

# Rosiglitazone Improves Exercise Capacity in Individuals With Type 2 Diabetes

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**OBJECTIVE** — Although exercise is recommended as a cornerstone of treatment for type 2 diabetes, it is often poorly adopted by patients. We have noted that even in the absence of apparent cardiovascular disease, persons with type 2 diabetes have an impaired ability to carry out maximal exercise, and the impairment is correlated with insulin resistance and endothelial dysfunction. We hypothesized that administration of a thiazolidinedione (TZD) agent would improve exercise capacity in type 2 diabetes.

**RESEARCH DESIGN AND METHODS** — Twenty participants with uncomplicated type 2 diabetes were randomly assigned in a double-blind study to receive either 4 mg/day of rosiglitazone or matching placebo after baseline measurements to assess endothelial function (brachial artery diameter by brachial ultrasound), maximal oxygen consumption ( $\dot{V}O_{2\max}$ ), oxygen uptake ( $\dot{V}O_2$ ) kinetics, and insulin sensitivity by hyperinsulinemic-euglycemic clamp. Measurements were reassessed after 4 months of treatment.

**RESULTS** — Participant groups did not differ at baseline in any measure. Rosiglitazone-treated participants ( $n = 10$ ) had significantly improved  $\dot{V}O_{2\max}$  ( $19.8 \pm 5.3 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  before rosiglitazone vs.  $21.2 \pm 5.1 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  after rosiglitazone,  $P < 0.01$ ), insulin sensitivity, and endothelial function. A change in  $\dot{V}O_{2\max}$  correlated with improved insulin sensitivity measured by clamp ( $r = 0.68$ ,  $P < 0.05$ ) and with improved brachial artery diameter ( $r = 0.70$ ,  $P < 0.05$ ). Placebo-treated participants ( $n = 10$ ) showed no changes in  $\dot{V}O_{2\max}$  ( $19.4 \pm 5.2 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  before rosiglitazone vs.  $18.1 \pm 5.3 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  after rosiglitazone, NS) or brachial artery diameter.

**CONCLUSIONS** — This is the first known report showing that a TZD improved exercise function in type 2 diabetes. Whether this is due to the observed improvements in insulin sensitivity and/or endothelial function or to another action of the TZD class requires further exploration.

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Even in the absence of cardiovascular disease, persons with type 2 diabetes have an impaired ability to carry out maximal exercise in that maximal oxygen consumption ( $\dot{V}O_{2\max}$ ) is reduced by ~20% compared with that in control subjects similar in terms of age and physical activity level (1–3). In addition, oxygen consumption ( $\dot{V}O_2$ ) at submaximal workloads is reduced during graded exer-

cise in type 2 diabetes compared with that in healthy control subjects as has previously been observed in disease states with impaired oxygen delivery (1,4). Also,  $\dot{V}O_2$  kinetics are slowed during constant load exercise in type 2 diabetes (5). Thus, there are many exercise abnormalities associated with type 2 diabetes.

The relationship between exercise capacity and insulin resistance is of interest

because the association between higher levels of physical activity/exercise training status and improved insulin sensitivity is well established (6–8). Conversely, decreased habitual physical activity is known to be associated with poorer diabetic status (9). Population studies reveal a direct correlation between all-cause mortality and reduced fitness in persons with and without type 2 diabetes (10,11). Previous work from our group and others demonstrates an inverse relationship between insulin resistance and  $\dot{V}O_{2\max}$  in type 2 diabetes in most, though not all, studies (1,4,12–15). In contrast, glycemic control does not correlate with decreased functional exercise capacity (1,2,16). We have also reported that  $\dot{V}O_{2\max}$  in type 2 diabetes is correlated with endothelial function. Rosiglitazone, an oral antidiabetic agent, improves insulin sensitivity in diabetic animals as well as in humans (17,18), and it has been observed that the thiazolidinedione (TZD) class of drugs improves endothelial function (19,20). Therefore, we hypothesized that administration of rosiglitazone would improve exercise capacity in persons with type 2 diabetes compared with placebo.

## RESEARCH DESIGN AND METHODS

Twenty adults with uncomplicated type 2 diabetes were randomly divided into two groups. One group received rosiglitazone (4 mg daily) and the other received a matching placebo. A dose of 4 rather than 8 mg daily was chosen because although this dose has previously been reported to improve insulin sensitivity and endothelial function, we also wished to minimize the possible weight gain and other side effects that could confound the primary end point. Participants and investigators were blinded to treatment.

The presence of type 2 diabetes was documented by chart review and treatment for diabetes. Persons with type 2 diabetes were included if their diabetes was treated by diet alone and/or oral antidiabetic medications. Subjects taking metformin, any TZD, or insulin were excluded. Persons with type 2 diabetes were accepted for the study if they had total HbA<sub>1c</sub> (A1C) levels <9% (adequate control) with therapy. The study was ap-

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**Abbreviations:** CWR, constant work rate; DEXA, dual-energy X-ray absorptiometry; HOMA-IR, homeostasis model assessment of insulin resistance; TZD, thiazolidinedione.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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proved by the institutional review board of the University of Colorado Health Sciences Center, and all participants consented to be studied.

History, physical examination, and laboratory testing confirmed absence of comorbid conditions. Exclusion criteria included cigarette use within 1 year before study, alanine aminotransferase levels  $>1.5$  times the upper limit of normal, evidence of acute liver disease, evidence of distal symmetrical neuropathy (by evaluation of symptoms [numbness or paresthesia] and signs [elicited by vibration, pinprick, light touch, and ankle jerks]), autonomic dysfunction ( $>20$  mm fall in upright blood pressure without a change in heart rate), proteinuria (urine protein  $>200$  mg/dl) or creatinine  $\geq 2$  mg/dl, evidence of ischemic heart disease by history or abnormal resting or exercise electrocardiogram ( $\geq 1$  mm ST segment depression), or angina or other cardiac or pulmonary symptoms potentially limiting exercise performance. Systolic blood pressure  $>190$  mmHg at rest or  $>250$  mmHg with exercise or diastolic blood pressure  $>95$  mmHg at rest or  $>105$  mmHg with exercise was also a reason for exclusion. All exclusions were made for reasons of safety or potential effects on exercise performance.

Subjects came to the Vascular Research Laboratory at the University of Colorado Health Sciences Center for 10 visits over a  $\sim 4$ -month period. During visit 1, participants had a history and physical examination performed, and blood was drawn for measuring A1C and liver enzymes. In addition, a resting electrocardiogram, urine analysis, and familiarization bicycle test were performed. Dual-energy X-ray absorptiometry (DEXA) and body composition tests were carried out during visit 2. During visit 3, plethysmography and brachial echo measurements were made. For visit 4, a hyperinsulinemic-euglycemic clamp was performed to determine insulin resistance. For visit 5, subjects had a graded bicycle exercise test to determine  $\dot{V}O_{2\max}$  and three constant-load tests to measure  $\dot{V}O_2$  kinetics. The two types of testing sessions ( $\dot{V}O_{2\max}$  and  $\dot{V}O_2$  kinetics) were separated by a 2-hour period to allow rest or were performed on two separate days. Participants were then randomly assigned to begin a course of rosiglitazone or placebo for 4 months. Liver enzymes were assessed during visits 6 and 7, 1 month and 3 months, respectively, after starting study medication. At visits 8–10 the entry

procedures were repeated 4 months after treatment initiation.

### **Body composition and DEXA**

Body composition and DEXA measures were performed according to standard methods (21).

### **Insulin resistance**

Insulin resistance was assessed by fasting insulin level, by calculation of the homeostasis model assessment of insulin resistance (HOMA-IR), and by hyperinsulinemic-euglycemic clamp (described later). HOMA-IR was calculated according to the following formula: fasting plasma insulin (milliunits per liter)  $\times$  fasting glucose (millimoles per liter)/22.5 (22,23).

### **Hyperinsulinemic-euglycemic clamp**

The clamp to measure insulin sensitivity was done with an infusion of  $40 \text{ mU} \cdot \text{m}^{-2} \cdot \text{min}^{-1}$  insulin and 20% dextrose being given over a 6-h period according to methods previously described (24,25).

### **Brachial artery diameter**

Endothelial function was assessed by the brachial artery ultrasound method. The ultrasound method for measuring endothelial function after cuff occlusion followed the protocol described by Celermajer et al. and other authors as previously reported (26–28).

After the hyperemic measures evaluating the endothelium-dependent vasodilation, subjects lay quietly for 15 min, and then sublingual nitroglycerin ( $300 \mu\text{g}$ ) was administered. After 3 min, measurements of brachial artery diameter were repeated to serve as a measure of endothelium-independent vasodilation.

### **Plethysmographic measurements**

Forearm reactive hyperemic blood flow was determined in supine participants by venous occlusion strain-gauge plethysmography (D.E. Hokanson, Issaquah, WA) using calibrated mercury-in-Silastic strain gauges and expressed in milliliters per 100 milliliters per minute according to established methods (29). Determination of resting forearm blood flow comprised at least five separate measurements performed at 10- to 15-s intervals. Peak reactive hyperemic forearm blood flow was recorded as the individual peak blood flow attained after release of the arterial occluding cuff.

**Exercise testing.**  $\dot{V}O_2$ , carbon dioxide production ( $\dot{V}CO_2$ ), minute ventilation, and heart rate were measured continu-

ously and recorded breath-by-breath using a metabolic measurement system (Medgraphics CPX/D; Medical Graphics, St. Paul, MN).

**Incremental (graded) exercise test.** To determine  $\dot{V}O_{2\max}$ , a graded bicycle test to exhaustion was carried out as previously described (1,5,8) using a cycle ergometer (Excalibur, Medical Graphics) and the metabolic cart. Three minutes of resting data were collected to obtain baseline measurements before exercise. After the start of exercise, the work rate was incremented in 10 to 20 W/min increments (depending on age and sex) to allow each subject to reach maximum within 7–12 min. During incremental exercise testing, the highest  $\dot{V}O_2$  and heart rate averaged over 20 s were defined as the maximum values. The respiratory exchange ratio was calculated as the ratio of  $\dot{V}CO_2/\dot{V}O_2$ .

### **Constant work rate exercise testing.**

Subjects performed three identical exercise transitions from rest to constant work rate (CWR) exercise (30 W) on a cycle ergometer as previously described (5,8,30). Each transition consisted of a resting period to obtain baseline gas exchange data, followed by 6 minutes of CWR exercise. Transitions were separated by a minimum of 10 min of rest. Respiratory gas-exchange measurements and heart rate data were recorded throughout each CWR bout.

**$\dot{V}O_2$  kinetic methods.** Gas-exchange and heart rate data for kinetic analysis were processed using a software program developed in our laboratory as previously described (5,8). The data for each exercise transition were time interpolated to 1-s intervals. The three CWR exercise transitions were then time aligned and averaged to provide a single, averaged exercise response for each subject.

Pulmonary  $\dot{V}O_2$  kinetic responses were evaluated using a two-component exponential model, allowing individual components of the  $\dot{V}O_2$  kinetic response to be evaluated as previously reported (5,8,30).

### **Blood collection and preparation**

Blood was drawn at baseline for the measurement of microalbuminuria, total cholesterol, LDL cholesterol, HDL cholesterol, triglyceride, glucose, insulin, and A1C levels. Values were assayed according to previously reported methods (1,5). Alanine aminotransferase levels were monitored to obtain a measure of liver function at screening and at months 1, 3, and 4.

**Table 1—Demographic and lipid data at baseline and fasting glucose, fasting insulin, hyperinsulinemic-euglycemic clamp, and HOMA-IR values before and after treatment**

|                           | Placebo       | Treated       |
|---------------------------|---------------|---------------|
| n                         | 10            | 10            |
| Age                       | 56 ± 1        | 55 ± 7        |
| Body weight (kg)          |               |               |
| Before                    | 90.0 ± 16.7   | 95.9 ± 14.7   |
| After                     | 90.0 ± 16.4   | 98.2 ± 16.1   |
| BMI (kg/m <sup>2</sup> )  | 30.4 ± 5.8    | 32.2 ± 5.6    |
| Body fat (%)              | 37.7 ± 7.8    | 35.3 ± 13.2   |
| A1C (%)                   | 7.2 ± 1.0     | 7.2 ± 1.1     |
| Microalbuminuria (μg/ml)  | 13.8 ± 10.2   | 12.7 ± 10.2   |
| Total cholesterol (mg/dl) | 179.5 ± 25.5  | 173.9 ± 30.8  |
| LDL cholesterol (mg/dl)   | 96.2 ± 22.8   | 95.5 ± 28.5   |
| Triglycerides (mg/dl)     | 143.6 ± 105.0 | 185.0 ± 87.1  |
| Fasting glucose (mg/dl)   |               |               |
| Before                    | 146.4 ± 31.3  | 144.9 ± 41.7  |
| After                     | 126.0 ± 29.8  | 119.9 ± 37.4* |
| Fasting insulin (mU/ml)   |               |               |
| Before                    | 20.0 ± 7.2    | 15.7 ± 14.6   |
| After                     | 13.3 ± 5.8*   | 8.1 ± 5.3*†   |
| Clamp (min 120–180)       |               |               |
| Before                    | 2.4 ± 1.4     | 2.8 ± 0.5     |
| After                     | 2.6 ± 2.0     | 5.3 ± 1.7*†   |
| HOMA-IR                   |               |               |
| Before                    | 7.0 ± 3.9     | 6.3 ± 5.9     |
| After                     | 4.2 ± 2.4*    | 2.8 ± 1.3*    |

Data are means ± SD. \**P* < 0.05 difference before and after within groups; †*P* < 0.05 difference between groups after treatment.

### Measurement of habitual physical activity

All participants were sedentary (defined as exercising one bout per week or less) and participation in the study was only permitted if participants did not plan to alter their exercise or diet efforts during the study.

### Statistical analysis

Data are reported as means ± SD. The two groups were compared using an unpaired *t* test. Within group comparisons before and after treatment were accomplished using the paired *t* test. Correlations were made using a Pearson product moment correlation coefficient.

**RESULTS** — The two groups of participants were of similar age ( $55.0 \pm 7.3$  years for rosiglitazone-treated subjects and  $56.1 \pm 10.7$  for placebo-treated control subjects, NS) and had similar body mass indexes ( $32.7 \pm 5.6$  kg/m<sup>2</sup> for rosiglitazone-treated subjects vs.  $30.4 \pm 5.8$  kg/m<sup>2</sup> for placebo-treated control subjects, NS). Each group comprised five men and five women. The two groups did

not differ with regard to any demographic or laboratory variable (Table 1).

### Measures of fasting glucose level and insulin resistance

Fasting blood glucose level improved significantly only in the rosiglitazone-treated group (Table 1). As expected, insulin sensitivity, measured by pre- and posttreatment measures of fasting insulin level, hyperinsulinemic-euglycemic clamp (measured over minutes 120–180 [last hour]), and HOMA-IR also improved in this group. The participants in the placebo-treated group did not improve their fasting blood glucose level but did have modest improvements in fasting insulin level and HOMA-IR consistent with a positive placebo effect. No significant changes were observed with insulin clamp results in the placebo group.

### Exercise capacity

Baseline exercise capacity did not significantly differ between groups (Table 2). Rosiglitazone-treated subjects had a significant improvement in  $\dot{V}O_{2\max}$  after 4 months of treatment whereas placebo-

treated subjects had no improvement (Table 2, Fig. 1). In addition,  $\dot{V}O_{2\max}$  was higher not only when expressed on a per kilogram basis (i.e., normalized for weight) but also when expressed as an absolute value (milliliters per minute) in the rosiglitazone-treated group compared with the placebo-treated group.

Maximal respiratory exchange ratio ( $\dot{V}CO_2/\dot{V}O_2$ ) did not significantly differ between or within groups before and after treatment, suggesting a similar (maximal) effort by the two groups at both time points (Table 2). Maximal heart rate similarly did not significantly differ between or within groups before or after treatment. Thus, effort appears to have been maximal for both groups before and after treatment.

The oxygen pulse can be used as a noninvasive indicator of stroke volume (31). This measure is obtained by dividing maximal  $\dot{V}O_2$  in milliliters per minute by maximal heart rate in beats per minute (Table 2). The oxygen pulse improved significantly in the rosiglitazone-treated group (Table 2) whereas that of the placebo-treated group did not improve.

$\dot{V}O_2$  kinetics are a measure of the rate of adaptive  $\dot{V}O_2$  after the onset of constant work rate exercise. In a two-component model, amplitude (A1) of the cardiodynamic  $\dot{V}O_2$  response was lower after rosiglitazone treatment but not after placebo treatment. The amplitude (A2) of the  $\dot{V}O_2$  increase during the second component was greater after rosiglitazone treatment with no change noted in the placebo-treated group. No change in the time constant of phase 2 was observed in either group after treatment although a shorter time delay was observed for phase 2 after rosiglitazone treatment compared with baseline. We observed a statistically faster time constant for phase 1 after 4 months of rosiglitazone treatment compared with baseline conditions. However, there were no differences between rosiglitazone- or placebo-treated groups for this parameter after treatment.

### Endothelial function and blood flow

At baseline, there were no differences between rosiglitazone- and placebo-treated groups in terms of brachial artery diameter response to cuff-induced hyperemia. Administration of rosiglitazone increased the brachial artery diameter response to cuff inflation by 83% over the baseline response (from  $0.024 \pm 0.03$  to  $0.044 \pm 0.03$  cm, *P* < 0.05), whereas no significant increase was seen in the response of

Table 2—Measures of maximal and submaximal exercise capacity before and after exercise

|                                                                                     | Placebo     | Treated      |
|-------------------------------------------------------------------------------------|-------------|--------------|
| <i>n</i>                                                                            | 10          | 10           |
| $\dot{V}O_{2\text{MAX}}$ ( $\text{ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ) |             |              |
| Before                                                                              | 19.4 ± 5.2  | 19.8 ± 5.3   |
| After                                                                               | 18.1 ± 5.3  | 21.2 ± 5.1*  |
| $\dot{V}O_{2\text{MAX}}$ (ml/min)                                                   |             |              |
| Before                                                                              | 1,744 ± 689 | 1,902 ± 603  |
| After                                                                               | 1,659 ± 681 | 2,074 ± 585* |
| Oxygen pulse ( $\dot{V}O_2/\text{heart rate}$ )                                     |             |              |
| Before                                                                              | 11.3 ± 3.7  | 13.3 ± 3.7   |
| After                                                                               | 11.1 ± 3.6  | 14.8 ± 4.1*† |
| Peak heart rate (beats/min)                                                         |             |              |
| Before                                                                              | 153 ± 16    | 145 ± 18     |
| After                                                                               | 146 ± 19    | 141 ± 19     |
| Maximal respiratory exchange ratio                                                  |             |              |
| Before                                                                              | 1.20 ± 0.07 | 1.19 ± 0.06  |
| After                                                                               | 1.14 ± 0.09 | 1.20 ± 0.04  |
| $\dot{V}O_2$ kinetics A1 (ml/min)                                                   |             |              |
| Before                                                                              | 267 ± 95    | 364 ± 183    |
| After                                                                               | 250 ± 87    | 256 ± 160*   |
| $\dot{V}O_2$ kinetics $\tau_1$ (s)                                                  |             |              |
| Before                                                                              | 2.5 ± 2.9   | 8.1 ± 5.9    |
| After                                                                               | 2.0 ± 2.6   | 2.9 ± 2.5*   |
| $\dot{V}O_2$ kinetics $td_1$ (s)                                                    |             |              |
| Before                                                                              | 0.53 ± 1.5  | 1.98 ± 3.8   |
| After                                                                               | 1.02 ± 3.0  | 1.48 ± 3.4   |
| $\dot{V}O_2$ kinetics A2 (ml/min)                                                   |             |              |
| Before                                                                              | 381 ± 141   | 376 ± 146    |
| After                                                                               | 402 ± 130   | 454 ± 194*   |
| $\dot{V}O_2$ kinetics $\tau_2$ (s)                                                  |             |              |
| Before                                                                              | 37.2 ± 9.5  | 33.1 ± 9.6   |
| After                                                                               | 38.7 ± 12.7 | 36.9 ± 8.3   |
| $\dot{V}O_2$ kinetics $td_2$ (s)                                                    |             |              |
| Before                                                                              | 28.2 ± 9.3  | 32.8 ± 5.6   |
| After                                                                               | 27.1 ± 8.2  | 23.2 ± 4.1*  |

Data are means ± SD. \* $P < 0.05$  difference within groups before and after treatment; †difference between groups after treatment. A1 =  $\Delta$ ;  $\tau$ , time constant; td, time delay.

placebo-treated control subjects (from  $0.010 \pm 0.02$  to  $0.017 \pm 0.02$  cm, NS). The change in brachial artery diameter

was greater in the rosiglitazone-treated group than in the placebo-treated group ( $P < 0.05$ ). No differences were seen from

before to after treatment in either group with regard to the brachial artery diameter response to nitroglycerin, which went from  $0.060 \pm 0.030$  to  $0.046 \pm 0.031$  cm (NS) in the rosiglitazone-treated group versus from  $0.058 \pm 0.17$  to  $0.056 \pm 0.26$  cm (NS) in the placebo group.

Hyperemic forearm blood flow response measured by plethysmography increased after rosiglitazone administration by 48% (from  $13.5 \pm 7.6$  to  $20.0 \pm 6.6$   $\text{ml} \cdot 100 \text{ ml}^{-1} \cdot \text{min}^{-1}$ ,  $P < 0.05$ ) whereas no significant change was observed in control subjects (from  $15.7 \pm 7.0$  to  $15.3 \pm 5.4$   $\text{ml} \cdot 100 \text{ ml}^{-1} \cdot \text{min}^{-1}$ , NS).

Of note, a change in brachial artery diameter before and after cuff inflation at baseline was not significantly lower at baseline in the placebo-treated group than in the rosiglitazone-treated group for reasons that are unclear. Reassuringly, the results for brachial artery diameter and plethysmography both support changes in the rosiglitazone-treated group not found in the placebo-treated group and thus are consistent.

#### Correlations between exercise performance and measures of insulin resistance/glycemic control

In the rosiglitazone-treated group only, a change in  $\dot{V}O_{2\text{MAX}}$  correlated with changes in fasting insulin ( $r = -0.75$ ,  $P < 0.01$ ), HOMA-IR ( $r = -0.89$ ,  $P < 0.001$ ), and insulin sensitivity as measured by clamp (min 120–180) ( $r = 0.68$ ,  $P < 0.05$ ). There was no significant correlation between any measure of exercise capacity and A1C or fasting blood glucose level in either of the groups. A change in  $\dot{V}O_{2\text{MAX}}$  also correlated with a change in brachial artery diameter ( $r = 0.70$ ,  $P < 0.05$ ) in the rosiglitazone-treated group.

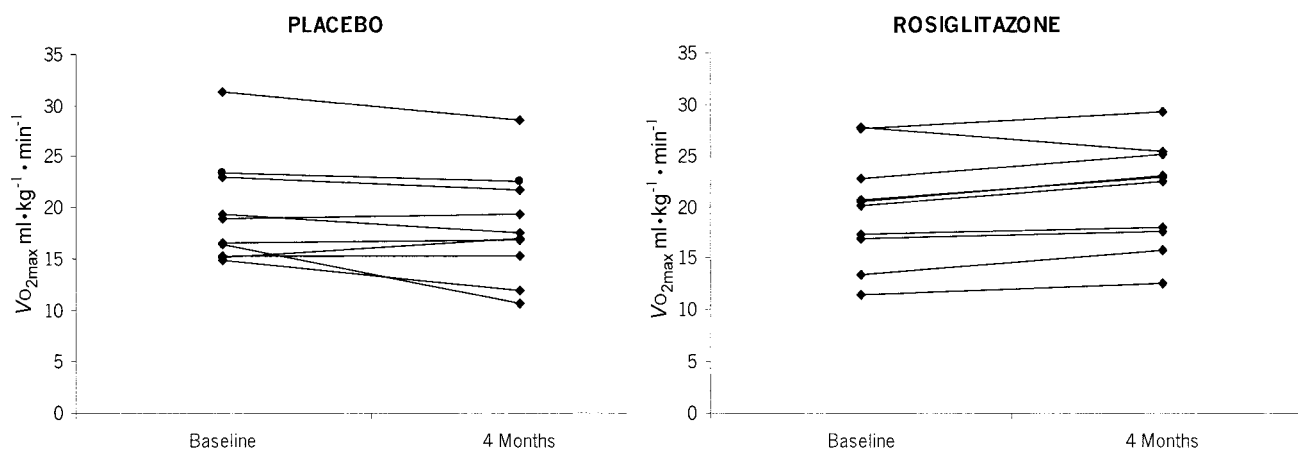


Figure 1— $\dot{V}O_{2\text{MAX}}$  before and after treatment with placebo (left) or rosiglitazone (right).

**CONCLUSIONS**— The primary finding of the present study was that  $\dot{V}O_{2\max}$  improved in participants with type 2 diabetes after the administration of a TZD. The improved exercise capacity was correlated with a reduction in insulin resistance and improved endothelial function and blood flow. Importantly, improvements in maximal exercise capacity were present whether  $\dot{V}O_{2\max}$  was reported on a per kilogram basis or as an absolute value. Further supporting the presence of improvements were improvements in  $\dot{V}O_2$  kinetics. To our knowledge, this finding marks the first report demonstrating that a pharmacological intervention with a TZD improves exercise capacity in persons with type 2 diabetes. The mechanism(s) leading to these improvements cannot be determined in the present study.

It has previously been reported that exercise capacity is reduced even in uncomplicated type 2 diabetes as was also observed in the present study (1–3). Schneider et al. (2) were among the first to note a decreased  $\dot{V}O_{2\max}$  in type 2 diabetes. Our group extended this work when we discovered that abnormalities not only occurred with maximal but also with submaximal exercise performance in persons with uncomplicated type 2 diabetes and that consistent linkages existed between exercise abnormalities and insulin resistance in persons with type 2 diabetes (1,5,8). The potential clinical relevance of the small but significant improvement in exercise capacity in the rosiglitazone-treated group is supported by the potent negative impact that physical inactivity has on diabetes control and weight management and the possible benefits a drug that improved exercise capacity might therefore confer (11,32). Because  $\dot{V}O_{2\max}$  is positively correlated with habitual physical activity (33,34), this relationship is of practical significance as well.

Previous investigations into the impact of drug therapy on exercise tolerance have primarily been in subjects with severe congestive heart failure, which profoundly reduces  $\dot{V}O_{2\max}$  (35,36). In one such study, a modest, but significant, increase of  $0.72 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  in  $\dot{V}O_{2\max}$  that was concordant with an increased ejection fraction was observed with administration of hydralazine and isosorbide dinitrate (35). In the present investigation, we evaluated type 2 diabetic subjects with no apparent clinical complications beyond decreased functional exercise capacity. Rosiglitazone in-

creased peak  $\dot{V}O_{2\max}$  by  $1.4 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  with concordant improvements in  $\dot{V}O_2$  kinetics and  $O_2$  pulse, suggesting an increase in stroke volume. Thus, whereas rosiglitazone exerts a modest effect on peak performance compared with exercise interventions, it is a consistent improvement and greater than that observed in congestive heart failure trials.

Improvements in  $\dot{V}O_{2\max}$  occur as a result of an increase in parameters of cardiac performance (heart rate and stroke volume) and/or peripheral oxygen extraction, as described by Fick's principle. In the rosiglitazone-treated group,  $\dot{V}O_{2\max}$  increased with no change in peak heart rate responses, resulting in a significantly increased peak oxygen pulse (the product of stroke volume and oxygen extraction). Moreover, the duration of the cardiodynamic phase (represented by the time delay of  $\dot{V}O_2$  kinetics during constant load submaximal exercise) became shorter, suggesting improvement in circulatory transit immediately after exercise onset. Importantly, this change in  $\dot{V}O_2$  kinetics was isolated to the cardiodynamic phase in the rosiglitazone group, and no changes in the phase 2 time constant (representing muscle  $O_2$  uptake) were observed from before to after treatment. Consistent with these observations, we have previously reported impaired cardiac function during acute exercise in persons with uncomplicated type 2 diabetes (37). Abnormalities in cardiac blood flow and subtle defects in autonomic function have also been reported in apparently uncomplicated type 2 diabetes (38–40). Although we did not directly evaluate cardiac function in the present study, study observations are most consistent with an improvement in cardiac performance in the rosiglitazone-treated group and suggest that a portion of the cardiac abnormality in type 2 diabetes may be amenable to TZD therapy. In addition, analogous findings in the skeletal muscle cannot be excluded.

The mechanisms by which type 2 diabetes per se is associated with impaired exercise capacity are not well understood. Typically, associations have not been observed between glucose level or A1C and exercise capacity in type 2 diabetes (1,2,16). In contrast, it has been established in most reports that increased insulin resistance is consistently associated with decreased  $\dot{V}O_{2\max}$  in persons with type 2 diabetes and other chronic disease states, as well as in healthy control subjects (5,8,12–14,41). These findings pro-

vided the rationale to evaluate whether TZDs, known insulin sensitizers, could improve exercise tolerance.

Insulin resistance is associated with blunted insulin-induced endothelial nitric oxide synthase activity, leading to decreased muscle and cardiac blood flow and decreased glucose transport into muscle (42). In the present study, we found that the improved exercise capacity in the rosiglitazone-treated group was associated with improved endothelial function in type 2 diabetes. This finding was not unexpected, given findings in previous studies in patients with heart failure, coronary heart disease, and diabetes showing correlations in these disease states between impaired exercise capacity and reduced endothelial function (43–45). The association between exercise capacity and endothelial function is further strengthened when the relationship of exercise training to endothelial function is examined. Exercise training improves endothelial function (43–45) in persons with diabetes or heart failure. Recent studies have showed that administration of L-arginine, a precursor of nitric oxide, has improved exercise capacity in patients with heart failure and pulmonary hypertension (46,47). However, because the present study was not designed to evaluate the mechanism by which rosiglitazone increased exercise capacity in type 2 diabetes, potential relationships between improved exercise capacity with endothelial function and insulin resistance, separately or together, require further investigation.

In addition to changes in endothelial function and insulin sensitivity, other mechanisms such as mitochondrial dysfunction could contribute to impaired exercise capacity in type 2 diabetes. Recent studies examining functional metabolism in rodents and humans with type 2 diabetes indicate inefficient mitochondrial function (48–51). A study of rats bred for increased exercise capacity and longevity revealed that mitochondrial dysfunction was associated with premature death, defective exercise capacity, and the metabolic syndrome (52). Whether mitochondrial dysfunction contributes to the impaired exercise capacity observed in type 2 diabetes remains to be determined but is plausible based on human and rodent studies (48–51). The role of the TZDs in treating the mitochondrial dysfunction of type 2 diabetes has not been completely determined, but in adipose tissue TZDs have been reported to increase mitochondrial mass (53).

Chronic exercise is a fundamental management tool for type 2 diabetes and yet exercise capacity is impaired in this population. The key observation in this study is that a TZD increased maximal exercise capacity in people with type 2 diabetes. The results of the present study support the hypothesis that treating persons with type 2 diabetes with a TZD augments exercise capacity. Future studies should explore the effects of rosiglitazone in combination with exercise training to investigate the potentially positive interaction of TZDs with this cornerstone of diabetes treatment.

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