Improvement in Glucose Tolerance After 1 Wk of Exercise in Patients With Mild NIDDM

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We investigated the effects of 1 wk of intense exercise on glucose tolerance in 10 men with abnormal glucose tolerance [7 had mild non-insulin-dependent diabetes mellitus (NIDDM), and 3 had impaired glucose tolerance]. The 7 days of exercise did not result in significant changes in body weight or maximal oxygen uptake. Plasma glucose concentration at 120 min averaged 227 ± 23 mg/dl in an oral glucose tolerance test (OGTT) before and 170 ± 18 mg/dl after the 7 days of exercise ($P < .001$). There was a 36% reduction in the area under the glucose tolerance curve. Plasma insulin concentration at 120 min of the OGTT averaged 172 ± 27 μU/ml before and 106 ± 13 μU/ml after 7 days of exercise ($P < .001$); the area under the insulin curve was decreased by 32%. In contrast to the response to 7 days of exercise, one bout of exercise did not result in an improvement in glucose tolerance. These results provide evidence that regularly performed, vigorous exercise can be effective in decreasing insulin resistance and improving glucose tolerance within 7 days in some patients with mild NIDDM. ***Diabetes Care*** **11:613–18, 1988**

Exercise training results in a blunted insulin response to oral or intravenous glucose (1–6). Despite the lower plasma insulin concentrations, glucose tolerance is unchanged or improved by exercise training (1–6). Studies with the euglycemic-clamp procedure have shown that at physiologic insulin concentrations, the rate of glucose disposal is increased in trained people (7–9) as the result of an increase in insulin sensitivity (9). The evidence that exercise training reduces resistance to the action of insulin has generated interest in the possibility that exercise may be useful in the treatment of mild non-insulin-dependent diabetes mellitus (NIDDM; 10). The results of several studies of exercise training in NIDDM have been discouraging; improvements in glucose tolerance did not occur or were small (11–15). Furthermore, in a recent NIH Consensus Development Conference it was stated that the effects of regular physical exercise alone on metabolic control is of small magnitude and that the possible benefits of body-fat reduction outweigh putative effects of exercise per se (16).

In a recent study, we found that 12 mo of vigorous exercise training normalized glucose tolerance in a small group of men with mild NIDDM (17). In that study, glucose tolerance was measured within 18 h of the patients' last bout of exercise. In trained people with normal glucose tolerance, the enhanced action of insulin is lost within a few days after exercise training is stopped (4,5,8). In this context, it seems that the decreased insulin resistance and improved glucose tolerance seen in patients with NIDDM in response to prolonged training may have been partly due to persistent short-term effects of the last bouts of exercise (as opposed to long-term adaptations to training; 17). This possibility provided the rationale for this study in which we investigated the effects of 1 wk of intense exercise training on glucose tolerance in patients with mild NIDDM. The study design enabled us to evaluate the effects of exercise in the absence of a significant decrease in body fat.

MATERIALS AND METHODS

Subjects. Ten men aged 53 ± 3 yr with abnormal glucose tolerance gave written consent to participate in the

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TABLE 1
Height, weight, estimated percent body fat, and $\dot{V}O_{2\,max}$

	Initial	After 7 days of exercise
Height (cm)	179 ± 2	
Weight (kg)	97.0 ± 3.6	96.4 ± 3.2
Estimated percent body fat	24.8 ± 1.2	24.8 ± 1.1
$\dot{V}O_{2\,max}$ (ml · kg^{-1} · min^{-1})	25.9 ± 1.0	26.9 ± 1.2
Systolic blood pressure (mmHg)	136 ± 4	134 ± 4
Diastolic blood pressure (mmHg)	93 ± 4	84 ± 3*

Values are means ± SE for 10 subjects.
*$P < .05$ vs. initial value.

study, which was approved by the Washington University Human Studies Committee. Seven men had mild NIDDM; the other three had impaired glucose tolerance (18). Descriptive information on the subjects is provided in Table 1. They were recruited from individuals found to have moderately elevated fasting and/or 2-h postprandial glucose levels in a screening program conducted by the St. Louis Chapter of the Missouri Affiliate of ADA. None of the men were taking oral hypoglycemic agents or other medications known to affect glucose tolerance.

Study design. An oral glucose tolerance test (OGTT) was performed after a 12-h overnight fast. The subjects were instructed to follow their usual diet during the study and, specifically, not to decrease their food intake. They kept detailed records of their food intake. The food records were reviewed by a registered dietitian and analyzed with a computer program obtained from the Nutrition Coding Center of the National Heart, Lung and Blood Institute (19).

After the initial OGTT, the subjects underwent a physical examination and a maximal treadmill exercise test according to the protocol of Bruce and Hornsten (20) with ECG monitoring and measurement of oxygen uptake ($\dot{V}O_2$). Individuals with evidence of ischemic heart disease or other disease processes that would interfere with, or are contraindications for, exercise were excluded from the study. The subjects exercised for 50–60 min/day for 7 consecutive days as described below. A second OGTT was administered in the morning on the 8th day of the study, 16–20 h after the last bout of exercise, and 12 h after the subject's last meal. On the 9th day of the study the maximal treadmill exercise test was repeated. Six to 12 mo after the study of the effects of 7 days of exercise, three of the men with mild NIDDM and two with impaired glucose tolerance, who had been sedentary for the preceding 6 mo or more, were studied again to evaluate the effect of one bout of exercise. An OGTT was performed when the subjects were sedentary, and a second OGTT was performed 16–20 h after one 50- to 60-min bout of exercise in the laboratory and 12 h after their last meal.

Procedures. OGTTs (100 g) were performed after a 12-h overnight fast. A catheter was placed in an antecubital vein, and blood samples were obtained before and 30, 60, 120, and 180 min after glucose ingestion. The blood was placed in heparinized tubes and kept on ice. Plasma was separated by centrifugation at 4°C and stored at −20°C until analysis. Plasma glucose concentrations were determined by the glucose oxidase method (YSI glucose analyzer; Yellow Springs, OH). Plasma insulin was determined by radioimmunoassay (21). The insulin assays on plasma samples from the first and second OGTTs were performed at the same time. An additional 10 ml of blood was drawn before the OGTTs, placed in tubes containing EDTA, and used for the determination of plasma lipid and lipoprotein concentrations according to standard procedures established by the Lipid Research Clinics (22).

Maximal oxygen uptake ($\dot{V}O_{2\,max}$) was determined during a treadmill exercise test (23). Expired air was collected and analyzed as previously described (23). Skin-fold thickness measurements were made with a Lange caliper at six sites, and the sum was used to estimate percent body fat (24).

Exercise program. For the first 3 days the subjects exercised in the laboratory. On the 4th day they walked for 60 min without supervision at an exercise intensity that elicited ~60% of their maximal heart rate. The subjects returned to the laboratory for the last three exercise sessions. During the sessions in the laboratory the subjects trained for 50–60 min at an exercise intensity requiring 68 ± 1% of $\dot{V}O_{2\,max}$. The subjects exercised for 30 min on a treadmill, rested for 10 min, and then cycled on an ergometer for an additional 20–30 min. The same exercise protocol was used in the study of the effect of one bout of exercise. During exercise the ECG was monitored continuously, and $\dot{V}O_2$ and blood pressure were measured at 10-min intervals.

Statistics. The total area under the glucose and insulin curves was determined by computer analysis with a trapezoidal model that summated only the areas above the fasting baseline level. Plasma glucose and insulin responses during the OGTT before and after 7 days of exercise were analyzed via a two-way analysis of variance with repeated measures. The Newman-Keuls test was used to make multiple comparisons when appropriate. Incremental areas for glucose and insulin were analyzed with dependent *t* tests. The data are presented as means ± SE.

RESULTS

During the six exercise sessions performed in the laboratory, $\dot{V}O_2$ averaged 1.77 ± 0.10 L/min. This required 68 ± 1% of the subjects' $\dot{V}O_{2\,max}$ and resulted in an expenditure of 470 ± 22 kcal per exercise session. During the one unsupervised bout of exercise, the subjects walked for 60 min at a pace that elicited ~60% of maximal heart rate and resulted in an energy expenditure of ~400 kcal.

Calorie intake estimated from the subjects' food records averaged 2217 ± 360 kcal/day before the first

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OGTT and 2168 ± 211 kcal/day before the second OGTT, providing evidence that there was no major change in food intake. These calorie intakes appear to be low for these large men and may reflect underreporting of food intake. However, the finding that body weight decreased only 0.6 kg supports the conclusion that there was no major change in calorie intake (Table 1). Although not statistically significant, this weight loss seems reasonable relative to the increase in calorie expenditure caused by the exercise. Carbohydrate intake, estimated from the diet records, averaged 229 ± 35 g before the first OGTT and 225 ± 17 g before the second OGTT.

The seven bouts of exercise did not result in a significant increase in $\dot{V}O_{2\,max}$ (Table 1). Percent body fat, estimated from the skin-fold thickness measurements at six sites, was unchanged by the 7 days of exercise.

As shown in Fig. 1, which includes the data on all 10 subjects, glucose tolerance was considerably improved after 7 days of exercise. Plasma glucose concentration at 120 min averaged 227 ± 23 and 170 ± 18 mg/dl, respectively, in the OGTT before and after 7 days of exercise. The area under the glucose tolerance curve decreased 36% from 14,918 ± 1561 to 9526 ± 1029 mg/dl ($P < .001$) as a result of the 7 days of exercise. As shown in Fig. 2, average plasma insulin concentrations during the OGTTs were significantly lower after 7 days of exercise. The plasma insulin concentration at 120 min averaged 172 ± 27 and 106 ± 13 μU/ml before and after 7 days of exercise, respectively ($P < .001$); the shape of the insulin curve was also altered, with the peak occurring at 60 min instead of 120 min after 7 days of exercise (Fig. 2). The area under the insulin curve decreased 32% from 17,780 ± 2658 before to 12,094 ± 1554 μU/ml after 7 days of exercise ($P < .001$).

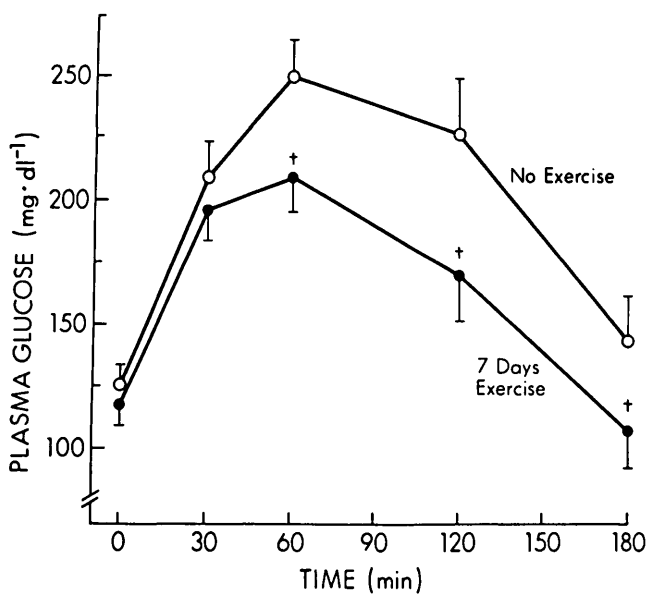

FIG. 1. Effect of 7 days of exercise on plasma glucose response to 100-g oral glucose tolerance test (OGTT) in 10 men with abnormal glucose tolerance. OGTT after 7 days of exercise was performed 18 h after last exercise bout. Values are means ± SE for 10 subjects. †$P < .001$.

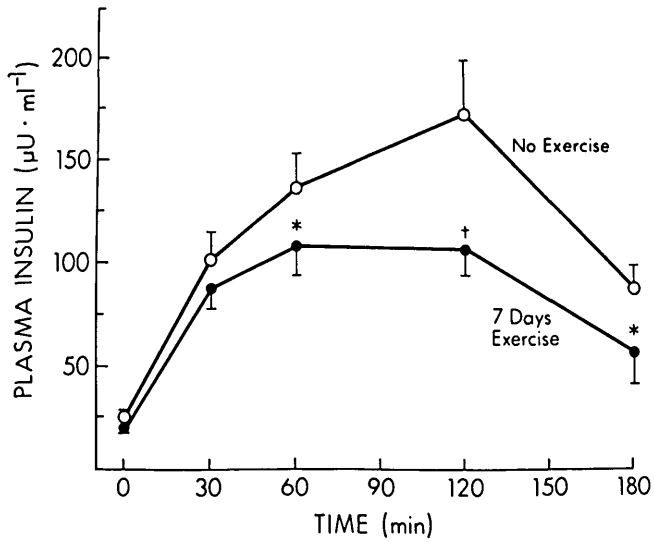

FIG. 2. Effect of 7 days of exercise on plasma insulin response to 100-g oral glucose tolerance test. Values are means ± SE for 10 subjects. *$P < .05$, †$P < .001$.

Of the three men with impaired glucose tolerance, two had normal OGTTs after 7 days of exercise. Of the seven men with NIDDM, three had normal OGTTs, two had impaired glucose tolerance, and two still had diabetic OGTTs after 7 days of training. The two diabetic men who did not show significant improvement in their OGTTs had relative hypoinsulinemia; the glucose and insulin levels obtained on these two patients are shown in Fig. 3 (their data are also included in the averages in Figs. 1 and 2). The other eight patients who all improved their OGTT had mild or moderate hyperinsulinemia initially.

As shown in Table 2, plasma triglyceride concentration decreased 32% in response to the 7 days of exercise. This finding of a rapid decrease in plasma triglyceride concentration in response to exercise training corresponds with the results of previous studies (25–27). Total plasma cholesterol concentration decreased slightly. However, there were no significant changes in high-density lipoprotein cholesterol or low-density lipoprotein cholesterol concentrations. The three patients, two with NIDDM and one with impaired glucose tolerance, who did not have hypertriglyceridemia (average preexercise value 142 ± 5 mg/dl) showed as great an improvement in glucose tolerance in response to the exercise as did those with hypertriglyceridemia (the area under the glucose tolerance curve for the 3 patients who did not have hypertriglyceridemia averaged 14,485 ± 1427 and 8763 ± 495 mg/dl before and after 7 days of exercise, respectively; $P < .02$).

Glucose tolerance was also measured in the morning on the day after one bout of supervised exercise, of the

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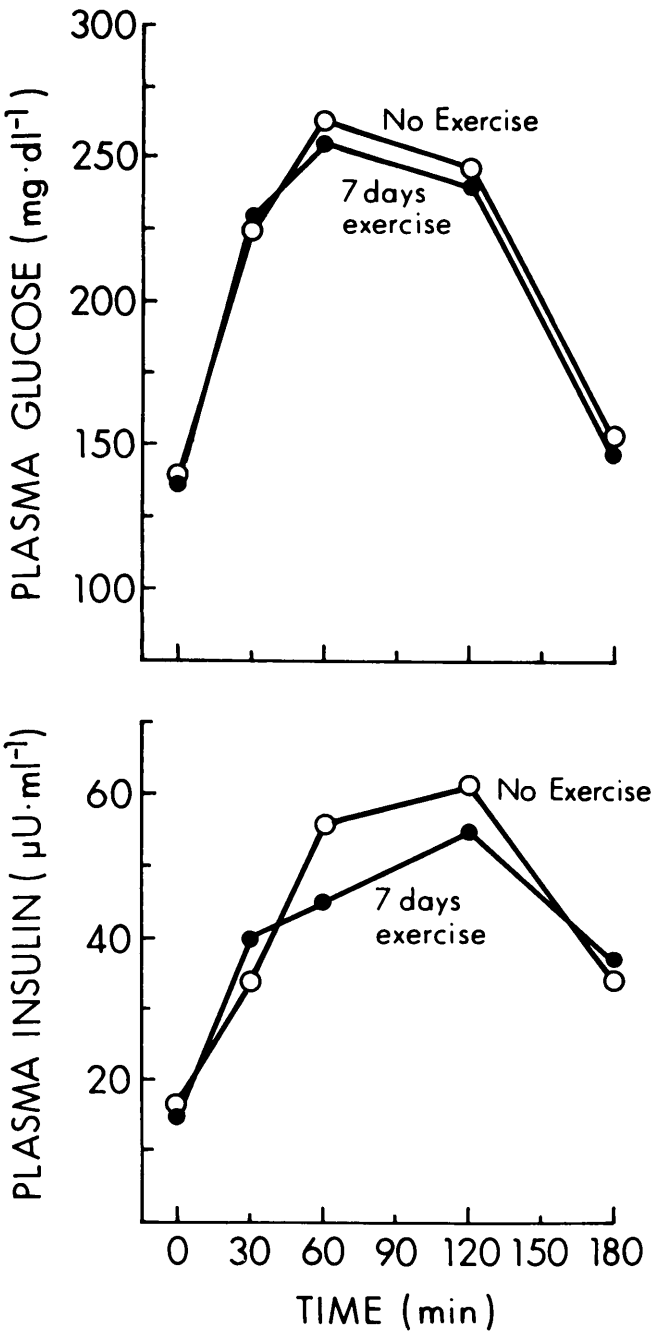

FIG. 3. Effect of 7 days of exercise on plasma glucose and insulin responses to 100-g oral glucose tolerance test in 2 patients with relative hypoinsulinemia.

same duration and intensity as in the 7-day exercise study, in three of the patients with NIDDM and two with impaired glucose tolerance. This group did not include the hypoinsulinemic patients. As shown in Fig. 4, there was no significant improvement in glucose tolerance in response to one bout of exercise. Plasma insulin concentrations during the OGTT were slightly lower after one bout of exercise (Fig. 4). This difference was not statistically significant.

DISCUSSION

The results of this study show that regularly performed vigorous exercise can result in a significant improvement in glucose tolerance within a short time in some patients with mild NIDDM. This improvement occurred despite a significantly smaller increase in plasma insulin levels in response to the OGTT performed after, compared with before, the 7 days of exercise. It appears from this finding that the improvement in glucose tolerance was due to a decrease in resistance to insulin, i.e., to a greater susceptibility to the action of insulin. The duration of the exercise program was too short to result in significant changes in body weight or in body-fat content as reflected in skinfold thickness measurements. There were also no major cardiovascular adaptations as reflected in an increase in $\dot{V}O_{2\,max}$. Thus, it appears that the improvement in glucose tolerance was a consequence of persistent but short-term effects of the last bouts of exercise rather than of long-term adaptations to training. This interpretation is supported by the results of studies on young, healthy trained individuals showing that the increased insulin action found in people who exercise regularly is lost within a few days after exercise is stopped (4,5,8).

In a previous study we found that 12 mo of vigorous exercise training resulted in normalization of glucose tolerance in a small group of patients with mild NIDDM; a similar improvement was seen in a group of patients with impaired glucose tolerance (17). As in this study, the OGTTs were performed ~18 h after the subjects' last bout of exercise, making it likely that the decrease in insulin resistance may also have been partly due to persistent effects of the last bouts of exercise. Additional studies are needed to determine the relative contributions of persistent effects of the last bouts of exercise and of more long-term adaptations, such as a decrease in adiposity, to the improvements in insulin resistance and glucose tolerance induced by prolonged training in patients with mild NIDDM.

With one exception (28), other studies of the effects of exercise training in patients with NIDDM have shown only small improvements in glucose tolerance (11–15). Interestingly, in several studies, despite little or no improvement in glucose tolerance, there was a significant

TABLE 2
Plasma lipid and lipoprotein concentrations

	Total cholesterol	LDL cholesterol	HDL cholesterol	Triglycerides
Initial	214 ± 13	137 ± 11	36 ± 2	305 ± 98
After 7 days of exercise	204 ± 13*	135 ± 11	37 ± 3	208 ± 51*

Values are means ± SE. LDL, low-density lipoprotein; HDL, high-density lipoprotein.
*$P < .05$ vs. initial value.

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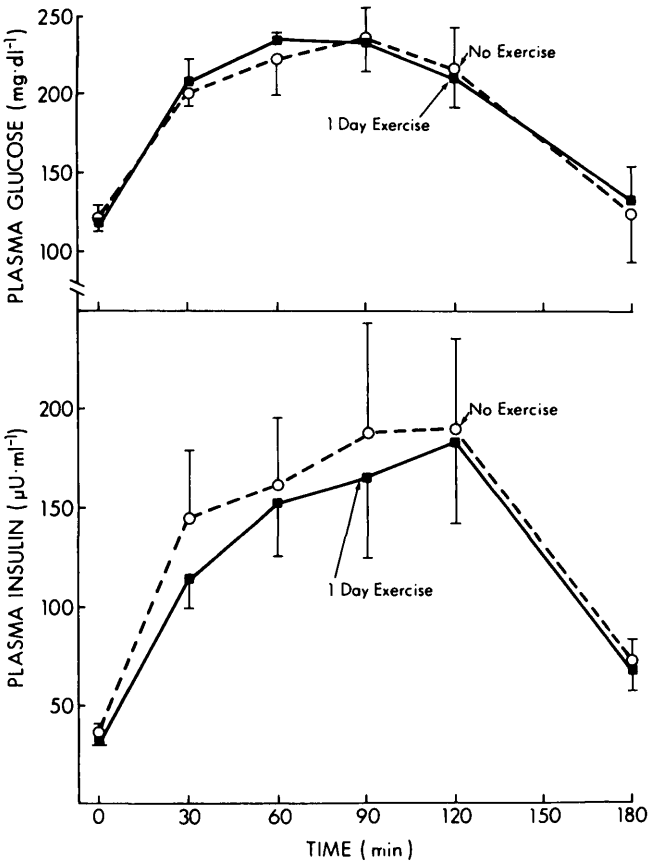

FIG. 4. Effect of 1 bout of exercise on plasma glucose and insulin responses to 100-g oral glucose tolerance test (OGTT) in 5 men with abnormal glucose tolerance. Post-exercise OGTT was performed 18 h after exercise bout. Values are means ± SE.

improvement in insulin action as reflected in an increased rate of glucose disposal during a hyperinsulinemic-euglycemic clamp (12,14,15). That exercise can improve glucose disposal during a hyperinsulinemic clamp without an improvement in glucose tolerance may, perhaps, be explained by an increase in insulin sensitivity being counterbalanced by a decrease in insulin secretion. The finding of an increase in insulin sensitivity without an improvement in glucose tolerance provided the rationale for our use of the OGTT instead of the hyperinsulinemic-euglycemic clamp to evaluate the effectiveness of exercise in the treatment of NIDDM in this study.

There are several differences between our studies and those in which there was little improvement in glucose tolerance. One difference is that the patients in some previous studies were more severely diabetic and had fairly marked insulin deficiency (12,13,15). It is interesting in this context that the two patients in our study whose glucose tolerance did not improve in response to the exercise had a relative insulin deficiency. It appears from these results that exercise training can decrease resistance to the action of insulin but cannot substitute for the action of insulin in patients with inadequate insulin secretion (12,13,15; Fig. 3).

A second difference is that in several previous studies, glucose tolerance was measured 4–7 days after the last bout of exercise to allow the acute effects of the last bout of exercise to wear off (11,13,14), whereas we studied our patients ~18 h after exercise. The one other study in which exercise training resulted in a major improvement in glucose tolerance was performed by Reitman et al. (28) on a group of young obese southwestern American Indians with NIDDM. It is of interest that in their study the OGTT was performed ~36 h after the last exercise bout (28). A third difference is that we used a considerably greater exercise stimulus than was used in most of the other studies.

In studies on obese insulin-resistant men and in patients with NIDDM, Devlin and Horton (29) and Devlin et al. (30) have shown that one bout of exercise can significantly increase peripheral insulin sensitivity as reflected in an increased rate of glucose disposal during a euglycemic-hyperinsulinemic clamp 12 h after exercise. In this study, one bout of exercise did not result in an improvement in oral glucose tolerance 18 h after exercise. The difference between our results and those of Devlin and associates (29,30) could be due to counterbalancing of an increase in peripheral insulin sensitivity (which would be evident during a hyperinsulinemic clamp) by somewhat lower insulin levels during the OGTT after exercise in our study. Another possible factor could be that the more strenuous exercise to exhaustion (~85% of $\dot{V}O_{2\,max}$) used by Devlin et al. (29,30) may have had a greater effect than that used in our study (68% of $\dot{V}O_{2\,max}$).

Despite a much greater reduction in the insulin response to an OGTT after 7 days (Fig. 2) than after 1 day (Fig. 4) of exercise, the cumulative effects of the 7 days of exercise apparently caused sufficient enhancement of peripheral insulin action to more than compensate for the lower insulin levels, resulting in a significant improvement in glucose tolerance (Fig. 1). In conclusion, the results provide evidence that regularly performed vigorous exercise can be effective in increasing peripheral insulin action sufficiently to improve glucose tolerance within 7 days in some patients with mild NIDDM. This suggests that the improvement in glucose tolerance that occurred in the patients with NIDDM in response to 12 mo of exercise training in our previous study may have been due partly to the effects of the last bouts of exercise rather than to long-term effects of exercise training (17).

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