Effects of 7 days of exercise training on insulin sensitivity and responsiveness in type 2 diabetes mellitus

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EXERCISE HAS A NUMBER OF BENEFICIAL EFFECTS that can play important roles in the prevention and treatment of the insulin resistance that leads to and mediates type 2 diabetes (23). In addition to increased energy expenditure, which helps to prevent and reverse obesity, exercise has short-term effects that enhance insulin action. Exercise acutely increases muscle glucose transport, and this effect is mediated by an increase in the glucose transporter 4 (GLUT4) isofrom of the glucose transporter in skeletal muscle (18). As this effect wears off, it is replaced by an increase in insulin sensitivity (19). As a result of these two adaptations, exercise results in increases in both insulin sensitivity and insulin responsiveness. Insulin sensitivity is evaluated in terms of the concentration of insulin required to induce 50% of its maximal effect on glucose transport (25). An increase in insulin sensitivity causes the insulin dose-response curve to shift to the left so that the insulin concentration required to cause 50% of its maximal effect is lower. Insulin responsiveness, in contrast, determines the magnitude of the increase in glucose transport induced by a maximally effective insulin stimulus (25). An increase in insulin responsiveness causes a larger increase in glucose transport in response to a maximal insulin stimulus and a proportional upward shift in the insulin dose-response curve.

Exercise training results in increases in insulin action in humans (9, 11, 12, 14, 20, 22). Exercise training also induces increases in muscle GLUT4 content in humans (10, 21, 22), and 7–10 days of training is sufficiently long to bring about this adaptation (15, 34). These are short-term effects of exercise that wear off in a few days after the last exercise bout (9, 27, 45). In light of this information, there has been considerable research on the effects of exercise in patients with insulin resistance and impaired or diabetic glucose tolerance. A number of studies utilized short-term exercise training, making it possible to evaluate the effects of exercise training in the absence of weight loss. In one of these studies, 7 days of exercise training for 50–60 min/day at −68% of maximal oxygen uptake capacity (V̇O2max), which did not result in weight loss, improved glucose tolerance from diabetic to impaired in patients with mild diabetes (39). Ten days of a similar exercise program resulted in a large improvement in insulin action, measured using a hyperglycemic clamp procedure, in obese individuals with impaired glucose tolerance (1). In two other studies on patients with type 2 diabetes, 1 wk of exercise training resulted in significant improvements in insulin-stimulated glucose disposal rates measured during euglycemic clamps (34, 51). Those authors referred to these improvements as increases in insulin sensitivity but examined only the effects of submaximally effective insulin stimuli. In the study of Winnick et al. (51), the improvement in insulin action was only on glucose disposal, with no improvement in insulin suppression of endogenous glucose production, which is predominantly of hepatic origin.

Impaired insulin suppression of hepatic glucose production is a key defect in type 2 diabetes and a major contributor to the hyperglycemia that characterizes type 2 diabetes (2, 31, 36). Although not much is known regarding the effects of exercise on hepatic glucose production, there is considerable evidence that activation of adenosine monophosphate-activated protein kinase (AMPK) in the liver results in repression of phosphoenolpyruvate carboxykinase and glucose-6-phosphatase.
expression and thus of gluconeogenesis (3, 26, 32, 44). Hepatic AMPK is activated during exercise (6), which suggests the possibility that an AMPK-induced adaptive response to exercise could mediate an improvement in suppression of hepatic glucose production.

One purpose of the present study was to determine whether the improvement in peripheral insulin action induced by short-term exercise training in insulin-resistant patients with type 2 diabetes is due to enhanced insulin sensitivity, enhanced insulin responsiveness, or increases in both insulin sensitivity and responsiveness. Our second purpose was to reevaluate the effect of short-term training on the resistance of hepatic glucose production to suppression by insulin in patients with type 2 diabetes.

EXPERIMENTAL PROCEDURES

Participants. Potential participants were screened via a medical history questionnaire, an oral glucose tolerance test, an exercise stress test, and blood chemistry profiles. Volunteers were excluded if they demonstrated any contraindications to exercise as evidenced by resting or exercise-induced ECG abnormalities, if they displayed any thyroid, cardiovascular, or hematological disease, or if they were taking any medications known to affect metabolism. In addition, all individuals with diabetic glucose tolerance as assessed by oral glucose tolerance test were accepted into the study (fasting glucose concentration >100 mg/dl and a 2-h plasma glucose >200 mg/dl). Following these screening procedures, 14 overweight/obese, diabetic volunteers (11 men, 3 women, age 64 ± 2 yr, BMI 31.9 ± 2.2 kg/m²) were enrolled in a 7-day exercise training intervention. Participants had not been previously diagnosed with diabetes and were therefore not being treated with insulin or oral hypoglycemic agents. All participants had been weight stable for the preceding 6 mo, were previously sedentary, and had not participated in any systematic exercise training in the past. In addition, all female subjects were postmenopausal. The study was approved by the Institutional Review Board at the Washington University School of Medicine and all subjects provided signed written consent in accordance with the guidelines for the protection of human subjects.

Intervention. On 7 consecutive days, all volunteers performed 50–60 min of exercise consisting of treadmill walking and stationary cycling at 80–85% of their maximum heart rate (~67–75% of their maximal aerobic capacity). Participants wore heart rate monitors (Polar Electro, Woodbury, NY) during each training session to monitor their individualized target heart rate. Each training session incorporated a brief standardized warmup and cooldown and included a series of stretching exercises. Every session was supervised by an exercise physiologist, and therefore, compliance with the training was carefully documented.

Dietary control. Prior to the study, a 3-day outpatient control period was used to monitor adequate caloric intake using dietary intake questionnaires. Macronutrient composition (%calories) was ~50% carbohydrate, 35% fat, and 15% protein. During this control period, all volunteers underwent measurements of body composition, aerobic fitness, and insulin action, as described below. These tests were repeated at the end of the study. Metabolic measurements (insulin action) were performed in the morning following an overnight fast. Poststudy metabolic measurements were performed 18–20 h after the last exercise session. During the 7-day exercise intervention, dietary intake was monitored using diet records. The records were checked on a daily basis by one of the investigators who counseled volunteers to maintain their usual dietary habits throughout the study.

Body composition. Body mass and height were measured by standard techniques using a calibrated scale and stadiometer. Body density was determined by hydrostatic weighing, with correction for residual lung volume, and body fat mass was calculated using the equations of Brozek, as described previously (29).

Aerobic fitness. Each participant performed an incremental treadmill exercise test to determine their VO₂max as described previously (46). Due to the acute effects of exercise on insulin sensitivity, the preintervention VO₂max test was performed ≥4 days prior to other metabolic measurements. Blood pressure was monitored using a sphygmomanometer; resting and maximal heart rates were also recorded.

Insulin action. A hyperinsulinemic euglycemic clamp combined with a [3-3H]glucose infusion was used to measure basal and insulin-stimulated glucose metabolism, as reported previously (29). At 8:00 AM, following fasting blood sample collection, a 2-h primed (25 μCi bolus) continuous (0.25 μCi/min) infusion of [3-3H]glucose was initiated into an antecubital vein (baseline stage). At 10:00 AM, a primed continuous 40 mU·m⁻²·min⁻¹ infusion of insulin began. This proceeded for 2 h (40 mU stage), at which point (12:00 PM) the infusion rate was increased to 1,000 mU·m⁻²·min⁻¹ for an additional 2 h (1,000 mU stage). During the insulin infusion periods, 0.5 ml of arterialized blood was drawn from a retrograde dorsal hand line every 5 min, and plasma glucose concentrations were determined (Beckman Instruments, Fullerton, CA). A variable-rate glucose infusion (20% dextrose) was used to maintain euglycemia (90 mg/dl) according to the calculations of DeFronzo et al. (8). [3-3H]Glucose was added to the cold glucose to minimize underestimating glucose rates of appearance. A continuous infusion of potassium chloride was also maintained throughout to prevent insulin-induced hypokalemia. Additional blood samples were collected at baseline and every 15 min throughout the clamp for insulin determination (33). Samples were also collected immediately before the insulin infusion and at 10-min intervals during the last 30 min of each insulinemic stage for 3-H specific activity determinations. Radioactivity of plasma [3-3H]glucose was measured by liquid scintillation counting after plasma deproteinization with 3 M perchloric acid, as described previously (29). Glucose rates of appearance and disappearance were calculated according to the equations of Steele (47) modified for variable-rate glucose tracer infusions (13). We refer to the rate of glucose disappearance as glucose disposal rate (GDR). Endogenous glucose production, which is predominantly hepatic glucose production (HGP), was calculated by subtracting the rate of glucose appearance from the glucose infusion rate. GDR and HGP are reported as the mean rates calculated during the final 30 min of each stage: baseline, 40 mU, and 1,000 mU. Postintervention clamps were begun within 24 h following the final exercise session.

Statistics. All data are presented as means ± SE. Intervention effects on insulin sensitivity and substrate metabolism at the two hyperinsulinemic infusion rates were assessed using two-way (insulin step × time) repeated measures ANOVA. Bonferroni post hoc tests were applied to significant F ratios where appropriate. Body composition and aerobic fitness were analyzed using paired Student’s t-tests. Due to technical problems, glucose kinetics analyses were not possible on two of the 14 volunteers. Statistical significance was accepted when P < 0.05. Analyses were carried out using StatView for Windows 5.0.1 (SAS Institute).

RESULTS

The participants exercised at 81 ± 2% of their maximum heart rate (~68% of their VO₂max) (48) for the 7 training days. As shown in Table 1, there were no significant changes in body weight, percent body fat, or VO₂max in response to 1 wk of training.

Insulin action. There was a decreasing trend in fasting plasma glucose concentration (P = 0.08) despite a significant decrease in fasting plasma insulin concentrations (P = 0.02) in response to the training. The steady-state plasma insulin con-
centrations attained during the 40 mU·m⁻²·min⁻¹ infusion stage of the euglycemic clamp was 70 ± 5 μU/ml before and 62 ± 5 μU/ml after the exercise program, whereas the steady-state plasma insulin levels attained during the 1,000 mU·m⁻²·min⁻¹ phase of the clamp averaged 5,959 ± 69.1 μU/ml before and 5,617 ± 30.0 μU/ml after training. Plasma glucose concentration was maintained at 89 ± 1 and 90 ± 0.6 mg/dl before and at 90 ± 0.8 and 90 ± 0.5 mg/dl after training during the 40 and 1,000 mU·m⁻²·min⁻¹ insulin infusion rates, respectively. In response to the 7 days of exercise, GDR increased from 1.84 ± 0.32 to 2.67 ± 0.37 mg·kg⁻¹·min⁻¹ during the 40-mU stage (P < 0.0001; Fig. 1) and from 7.57 ± 0.61 to 8.84 ± 0.56 mg·kg⁻¹·min⁻¹ during the 1,000-mU stage (P = 0.008; Fig. 1).

Basal HGP was lower following 7 days of exercise: 3.17 ± 0.43 vs. 2.54 ± 0.26 mg·kg⁻¹·min⁻¹ (P = 0.05; Fig. 2). HGP during the 40-mU insulin stage was also decreased following exercise: 1.15 ± 0.41 vs. 0.46 ± 0.20 mg·kg⁻¹·min⁻¹ (P = 0.03; Fig. 2). Compared with basal, the exercise program resulted in greater suppression of HGP during the 40-mU stage (−69.1 ± 9.1 vs. −84.5 ± 4.3%; P = 0.05). HGP was completely suppressed during the 1,000-mU stage both before and after the exercise program (Fig. 2). These findings provide evidence for an increased insulin suppression of HGP after the 7 days of exercise training.

### DISCUSSION

The results of this study show that 7 days of vigorous exercise training that did not result in weight loss induced increases in both insulin sensitivity and responsiveness of glucose disposal. Previous studies on healthy young humans and on laboratory rodents have shown that exercise can result in increases in insulin sensitivity and responsiveness (9, 18). Numerous studies have also shown that exercise training can improve insulin action on peripheral glucose disposal in patients with type 2 diabetes and obese insulin-resistant individuals with impaired glucose tolerance (4, 11, 12, 34, 46, 51). However, in these studies, this improvement was referred to as an increase in insulin sensitivity, and insulin responsiveness was not evaluated. Our results show that an increase in insulin responsiveness is also a major contributor to the improvement in insulin action induced by short-term exercise training in patients with type 2 diabetes.

Most of the glucose removed from blood in response to insulin is taken up by skeletal muscle, so it seems reasonable to assume that the improvements in insulin sensitivity and responsiveness that occurred in this study were due to exercise-induced adaptations in muscle. It is well documented that exercise training induces increased expression of the GLUT4 isoform of the glucose transporter in muscle of humans and laboratory rodents (10, 15, 19, 21, 22, 34). Studies on rodent skeletal muscle have shown that this adaptive increase in GLUT4 results in a proportional increase in the number of GLUT4 glucose transporters that are translocated to the cell surface in response to a given insulin stimulus (38). This appears to be the mechanism by which exercise results in an increase in insulin responsiveness. Exercise also induces an increase in muscle insulin sensitivity (19). It has been shown...
that the same submaximal insulin stimulus results in translocation of more GLUT4 to the cell surface in muscle following exercise than in the absence of exercise (16). The mechanisms underlying the increase in muscle insulin sensitivity have not been established, but some evidence suggests that it may be mediated by enhanced insulin signaling (14, 20, 28).

The average rate of glucose disposal during the 40 mU·m⁻²·min⁻¹ insulin infusion was 1.84 mg·kg⁻¹·min⁻¹ before training, which is 24% of that attained during the maximal insulin stimulus, which averaged 7.57 ± 0.61 mg·kg⁻¹·min⁻¹. After training, the rate of glucose disposal during the 40 mU·m⁻²·min⁻¹ insulin infusion rate averaged 2.67 mg·kg⁻¹·min⁻¹, which is 30% of that attained during the maximal insulin stimulus, which averaged 8.84 ± 0.56 mg·kg⁻¹·min⁻¹. Thus, whereas the actual rate of glucose disposal during the 40 mU·m⁻²·min⁻¹ glucose disposal rate was 45% higher after training, the rate of glucose disposal expressed relative to the maximal rate was 25% higher. Evaluation of the dose-response curve. So, the increase in insulin responsiveness as a result of the 7-day exercise program.

An important point regarding the improvements in insulin sensitivity and responsiveness induced by exercise is that they are short-term effects that wear off in 3–4 days (9, 27, 45). That these short-lived effects might also be related to transient exercise-induced changes in skeletal muscle mitochondrial function has been suggested by Kacerovsky-Bielsz et al. (24). Therefore, frequent exercise is needed to maintain the beneficial effects of exercise. Furthermore, even rather vigorous training that does not result in negative energy balance and fat loss improves but does not normalize insulin action or glucose tolerance (4, 7, 22, 35). The obesity/insulin resistance-mediated form of type 2 diabetes is a completely reversible disease in its early stage, before there is severe pancreatic β-cell damage that causes insulin deficiency. The best evidence for this statement is the rapid reversal of insulin resistance and diabetes in patients who have undergone gastric bypass surgery (5, 43). Therefore, it would be interesting in future studies to determine whether long-term exercise training that induces a significant negative energy balance can reverse type 2 diabetes. This would require a study design in which calorie intake is not increased to compensate for the increase in energy expenditure. To our knowledge, there have been no such studies on patients with type 2 diabetes. However, a number of studies on nondiabetic middle-aged people have shown that this approach is feasible and, in addition to improving insulin action, can bring about large decreases in visceral and total abdominal fat (35, 37, 40, 41, 50).

Hepatic insulin resistance resulting in increased glucose production is a key defect in type 2 diabetes and is an important factor contributing to development and maintenance of hyperglycemia (2, 31, 36). AMPK inhibits gluconeogenesis by suppressing expression of the key gluconeogenic enzymes phosphoenolpyruvate carboxykinase and glucose-6-phosphatase (3, 26, 44). Exercise results in activation of AMPK in the liver (6) and should, therefore, induce an adaptive response that results in decreased HGP. Therefore, we reevaluated the effect of short-term exercise training on insulin suppression of HGP. We found that HGP in the basal state and at a plasma insulin concentration of ~60–70 µU/ml was significantly reduced after 7 days of exercise. Thus, it appears that a reduction in HGP may contribute to the beneficial effect of exercise training on glucose homeostasis in type 2 diabetes. Although the precise mechanism explaining exercise-induced changes in hepatic insulin sensitivity is largely unknown, recent work suggests that liver lipid partitioning may play a role. Hepatic lipid content and insulin suppression of HGP are related (42).

In conclusion, the results of this study show that vigorous exercise training for only 7 days results in significant improvements in insulin action in insulin-resistant patients with type 2 diabetes. These improvements in insulin action involve enhanced sensitivity and responsiveness of peripheral glucose uptake, presumably by muscle, to insulin as well as an increased inhibition of HGP by insulin.

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