determined every 5–10 min from arterialized venous blood, and insulin and FFA concentrations were determined every 30 and 60 min, respectively. Myocardial glucose uptake was measured for 40 min starting from the time point of 90 min of the euglycemic-hyperinsulinemic clamp (Fig. 1). The electrocardiogram and heart rate were monitored throughout the study. Blood pressure was measured every 15 min throughout the study.

Image acquisition, processing, and corrections. [¹⁸F]FDG, was produced as previously described (23). Patients were positioned supine in an eight-ring ECAT 931/08-12 tomograph (Siemens/CTI, Knoxville, TN). Photon attenuation was corrected by a transmission scan of 5 min with a removable ring source of ⁶⁸Ge. [¹⁸F]FDG (220–260 MBq) was injected intravenously over 1 min, and

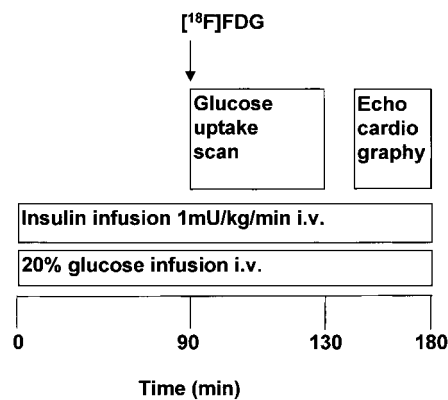


FIG. 1. The PET study protocol.

dynamic imaging was performed with frames of 8×15 s, 2×30 s, 2×120 s, 1×180 s, and 6×300 s. All data were corrected for dead time, decay, and photon attenuation and reconstructed in a 128×128 matrix.

Alignment of myocardial segments with different methods. SPECT, echocardiography, and angiography results were used to determine ischemic and nonischemic regions in the myocardium. A 20-segment model of left ventricle was used for SPECT analysis, as earlier described (20). PET data were analyzed by MunichHeart software (Nuklearmedizinische Klinik und Poliklinik der Technischen Universität München, Munich). We placed 20 regions of interest on the "bull's eye" display of the left ventricle similarly to the 20-segment model used in SPECT analysis. Angiographic data were assigned to the eight segments, as previously described (4). Wall motion abnormalities were visually determined by echocardiography, and they were localized to the eight-segment model. Angiographic and echocardiographic data were further applied to the 20-segment model used in PET and SPECT analysis.

Classification of the regions. In all subjects, ischemic and nonischemic regions of the myocardium were identified. The segments were classified as normal when they had normal wall motion, had no reversible perfusion defect in SPECT, and were associated with a nonstenotic coronary artery. The criteria for ischemic region were completely or partially reversible perfusion defect in SPECT and a coronary artery stenosis on angiography. We took 2–3 segments from the 20-segment model to represent each ischemic and nonischemic region.

Measurement of regional glucose uptake. The three-compartmental model of $[^{18}\text{F}]\text{FDG}$ was used as previously described (24). Plasma time activity was measured with an automatic gamma counter (Wizard 1480 3⁺; Wallac, Turku, Finland) from manually drawn samples. Myocardial glucose uptake was calculated as previously published (25) with a lumped constant value of 1.0 (26).

TABLE 2
The metabolic data of the study groups

	Baseline		After 16 weeks	
	Placebo	Rosiglitazone	Placebo	Rosiglitazone
At fast				
Plasma glucose mmol/l	7.7 ± 1.7	7.3 ± 2.0	8.1 ± 2.3	$6.0 \pm 1.1^*$
A1C (%)	7.1 ± 0.9	7.3 ± 0.9	7.3 ± 1.0	$6.9 \pm 0.6^*$
Serum insulin (pmol/l)	53 ± 26	49 ± 34	56 ± 36	$34 \pm 17^\dagger$
Serum FFAs (mmol/l)	0.81 ± 0.29	0.73 ± 0.24	0.80 ± 0.25	0.67 ± 0.22
Serum C-peptide (nmol/l)	0.87 ± 0.31	0.82 ± 0.34	0.85 ± 0.38	0.69 ± 0.24
Total cholesterol (mmol/l)	4.7 ± 0.8	4.2 ± 0.7	4.7 ± 0.9	4.7 ± 0.9
LDL (mmol/l)	2.7 ± 0.7	2.3 ± 0.8	2.7 ± 0.7	2.8 ± 0.7
HDL (mmol/l)	1.2 ± 0.3	1.1 ± 0.2	1.2 ± 0.3	1.1 ± 0.2
Triglycerides (mmol/l)	1.9 ± 1.0	1.7 ± 0.8	1.8 ± 1.0	1.7 ± 1.2
During hyperinsulinemia				
Plasma glucose (mmol/l)	5.24 ± 0.53	5.28 ± 0.42	5.36 ± 0.75	5.23 ± 0.36
Serum insulin (pmol/l)	439 ± 88	440 ± 78	441 ± 76	$405 \pm 66^\ddagger$
Serum FFAs (mmol/l)	0.16 ± 0.08	0.14 ± 0.06	0.15 ± 0.06	$0.10 \pm 0.06^\S$
Whole-body glucose uptake (M value) ($\mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$)	11.5 ± 4.2	12.3 ± 6.0	12.0 ± 5.5	$17.8 \pm 6.8^*$

Data are means \pm SD. $^*P < 0.0001$, $^\dagger P = 0.003$, $^\ddagger P = 0.006$, $^\S P = 0.014$ change in rosiglitazone group vs. change in placebo group.

Biochemical analysis. Plasma glucose concentration during the clamp was measured in duplicate by a glucose oxidase method (GM7 or GM9; Analox Instruments, London). Other laboratory samples were sent to a central laboratory (Quest Diagnostics, London). Standard methods and quality control were performed. LDL cholesterol concentration was calculated with Friedewald's formula.

Statistical methods. Statistical analysis was performed with 54 patients who completed the intervention period. The intended analysis was on all of the 58 subjects who completed the study with a primary end point of myocardial glucose uptake in ischemic regions. Four subjects were considered violators because of discrepancies in the medication breaks (β -blockers) before the PET studies ($n = 3$) and acute ischemic period during the PET study ($n = 1$). The results are consistent with the analysis of all subjects, unless otherwise stated. All data are reported as the means \pm SD. ANCOVA, adjusting for sex and baseline, was used to compare myocardial glucose uptake, glycemic control, and metabolic characteristic end points between rosiglitazone and placebo groups. Unpaired t tests were used to compare the other variables between the treatment groups. Student's paired t test was used to compare the values between baseline and week 16 in each group. For correlation analysis, Pearson's correlation coefficients were calculated. Linear regression analysis and ANCOVA, adjusting for the change in FFA levels, were performed to determine the role of FFA levels in myocardial glucose uptake values. A P value of < 0.05 was considered statistically significant; no adjustments were made for multiplicity. All statistical analyses were performed with the SAS statistical analysis system 8.2 (Cary, NC).

RESULTS

Coronary angiography. One-vessel disease was found in 57% (31 of 54) of the patients, two-vessel disease in 32% (17 of 54), and three-vessel disease in 11% (6 of 54). Main stenosis was located in left anterior descending coronary artery in 65% (35 of 54), left circumflex coronary artery in 9% (5 of 54), and right coronary artery in 26% (14 of 54) of the patients. The median of the degree of stenosis was 60% (range 9–100). Collateral circulation was found in seven patients. The severity of the disease according to the degree of stenosis did not differ between the groups.

Glycemic control. At randomization, the groups were well matched for fasting plasma glucose, C-peptide, and for insulin levels (Table 2.). Fasting plasma glucose decreased during the intervention from 7.3 ± 2.0 to 6.0 ± 1.1 mmol/l ($P = 0.0003$ vs. baseline, $P < 0.0001$ vs. placebo) and A1C from 7.3 ± 0.9 to $6.9 \pm 0.6\%$ ($P = 0.001$ vs. baseline, $P < 0.0001$ vs. placebo) in the rosiglitazone group. C-peptide concentration was not changed, but the

TABLE 3
The hemodynamic, echocardiography, and SPECT findings

	Baseline		After 16 weeks	
	Placebo	Rosiglitazone	Placebo	Rosiglitazone
Systolic blood pressure (mmHg)	145 ± 19	143 ± 17	141 ± 21	140 ± 17
Diastolic blood pressure (mmHg)	79 ± 8	77 ± 10	75 ± 8	76 ± 9
Heart rate/min	66 ± 10	65 ± 11	63 ± 9	67 ± 10*
Rate pressure product (mmHg/min)	9,525 ± 1,720	9,216 ± 2,003	8,914 ± 1,633	9,339 ± 2,022
Ejection fraction (%)	66 ± 6	62 ± 7†	66 ± 6	62 ± 8‡
Myocardial workload (mmHg · l ⁻¹ · min ⁻¹)	931.7 ± 195.5	866.0 ± 177.1	882.3 ± 147.0	847.5 ± 145.0
Myocardial workload per gram of tissue (mmHg · l ⁻¹ · g ⁻¹ · min ⁻¹)	3.96 ± 0.89	3.75 ± 1.03	3.74 ± 0.71	3.64 ± 0.88
Wall stress (mmHg)	62.3 ± 11.6	69.4 ± 24.7	59.8 ± 12.0	69.4 ± 23.2
Ischemic score	7.2 ± 4.5	8.0 ± 4.8	7.7 ± 3.2	7.8 ± 4.3

Data are means ± SD. **P* = 0.038 change in the placebo group vs. the rosiglitazone group; †*P* = 0.030 difference between the groups at baseline; ‡*P* = 0.047 difference between the groups after intervention.

fasting insulin concentration decreased in the rosiglitazone group compared with the placebo group (*P* = 0.003).

Metabolic characteristics. Steady-state plasma glucose concentrations during the clamp were similar between the groups (Table 2). Serum FFA concentrations decreased during hyperinsulinemia in the rosiglitazone group (*P* = 0.04 vs. baseline, *P* = 0.014 vs. placebo), and insulin levels during clamp decreased in the rosiglitazone group (*P* = 0.004 vs. baseline, *P* = 0.006 vs. placebo). Whole-body glucose uptake increased by 44% in the rosiglitazone group compared with the placebo group (*P* < 0.0001). During treatment, rosiglitazone slightly increased body weight compared with placebo (from 85.3 ± 17.4 to 87.2 ± 17.7 kg, *P* = 0.03). There was no change in weight in the placebo group.

Hemodynamic, echocardiographic, and SPECT measurements. There were no significant differences in blood pressure, heart rate, or left ventricular work between the groups at baseline (Table 3). Heart rate was slightly lower in the placebo group compared with the rosiglitazone group (*P* = 0.038) after intervention; however, no significant change was found in blood pressure or in left ventricular work in either of the groups. Ejection fraction was slightly lower in the rosiglitazone group at baseline

(62 ± 7 vs. 66 ± 6, *P* = 0.030), but no significant change was observed in either group during intervention. In SPECT, there were no significant differences in ischemic score between the groups at baseline or after intervention.

Myocardial glucose uptake. Rosiglitazone improved myocardial glucose uptake by 24% in the ischemic region from 20.6 ± 11.8 to 25.5 ± 12.4 μmol · 100 g⁻¹ · min⁻¹ (comparison to placebo: 6.12, 95% CI 0.89–11.34, *P* = 0.023; *P* = 0.038 vs. baseline) and by 29% in the nonischemic region from 21.7 ± 12.1 to 28.0 ± 12.7 μmol · 100 g⁻¹ · min⁻¹ (comparison to placebo: 8.40, 2.99–13.81, *P* = 0.003; *P* = 0.014 vs. baseline). The placebo group showed no apparent change (Fig. 2). An analysis of myocardial glucose uptake in ischemic regions that included all subjects (including protocol violators) showed a smaller trend for an effect relative to placebo (4.77 μmol · 100 g⁻¹ · min⁻¹, 95% CI -0.37 to 9.90, *P* = 0.068). Improvement in glucose uptake was also observed when myocardial glucose uptake was corrected for myocardial workload; rosiglitazone improved myocardial glucose uptake both in ischemic (*P* = 0.015) and nonischemic regions (*P* = 0.002) compared with placebo. There were no changes in myocardial workload–corrected myocardial glucose uptake in the placebo group.

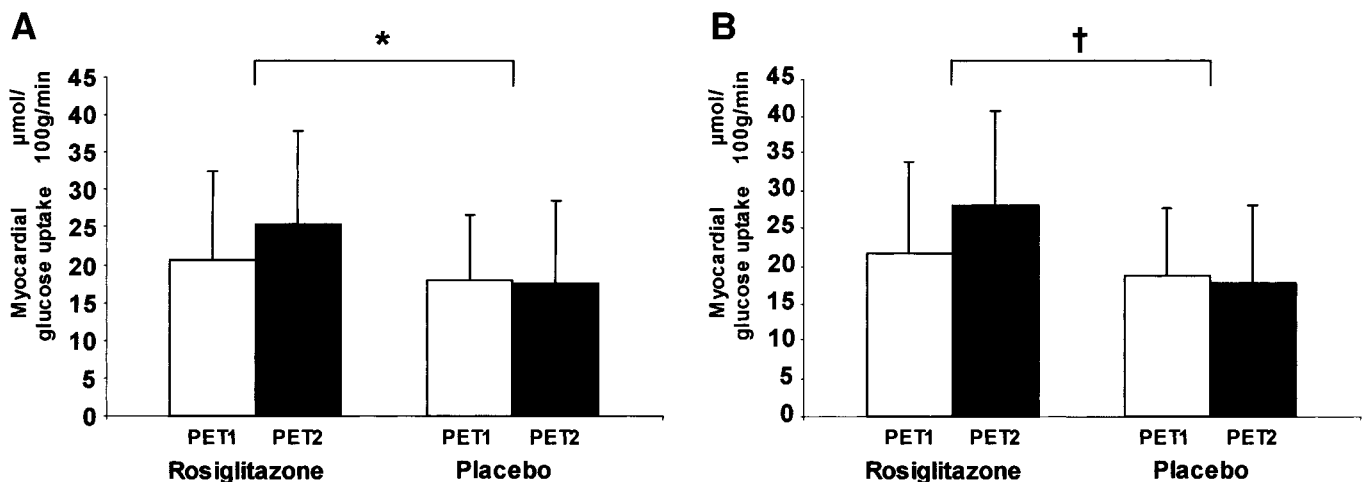


FIG. 2. Rosiglitazone improves myocardial glucose uptake by 24% (6.12 μmol · 100 g⁻¹ · min⁻¹, 95% CI 0.89–11.34) for ischemic (A) and by 29% (8.40 μmol · 100 g⁻¹ · min⁻¹, 2.99–13.81) for nonischemic (B) regions. PET1 = baseline, PET2 = week 16. **P* = 0.023 vs. placebo; †*P* = 0.003 vs. placebo.

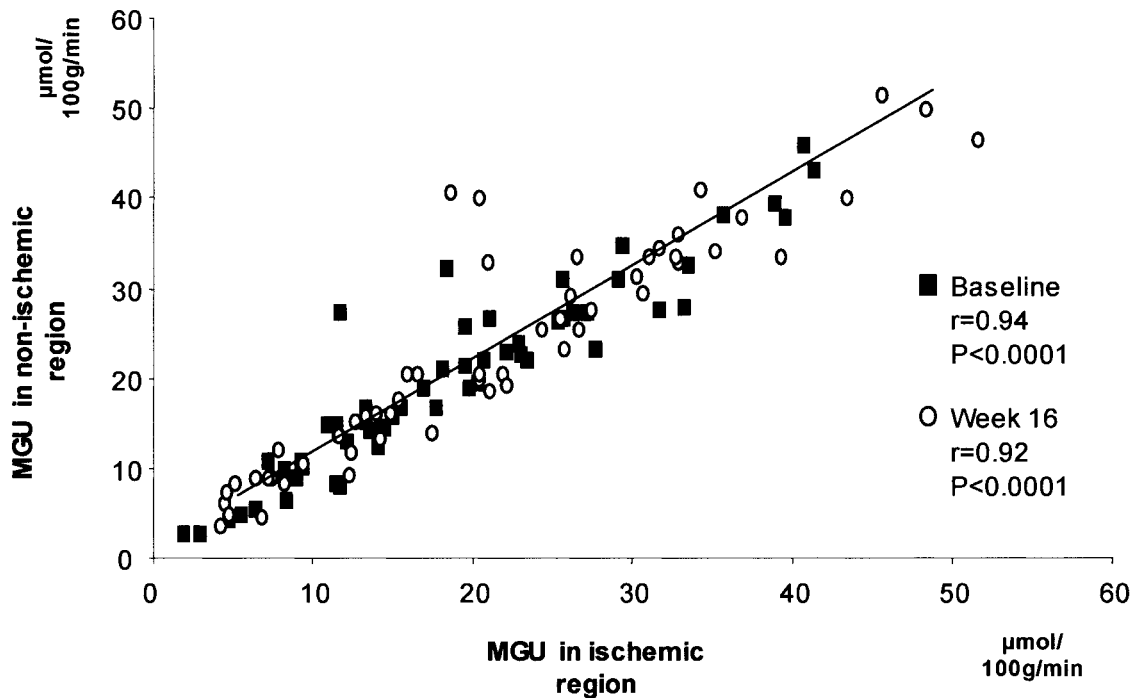


FIG. 3. Myocardial glucose uptake (MGU) in ischemic regions is strongly associated with myocardial glucose uptake in nonischemic regions.

Myocardial glucose uptake did not differ between ischemic and nonischemic regions or between the study groups before the intervention. Both at baseline and after treatment, myocardial glucose uptake in ischemic regions correlated strongly with myocardial glucose uptake in nonischemic regions (Fig. 3).

The relationship between myocardial metabolism, whole-body insulin sensitivity, and FFA levels. At randomization, whole-body glucose uptake was associated with myocardial glucose uptake in both ischemic and nonischemic regions (Fig. 4). When FFA level during clamp was used as a covariate, the relationship remained significant in both ischemic ($r = 0.29$, $P = 0.038$) and nonischemic ($r = 0.32$, $P = 0.021$) regions. There was a weakly significant inverse correlation between the increase in myocardial glucose uptake and the decline in the FFA levels during clamp in the rosiglitazone group in both ischemic ($r = -0.39$, $P = 0.047$) and nonischemic ($r = -0.39$, $P = 0.045$) regions. When the changes in myocardial glucose uptake were adjusted for the changes in FFA levels during clamp, the effect of rosiglitazone treatment was not significant in either ischemic ($P = 0.170$) or nonischemic regions ($P = 0.053$). From the linear regression analysis, the change in FFA levels explained $\sim 15\%$ of the change in myocardial glucose uptake levels in both regions.

DISCUSSION

This study presents a novel finding that rosiglitazone therapy enhances myocardial glucose uptake in ischemic and nonischemic regions in addition to its positive effects on whole-body insulin sensitivity and on glycemic control in type 2 diabetic patients with CAD. Moreover, myocardial glucose uptake is associated with whole-body insulin sensitivity, suggesting a direct relationship between myo-

cardial insulin sensitivity and the capacity of whole-body glucose disposal in these patients.

Although glucose is considered to be important for

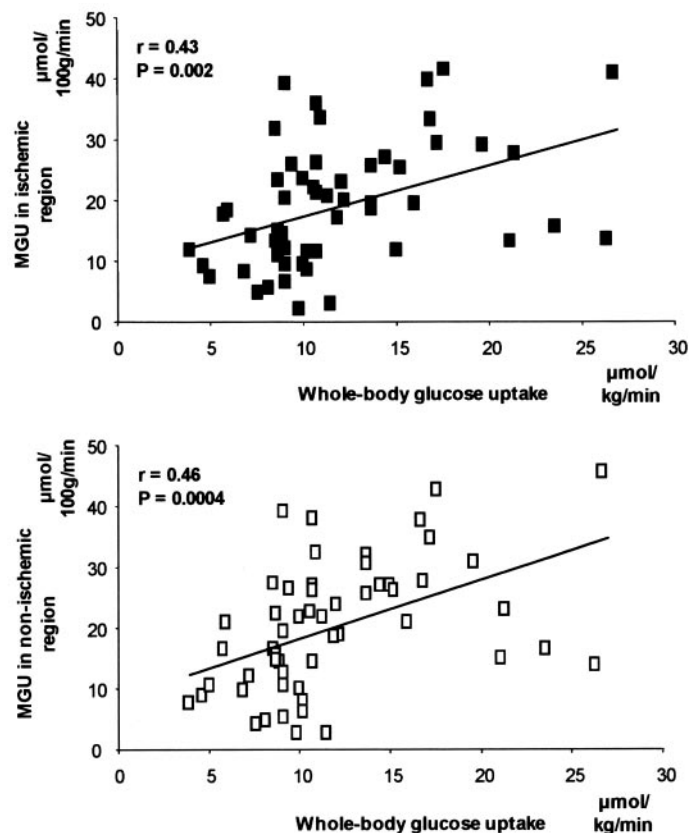


FIG. 4. Myocardial glucose uptake (MGU) is significantly correlated with the whole-body glucose uptake.

metabolism in ischemic myocardium, most human studies until now have evaluated myocardial glucose uptake in regions of normal perfusion and wall motion (5,7,10). In a study with intracoronary insulin infusions and the measurement of arterial-coronary sinus glucose balance, cardiac glucose uptake was similar in type 2 diabetic patients with and without CAD (8). This is in agreement with our previous studies with PET and FDG (5,6). Some other studies have suggested that in states of whole-body insulin resistance, myocardial insulin resistance also exists (7,9,10). However, absolute values for myocardial glucose uptake differ from one study to another. Under physiological insulin levels, myocardial glucose uptake varies from 35 to 71 $\mu\text{mol} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$ (5,7,9,10,27), from 34 to 53 $\mu\text{mol} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$ for patients with CAD (4,5,7,10,27) and from 27 to 46 $\mu\text{mol} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$ for patients with uncomplicated type 2 diabetes (5,7,9). Because the variability for myocardial glucose uptake is high between the previous studies, the reference value for myocardial glucose uptake is difficult to determine. In the current study, myocardial glucose uptake was $\sim 21 \mu\text{mol} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$ before any intervention. To our knowledge, only one study has previously reported myocardial glucose uptake values for normal myocardial regions for type 2 diabetic patients with CAD by PET techniques, and it suggested slightly higher values than the current study ($34 \mu\text{mol} \cdot 100 \text{ g}^{-1} \cdot \text{min}^{-1}$) (7). However, in that study the absolute values for myocardial glucose uptake were divided by perfusable tissue fraction; thus, they were similar to those reported in the current study. The minor difference between the studies may be explained by the limitations in the capability of partial volume correction in the analysis program used (MunichHeart). However, all of the analysis in the current study was performed with the same program; thus, we may assume errors were constant. Our finding of similar myocardial glucose uptake in both myocardial segments suggests higher glucose extraction in the ischemic walls. At fast, this response is typical of ischemic myocardium (4). The physiological enhancement of glucose uptake in normal segments during insulin stimulation may have blunted this difference in our study while being instrumental to the main purpose of the study, i.e., to demonstrate that rosiglitazone treatment would reverse myocardial insulin resistance in type 2 diabetes (7). Hence, during insulin stimulation myocardial glucose uptake in ischemic regions is similar to that of nonischemic regions, and there is a direct relationship between myocardial glucose uptake and whole-body insulin sensitivity.

Rosiglitazone belongs to the group of PPAR γ agonists that regulate adipogenesis and glucose homeostasis. Adipose tissue is considered as the most important site for its action (28). Rosiglitazone improves glucose uptake in peripheral tissues and consequently reduces insulin resistance in patients with uncomplicated type 2 diabetes (16–18,29). Here, we found a direct association between myocardial glucose uptake and whole-body insulin sensitivity. This is in agreement with a previous study (7), although the absolute values for whole-body glucose uptake are lower than those previously reported. It is clear with these patients that whole-body insulin sensitivity may be altered because of concomitant medications. Of the patients in each group, >70% were using β -blockers,

which have been linked to increased insulin resistance (30). However, the β -blocker dosage was kept constant during the intervention period in this study; thus, the net result remains unaffected. To our knowledge, the effects of rosiglitazone in type 2 diabetic patients with CAD have not been previously studied; consequently, this study shows that insulin-sensitizing effects of rosiglitazone may be also applicable in type 2 diabetic patients with CAD.

In ischemic myocardium, increased glucose utilization has been shown to enhance energy yield and improve cardiac function in an animal model (31). At the cellular level, myocardial glucose uptake is catalyzed by members of the GLUT family. The most important GLUT, GLUT4, is translocated from the cytosol to the plasma membrane by insulin stimulation, workload, and ischemia (32,33). Restrictions in glucose utilization during ischemia come from the slow rate of glucose transport because of the shortage of GLUTs and high levels of circulating FFAs (34,35). In addition, myocardial glucose uptake is equally mediated by a direct effect of insulin on the myocardium (36). The FFA inhibition of myocardial glucose utilization may be overcome by decreasing the FFA concentration (37). Previously, it has been shown that PPAR γ agonists increase insulin-mediated FFA suppression (38,39). In the current study, rosiglitazone therapy decreased FFA levels during hyperinsulinemia, and the improvement in myocardial glucose uptake was significantly associated with the decrease in the circulating FFA levels. When the change in myocardial glucose uptake was adjusted for FFA suppression, there was no significant difference between the study groups. Consequently, FFA suppression may be one of the main underlying mechanisms explaining the enhancement in myocardial glucose uptake. However, according to the linear regression analysis, the decrease in FFA levels explains only 15% of the change in myocardial glucose uptake in the rosiglitazone group, which suggests that there are also other factors involved. This is in agreement with previous work, in which FFA levels were decreased with metformin therapy, but there were no changes in myocardial glucose uptake (19). Although PPAR γ receptors are located in myocardium and macrophage-derived foam cells of the early and the advanced atherosclerotic lesions (40), their functional relevance is not yet clear. Our data do not allow the discrimination of direct drug mechanisms, but they support a role for indirect mediators, including, but not limited to, serum FFA levels. In animal studies, rosiglitazone increased the concentrations of GLUT1 and -4, improved myocardial glucose uptake (41), and protected from ischemic injury (14,15). Furthermore, rosiglitazone significantly reduced ischemia-induced apoptotic cell death and attenuated postischemic contractile dysfunction (42).

In the current study, rosiglitazone did not significantly affect the SPECT-determined ischemic score and the echocardiographic parameters of the left ventricular function, which is in agreement with previous studies in patients with uncomplicated type 2 diabetes (43,44). This might be because the patients had only minor impairment in cardiac function in this study. At baseline, the patients were randomized into two groups receiving either active medication or placebo. Because of ethical reasons, we could not keep dysfunctional CAD patients without any medica-

tion (placebo) or intervention for the duration of the trial; thus, severe ventricular dysfunction was defined as an exclusion criterion. In addition, diabetic patients have an increased risk of left ventricular failure, a clinical feature of diabetic cardiomyopathy that is preceded by myocardial ischemia, increased oxidative stress, and endothelial dysfunction (35). Previously, it has been suggested that rosiglitazone may cause fluid retention, which may present as clinically evident edema and rarely as congestive heart failure (45). In the current study, there was a slight increase in weight in the rosiglitazone group. However, no clinical signs of fluid retention were observed, nor did this weight gain negatively affect the parameters of left ventricular function. Our results suggest that rosiglitazone therapy is beneficial for myocardial metabolism, in that it alleviates myocardial insulin resistance (7). However, the potential functional benefits have yet to be demonstrated in humans; hence, further studies in patients with existing left ventricular dysfunction are needed to clarify the effects of rosiglitazone on cardiac function, as well as the potential consequences of slight weight gain in more severe disease.

Chronic hyperglycemia has been demonstrated to cause formation of free radicals, thus provoking oxidative stress in cardiomyocytes, leading to apoptosis, cell loss, myocardial thinning, and compensatory hypertrophy (46). In our study, rosiglitazone removed such toxic chronic overload, as shown by reduced A1C and fasting plasma glucose levels, and by the reversal of chronic hyperinsulinemia. In addition to their metabolically mediated effects, PPAR γ agonists have been shown to counteract oxidative stress by direct mechanisms (47). The lack of any change in left ventricular function would be in keeping with animal studies, showing that the prevention of oxidative stress attenuated hyperglycemia-induced myocardial cell death, without any measurable effect on echocardiographic findings (46).

In summary, this study shows a salient finding that rosiglitazone improves overall insulin sensitivity and increases myocardial glucose uptake in ischemic and non-ischemic regions in patients with type 2 diabetes and CAD. According to these results, rosiglitazone therapy may decrease FFA dependence and thus increase myocardial glucose utilization in these patients.

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