Resistance to Exercise-Induced Increase in Glucose Uptake During Hyperinsulinemia in Insulin-Resistant Skeletal Muscle of Patients With Type 1 Diabetes

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Insulin and exercise have been shown to activate glucose transport at least in part via different signaling pathways. However, it is unknown whether insulin resistance is associated with a defect in the ability of an acute bout of exercise to enhance muscle glucose uptake in vivo. We compared the abilities of insulin and isometric exercise to stimulate muscle blood flow and glucose uptake in 12 men with type 1 diabetes (age 24 ± 1 years, BMI 23.0 ± 0.4 kg/m²) and in 11 age- and weight-matched nondiabetic men (age 25 ± 1 years, BMI 22.3 ± 0.6 kg/m²) during euglycemic hyperinsulinemia (1 mU·kg⁻¹·min⁻¹ insulin infusion for 150 min). One-legged exercise was performed at an intensity of 10% of maximal isometric force for 105 min (range 45–150). Rates of muscle blood flow, oxygen consumption, and glucose uptake were quantitated simultaneously in both legs using [¹⁵O]water, [¹⁵O]oxygen, [¹⁸F]-2-fluoro-2-deoxy-D-glucose, and positron emission tomography. Resting rates of oxygen consumption were similar during hyperinsulinemia between the groups (2.4 ± 0.3 vs. 2.0 ± 0.5 ml·kg⁻¹·muscle·min⁻¹; normal subjects versus patients with type 1 diabetes, NS), and exercise increased oxygen consumption similarly in both groups (25.3 ± 4.3 vs. 20.1 ± 3.0 ml·kg⁻¹·muscle·min⁻¹, respectively, NS). Rates of insulin-stimulated muscle blood flow and the increments in muscle blood flow induced by exercise were also similar in normal subjects (129 ± 14 ml·kg⁻¹·min⁻¹) and in patients with type 1 diabetes (115 ± 12 ml·kg⁻¹·min⁻¹). The patients with type 1 diabetes exhibited resistance to both insulin stimulation of glucose uptake (34 ± 6 vs. 76 ± 9 μmol·kg⁻¹·muscle·min⁻¹, P < 0.001) and also to the exercise-induced increment in glucose uptake (82 ± 15 vs. 162 ± 29 μmol·kg⁻¹·muscle·min⁻¹, P < 0.05). We conclude that the ability of exercise to increase insulin-stimulated glucose uptake in vivo is blunted in patients with insulin-resistant type 1 diabetes compared with normal subjects. This could be caused by either separate or common defects in exercise- and insulin-stimulated pathways. Diabetes 50:1371–1377, 2001

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sulin resistance characterizes patients with type 1 diabetes (1,2). Contraction increases glucose uptake independent of insulin (3,4). For example, contraction results in recruitment of GLUT4 to the cell membrane, activation of glycogen synthase, and induction of hexokinase II gene expression independently of insulin (5–7). These data raise the possibility that exercise increases glucose uptake normally in skeletal muscle of insulin-resistant subjects. This has indeed been shown to be true in soleus muscles from muscle-specific insulin-receptor knockout (MIRKO) mice (6). Although exercise and insulin can stimulate glucose uptake independently, the two stimuli also seem to have synergistic effects on glucose uptake. In MIRKO mice, despite extreme insulin resistance, insulin and exercise stimulate glucose uptake together more than either stimuli alone (6). This phenomenon has been attributed to insulin action on nonmuscle cells within skeletal muscle or to signaling events downstream, insulin receptor tyrosine phosphorylation, and phosphatidylinositol (PI) 3-kinase activity. In humans, the ability of exercise to increase insulin-stimulated glucose uptake is higher in trained than in untrained muscle (8).

Most patients with type 1 diabetes are characterized by varying degrees of insulin resistance. Numerous studies have documented 30–50% average reductions in rates of insulin-mediated glucose uptake in type 1 diabetic patients (1,2,9,10). Chronic hyperglycemia, i.e., glucose toxicity, is believed to be largely responsible for insulin resistance in type 1 diabetic patients (2). Elevation of plasma glucose concentrations for 24 h, to pathophysiologically relevant glucose concentrations (14–20 mmol/l), significantly decreases insulin-stimulated glucose uptake (9). One possible mechanism underlying the defect in insulin stimulation of glucose uptake has been suggested to be an overactivity of the hexosamine pathway (11,12). Activation of this pathway induces, at least in rats, defects in the insulin-signaling cascade, such as decreases in insulin receptor substrate-1 (IRS-1) tyrosine phosphorylation, IRS-1 association with PI 3-kinase, and PI 3-kinase activity (13). It is unknown whether exercise stimulates glucose uptake normally in insulin-resistant type 1 diabetic patients.

It is not possible to compare the abilities of insulin and exercise to stimulate muscle glucose uptake if the studies are not performed under identical metabolic conditions. In the present study, both resting and exercising legs were
exposed to similar concentrations of insulin and other hormones and metabolites to determine whether the ability of acute exercise to increase glucose uptake is preserved in insulin-resistant type 1 diabetic patients compared with nondiabetic subjects.

**RESEARCH DESIGN AND METHODS**

A total of 12 men with type 1 diabetes with no family history of diabetes or hypertension volunteered for the study (Table 1). Duration of type 1 diabetes averaged 8 ± 2 years. The patients were treated with multiple regimens of insulin injection. The mean daily dose was 53 ± 4 U. The subjects with diabetes were normotensive and had no clinical or laboratory evidence of disease, other than type 1 diabetes, and had no signs of microvascular or macrovascular disease, as determined by retinal photographs and autonomic nervous system function tests. The normal men were healthy as judged by history, physical examination, and routine laboratory tests and were not taking any medications. The normal subjects and the patients with type 1 diabetes performed regular aerobic exercise an average of 3.4 ± 0.8 and 3.1 ± 0.5 h per week, respectively (P = 0.81). Written informed consent was obtained after the nature, purpose, and potential risks of the study were explained to the subjects. The study was approved by the Joint Commission of the Ethics of the University of Turku and Turku University Central Hospital.

Before the positron emission tomography (PET) study, maximal oxygen consumption and maximal isometric contractile force of the quadriceps femoris muscle were determined as detailed below. The design of this study is shown in Fig. 1. The PET study was performed after an overnight fast. Alcohol and caffeine were prohibited 1 day before the study, and the subjects were instructed to avoid strenuous physical activity for 1 day before the study. In the morning of the study, the usual dose of intermediate-acting insulin was reduced by one-half, and no short-acting insulin was given. Two catheters were inserted: one in an antecubital vein of the left hand for the infusion of glucose and insulin and injections of [15O]H2O and [18F]-2-fluoro-2-deoxy-D-glucose (FDG), and the other in the radial artery for blood sampling. The subjects were lying supine during the study, resting between 0 and 45 min and

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**TABLE 1**

<table>
<thead>
<tr>
<th>Subject characteristics</th>
<th>Type 1 diabetic patients</th>
<th>Normal subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>12</td>
<td>11</td>
</tr>
<tr>
<td>Age (years)</td>
<td>24 ± 1</td>
<td>25 ± 1</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>74 ± 2</td>
<td>71 ± 2</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23 ± 0.4</td>
<td>22 ± 0.6</td>
</tr>
<tr>
<td>Percentage body fat</td>
<td>15.1 ± 1.0</td>
<td>13.9 ± 1.2</td>
</tr>
<tr>
<td>V̇O₂max (ml·kg⁻¹·min⁻¹)</td>
<td>45 ± 2</td>
<td>50 ± 3</td>
</tr>
<tr>
<td>Maximal isometric force (N)</td>
<td>618 ± 37</td>
<td>583 ± 51</td>
</tr>
<tr>
<td>Work load during PET study absolute (N)</td>
<td>50 ± 3</td>
<td>62 ± 7</td>
</tr>
<tr>
<td>Percentage of maximal work load</td>
<td>9.6 ± 0.1</td>
<td>10.4 ± 0.1</td>
</tr>
<tr>
<td>Fasting glucose (mmol/l)</td>
<td>11.1 ± 1.2</td>
<td>5.0 ± 0.2†</td>
</tr>
<tr>
<td>Fasting Insulin (mU/l)</td>
<td>4.9 ± 1.4</td>
<td>4.5 ± 0.6</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>7.0 ± 0.3</td>
<td>5.1 ± 0.1†</td>
</tr>
<tr>
<td>Fasting cholesterol (mmol/l)</td>
<td>4.2 ± 0.3</td>
<td>4.0 ± 0.2</td>
</tr>
<tr>
<td>Fasting HDL cholesterol (mmol/l)</td>
<td>1.5 ± 0.1</td>
<td>1.4 ± 0.1</td>
</tr>
<tr>
<td>Fasting LDL cholesterol (mmol/l)</td>
<td>2.4 ± 0.2</td>
<td>2.2 ± 0.2</td>
</tr>
<tr>
<td>Fasting triglycerides (mmol/l)</td>
<td>0.8 ± 0.1</td>
<td>1.0 ± 0.2</td>
</tr>
</tbody>
</table>

Data are n and means ± SE. *Maximal isometric force of knee extensors; †P < 0.001.

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![Diagram of PET scanning and exercise protocol](image)
performing intermittent isometric exercise with one leg between 45 and 150 min, as described in detail below (Fig. 1). At 0 min, an intravenous infusion of insulin (1 mU·kg⁻¹·min⁻¹) was started. The study for each subject consisted of a 150-min normoglycemic hyperinsulinemia (1 mU·kg⁻¹·min⁻¹) period.

During hyperinsulinemia, normoglycemia was maintained using variable rate of infusion of 20% glucose. Muscle blood flow (at 60 min) and muscle oxygen consumption (at 90 min) were measured in both femoral regions simultaneously, using [¹⁵O]H₂O infusion and [¹⁵O]O₂ inhalation techniques, as described in detail below. Thereafter, at 120 min, a bolus of [¹⁸F]FDG was injected for quantitation of muscle glucose uptake. Blood samples for measurement of radioactivity were collected as detailed below. Blood samples for measurement of radioactivity were collected as detailed below. Blood samples for measurement of radioactivity were collected as detailed below. Blood samples for measurement of radioactivity were collected as detailed below. Blood samples for measurement of radioactivity were collected as detailed below. Blood samples for measurement of radioactivity were collected as detailed below.

Production of PET tracers. For production of [¹⁵O]O₂ (t₁/₂ = 123 s), a low-energy deuterium accelerator Cyclone 3 was used (Ion Beam Application, Louvain-la-Neuve, Belgium). [¹⁵O]O₂ was produced by the [¹⁴N](d,n)[¹⁵O] reaction on natural nitrogen gas (14). Radiochemical purity of [¹⁵O]O₂ was 97%. [¹⁵O]H₂O was produced using a dialysis technique in a continuously working water module (15). Sterility and pyrogenity tests were performed daily to verify the purity of the product. [¹⁸F]FDG (t₁/₂ = 109 min) was synthesized with an automatic apparatus as described by Hamacher et al. (16). At the end of the synthesis, the specific radioactivity was 76 GBq/μmol, and the radiochemical purity exceeded 98%.

Image acquisition and processing. An 5-ring ECAT 931/88 tomograph (Siemens/CTI, Knoxville, TN) was used for image acquisition. The scanner has an axial resolution of 6.5 mm and an in-plane resolution of 6.5 mm (17). The images were obtained from the femoral region. Before the emission scannings, a transmission scan for correction of photon attenuation was performed for 20 min with a removable ring source containing ⁶⁷Ga. All data were corrected for dead time, decay, and measured photon attenuation. For image processing, a recently developed Bayesian iterative reconstruction algorithm using median root prior with 150 iterations and the Bayesian coefficient of 0.3 was applied (18).

Regions of interest. Regions of interests were drawn in the anteromedial muscle compartments of both femoral regions in four consecutive cross-sectional slices in both legs, carefully avoiding large blood vessels. Localization of the muscle compartments was verified by comparing the flow images with the transmission image, which provides a topographical distribution of tissue density. The regions of interest outlined in the flow images were copied to the [¹⁵O]O₂ and [¹⁸F]FDG images to obtain quantitative data from identical regions.

Measurement of muscle blood flow oxygen consumption. For measurement of blood flow, 1.2–1.7 GBq of [¹⁵O]H₂O was injected intravenously and dynamic scanning was performed for 6 min (6 × 5 s, 6 × 15 s, and 8 × 30 s frames). To determine the input function, radioactivity of arterial blood was measured using a two-channel detector system (Scanditronix, Uppsala, Sweden) as previously described (19,20). The arterial input curve was corrected for dispersion and delay, as previously described (20). The autoradiographic method and a 250-s integration time were applied to verify the purity of the product. [¹⁸F]FDG (t₁/₂ = 109 min) was synthesized with an automatic apparatus as described by Hamacher et al. (16). At the end of the synthesis, the specific radioactivity was 76 GBq/μmol, and the radiochemical purity exceeded 98%.

Exercise during the PET study. The subjects were lying supine in the PET scanner with the femoral regions in the gantry and the right leg, fixed at a 50° ankle, fastened to a dynamometer (I-KON; Chattanooga Group, Oxfordshire, England) (Fig. 1). Exercise consisted of 2-s isometric extension intermittent with 2 s of rest during 45–150 min of hyperinsulinemia. Exercise intensity was set at 10% of maximal isometric force because preliminary studies showed it to be feasible to maintain this intensity for the entire study period. The subject performed isometric exercise after a short signal. The intensity of the exercise was monitored by a light signal, which was green if the intensity of the exercise corresponded to 10% of maximal isometric force (Fig. 1). Maximal metabolic intensity of the knee extenders was measured before the PET study with a dynamometer (KimCom; Chattex, Chattanooga, TN). During the extended uptake ([¹⁸F]FDG uptake), a bolus of [¹⁸F]FDG was injected intravenously over 2 min, and 0.1 mmol/l, respectively, NS) and plasma lactate concentrations were measured using a fluorometric method and lactate was measured by a spectrophotometric method (34). Body fat content was estimated from four skin folds (subscapular, triceps brachii, biceps brachii, and crista iliaca), as measured with caliper (35). Retinal photography was performed after mydriatic installation with a Canon CR4–45NM fundus camera (Canon, Kanagawa, Japan); one 45% field photograph, taken at each examination, was taken of each eye. Retinal photographs were analyzed by the same person (T.R.). To exclude significant autonomic neuropathy, a series of standardized noninvasive cardiovascular reflex tests were performed on subjects with diabetes (36). Autonomic nerve function tests measuring mainly the parasympathetic control included a deep breathing test and an orthostatic test. Diastolic blood pressure response to isometric hand-grip test was used as the measure of sympathetic autonomic nervous system control.

Statistical methods. All results are expressed as mean ± SE. The differences between the two groups were compared using Student’s unpaired t test when appropriate. Concentrations of insulin and metabolites over time between the two groups were analyzed using analysis of variance for repeated measures, followed by pairwise comparison using the Tukey’s studentized range test. Spearman’s rank correlation coefficients were calculated when appropriate. Statistical calculations were performed using the SAS statistical program package (SAS Institute, Cary, NC). Significance was set at the 0.05 level.

RESULTS

Metabolic characteristics. Absolute and relative work force of knee extensors and Vmax were similar in both groups (Table 1). During hyperinsulinemia, serum free insulin concentrations were comparable (59 ± 1 vs. 56 ± 4 mU/l, normal subjects versus type 1 diabetic patients, NS), as were plasma glucose concentrations (5.3 ± 0.1 vs. 5.5 ± 0.1 mmol/l, respectively, NS) and plasma lactate concentrations (0.8 ± 0.09 vs. 0.9 ± 0.07 mmol/l, respectively, NS) during the time period when blood flow and
whole-body and femoral muscle glucose uptake measurements were recorded (60–150 min). During the 60- to 150-min period, serum FFA concentrations were higher in type 1 diabetic patients than in normal subjects (231 ± 23 vs. 155 ± 12 μmol/l, respectively, $P < 0.05$).

**Whole-body glucose uptake.** Insulin-stimulated whole-body glucose uptake, expressed per body weight, was 73% higher in the normal subjects (45 ± 3 μmol · kg$^{-1}$ body weight · min$^{-1}$) than in the type 1 diabetic patients (26 ± 4 μmol · kg$^{-1}$ body weight · min$^{-1}$, $P < 0.01$). The correlation coefficient between glucose uptake in femoral muscles and whole body was 0.83 in the normal subjects ($P < 0.001$) and 0.75 ($P < 0.01$) in the type 1 diabetic patients.

**Femoral muscle blood flow.** Resting rates of muscle blood flow were similar in both groups (37 ± 6 vs. 29 ± 6 ml · kg$^{-1}$ muscle · min$^{-1}$, normal subjects versus type 1 diabetic patients, NS). During exercise and insulin stimulation, muscle blood flow increased fivefold in both groups (165 ± 18 vs. 145 ± 15 ml · kg$^{-1}$ muscle · min$^{-1}$, normal subjects versus type 1 diabetic patients, NS between groups). The increment induced by exercise in blood flow was similar in both groups (37 ± 3 and 29 ± 4 ml · kg$^{-1}$ muscle · min$^{-1}$, NS between groups) (Fig. 2).

**Femoral muscle oxygen consumption.** Resting rates of oxygen consumption were comparable during hyperinsulinemia (2.4 ± 0.3 vs. 2.0 ± 0.5 ml · kg$^{-1}$ muscle · min$^{-1}$, normal subjects versus patients with type 1 diabetes, NS) and during combined exercise and insulin stimulation (Fig. 2). The exercise-induced increments in muscle oxygen consumption were also comparable (25.3 ± 4.3 vs. 20.1 ± 3.0 ml · kg$^{-1}$ muscle · min$^{-1}$, respectively). The increment induced by exercise in muscle blood flow was significantly correlated with the increment in oxygen consumption in the normal subjects ($r = 0.77$, $P < 0.01$) and in the patients with type 1 diabetes ($r = 0.66$, $P < 0.05$) (Fig. 3).

**Femoral muscle glucose uptake.** During hyperinsulinemia, glucose uptake in resting femoral muscle was 124% higher in the normal subjects (76 ± 9 μmol · kg$^{-1}$ muscle · min$^{-1}$) than in the patients with type 1 diabetes (34 ± 6 μmol · kg$^{-1}$ muscle · min$^{-1}$, $P < 0.001$) (Figs. 2 and 4). Exercise superimposed upon hyperinsulinemia increased rates of muscle glucose uptake significantly in both groups (to 238 ± 34 vs. 116 ± 20 μmol · kg$^{-1}$ muscle · min$^{-1}$, normal subjects versus patients with type 1 diabetes, $P < 0.01$). The increment induced by exercise was, however, 49% lower in the type 1 diabetic patients (82 ± 15 μmol · kg$^{-1}$ muscle · min$^{-1}$) than in the normal subjects (162 ± 29 μmol · kg$^{-1}$ muscle · min$^{-1}$, $P < 0.05$).

**Glucose extraction.** The fraction of glucose extracted by resting muscle during hyperinsulinemia was significantly higher in the normal subjects (0.54 ± 0.06) than in the patients with type 1 diabetes (0.34 ± 0.08, $P < 0.05$). Exercise decreased glucose extraction significantly and by ~40% in both groups (−0.19 ± 0.06 vs. −0.14 ± 0.05 in normal subjects versus patients with type 1 diabetes, NS between groups). In the leg exposed to both insulin and exercise, fractional extraction was significantly higher in
the normal subjects (0.35 ± 0.04) than in the patients with type 1 diabetes (0.20 ± 0.04, \( P < 0.05 \)).

**DISCUSSION**

In the present study, we compared the abilities of acute isometric exercise and insulin to stimulate glucose uptake in patients with type 1 diabetes and in normal subjects. The effects of exercise and insulin were studied under identical metabolic conditions, i.e., where both legs were exposed to similar concentrations of insulin and other hormones and metabolites. We found a clear defect in the ability of isometric exercise to increase skeletal muscle glucose uptake in the type 1 diabetic patients, who also had a defect in insulin-stimulated glucose uptake. These data imply that type 1 diabetic patients have defects in either exercise- and insulin-stimulated signaling pathways or in a pathway that the two stimuli share in skeletal muscle.

Use of PET combined with radioactive tracers for quantitation of skeletal muscle perfusion and metabolism offers some advantages over other methods. First, these parameters can be measured directly in skeletal muscle, thus avoiding artifacts induced by interindividual variation in subcutaneous fat (37). Also, any confounding effects caused by intra-arterial catheters can be avoided. \([^{18}F]FDG\) was used for measurement of femoral muscle glucose uptake (23), applying a lumped constant of 1.2, which was recently validated for human skeletal muscle (25–27). The lumped constant during exercise has not been determined in human studies; therefore, the calculated glucose uptake rates during exercise may be quantitatively inaccurate. However, because normoglycemic type 1 diabetic patients are normally insulin-sensitive (2,10) and insulin action involves both stimulation of glucose transport and phosphorylation, it is unlikely that the affinities of glucose transporters or hexokinases for glucose and 2-deoxy-glucose differ between normal subjects and type 1 diabetic patients. In previous studies in which glucose uptake has been measured across the whole leg during moderate- (38) to high-intensity (39) bicycle ergometer exercise and supraphysiological or physiological insulin concentrations, rates of glucose uptake have averaged 230 (39) and 281 (38) \( \mu \text{mol} \cdot \text{kg}^{-1} \cdot \text{muscle} \cdot \text{min}^{-1} \). In the present study, glucose uptake averaged 238 \( \mu \text{mol} \cdot \text{kg}^{-1} \cdot \text{muscle} \cdot \text{min}^{-1} \).

Skeletal muscle oxygen consumption was quantitated using a bolus inhalation of \( ^{15} \text{O}\)-labeled oxygen, as previously described and validated in humans (22). Measurement of oxygen consumption was considered important because fuel use can only be reliably compared between two groups if rates of oxygen consumption are similar. In this study, \( V_{O2\max} \) was similar between the groups. This is in keeping with previous studies in which patients with uncomplicated type 1 diabetes had a normal aerobic exercise capacity (40). We chose the intensity of isometric exercise based on individual muscular strengths, rather than on \( V_{O2\max} \), because use of the latter would lead to different work loads if groups differed with respect to \( V_{O2\max} \). Because maximal isometric contraction forces were similar between the groups, both absolute and relative work loads and rates of oxygen consumption were matched between the groups.

Several studies have recently demonstrated that human skeletal muscle contains both intramyocellular and extramyocellular fat (41,42). Possibly, impaired insulin action on extramyocellular fat within muscle or on lipolysis in adipose tissue could diminish the ability of exercise to stimulate glucose uptake. In the present study, the finding of slightly but significantly higher FFA concentrations during hyperinsulinemia in the type 1 diabetic patients than in the normal subjects is consistent with this possibility. Even if FFAs were not the cause of the impaired exercise-induced glucose uptake, and considering that plasma lactate concentrations were similar between the groups, FFA was the most likely fuel that compensated for the decrease in glucose uptake in the type 1 diabetic patients. It is also possible that the higher FFA concentrations might have caused the lower rate of glucose uptake, either via impairing insulin signaling (43,44) or via substrate competition (23).

Previous studies have documented insulin resistance in type 1 diabetes to be fully reversible if glycemic control is normalized (2,10,45,46). The improvement is observed even in the absence of an increase in insulin requirements,
and insulin resistance can be induced within 24 h by chronic hyperglycemia (2,9). One molecular mechanism that might underlie glucose-induced insulin resistance is overactivation of the hexosamine pathway (11,12). Activation of this pathway induces, at least in rats, defects in the insulin-signaling cascade, such as decreases in IRS-1 tyrosine phosphorylation, IRS-1 association with PI 3-kinase, and PI 3-kinase activity (13). These defects are similar to those characterizing obese subjects and patients with type 2 diabetes (47), although the cause of the alterations may differ (13,47). Regarding exercise-stimulated signaling pathways, an AMP-activated protein kinase (AMPK) has recently been proposed to be one potential regulator of GLUT4 translocation in response to muscle contraction (48–51). AMPK is activated by an increase in the AMP-to-ATP ratio and by a decrease in phosphocreatine. Activation of AMPK with nucleoside 5-aminocimidazole-4-carboxyamide-1-beta-D-ribofuranoside has been shown to increase skeletal muscle glucose uptake, but this increase is insensitive to wortmannin, a known PI-3 kinase inhibitor (49,52). It is currently unknown whether type 1 diabetic patients have defects in the PI 3-kinase–independent pathway stimulating glucose uptake. If not, the mechanism explaining the resistance of skeletal muscle to exercise-induced increases in glucose uptake could be located in insulin-signaling pathways that are common to both stimuli (6).

The present data do not exclude the possibility that the ability of exercise alone to stimulate glucose uptake in type 1 diabetic patients is intact. This possibility cannot, however, be tested in the absence of insulin in humans.

In conclusion, these in vivo data demonstrate that the ability of exercise to increase glucose uptake is blunted in patients with insulin-resistant type 1 diabetes compared with normal subjects. Whether this is because of separate or common defects in exercise- and insulin-stimulated pathways leading to decreased glucose uptake cannot be resolved based on the present data.

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