Effects of Exercise Training on Insulin Sensitivity in Adolescents with Type I Diabetes

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We investigated the influence of a program of exercise training consisting of three weekly sessions, each 45 min long, for 12 wk, on indices of physical fitness, glycemic control, and insulin sensitivity in nine adolescents with type I diabetes; six age-matched adolescents with diabetes of equivalent duration served as nonexercised controls. All subjects were instructed not to change daily insulin dose or caloric intake. In the exercised group, maximal oxygen uptake during graded cycle ergometry to volitional exhaustion increased by 9 ± 2.7% (P < 0.01) and lean body mass increased by 4 ± 1.8% (P < 0.05). Insulin sensitivity, assessed via the euglycemic clamp technique at insulin infusion rates of 100 mU/M^2/min, showed an increase of insulin-mediated glucose disposal from 274 ± 33 to 338 ± 28 mg/M^2/min, representing an increase in insulin sensitivity of 23 ± 5% (P < 0.01). None of these indices changed in the control group. Despite increased insulin sensitivity, glycohemoglobin levels remained at 12 ± 1% before and after the 12 wk of exercise training, indicating no improvement in overall glycemic control. No increase in hypoglycemic reactions was reported in either group. We conclude that exercise training may be a valuable adjunct in managing type I diabetes providing there is concomitant attention to diet and insulin. Exercise training alone, however, does not improve glycemic control, although it improves physical fitness and insulin sensitivity. DIABETES CARE 1985; 8:461-65.

The foundations of routine treatment for insulin-dependent (type I) diabetes rest on three pillars: the provision of insulin, attention to diet, and exercise. Although a central role for exercise in the management of diabetes has been advocated for over 50 yr, the precise influence of acute and chronic exercise on metabolic events and the mechanisms by which these effects are mediated remain the subject of ongoing research. In normal people, during acute exercise of moderate duration, blood glucose remains constant as a result of hormonal adaptations that insure increased hepatic glucose production to match precisely the increased glucose utilization rate of exercising muscle. In insulin-treated diabetic subjects, however, acute exercise may predispose to hypoglycemia due to more rapid absorption of injected insulin, which results in insulin concentrations that restrain hepatic glucose production and prevent its matching the increase of glucose utilization. Alternatively, diabetic subjects in already poor metabolic control may be precipitated into ketoacidosis during acute exercise if they lack sufficient insulin to blunt the metabolic effects of glucagon, cortisol, growth hormone, and catecholamines, all of which rise during acute exercise. Nevertheless, acute exercise and exercise training are advocated for individuals with diabetes. Since exercise training in normal subjects increases sensitivity to endogenous and exogenous insulin and is correlated to maximal aerobic power and body composition, it is believed that exercise training will facilitate metabolic control in diabetic subjects. The extent of any potential benefits of exercise training in adolescents with type I diabetes has not been extensively investigated. The present study was therefore undertaken to quantify the effects of a program of regular exercise training on insulin sensitivity, as well as indices of physical fitness and metabolic control in adolescents with type I diabetes.

SUBJECTS

The study protocol was reviewed and approved by the Institutional Review Board on Human Investigations. The participants in the study were adolescents with insulin-dependent diabetes mellitus recruited from among patients regularly attending the Diabetes Clinic at Children’s Hospital Medical
TABLE 1
Characteristics of study population

<table>
<thead>
<tr>
<th></th>
<th>Exercise group (N = 9)</th>
<th>Control group (N = 6)</th>
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<tbody>
<tr>
<td>Age (yr)</td>
<td>16.1 ± 0.8</td>
<td>15.9 ± 0.3</td>
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<tr>
<td>Wt (kg)</td>
<td>61.9 ± 3.2</td>
<td>63.6 ± 2.8</td>
</tr>
<tr>
<td>Women/men</td>
<td>6/3</td>
<td>2/4</td>
</tr>
<tr>
<td>Duration of diabetes (yr)</td>
<td>6.7 ± 1.1</td>
<td>7.7 ± 1.5</td>
</tr>
<tr>
<td>Daily insulin dose (U/kg)</td>
<td>1.11 ± 0.1</td>
<td>0.98 ± 0.1</td>
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Center in Cincinnati. Each patient had known disease of >1 yr duration and an insulin requirement of =1 U/kg/day (Table 1). Each subject was randomly assigned to a study or control group after presenting informed consent from himself as well as from the legal guardian.

STUDY PROTOCOL

Assessment of metabolic control, insulin sensitivity, dietary intake, physical fitness, and lean body mass was performed on each subject on two occasions separated by 12 wk, during which time subjects in the study group underwent supervised exercise training while subjects in the control group were instructed not to change their usual routines. Each subject was admitted to the Clinical Research Center (CRC) on the evening before each set of studies. To establish relative uniformity of blood glucose concentration at the time of determining insulin sensitivity,14 patients were fasted overnight (12 h) and blood glucose stabilized between 100 and 150 mg/dl by overnight infusion of i.v. insulin that was periodically adjusted according to blood glucose concentrations. At 08:00 a.m. on the morning of the study, fasting blood was obtained for measurement of glycohemoglobin (HbA1c), followed by determination of insulin sensitivity by the hyperinsulinemic-euglycemic clamp technique.15 All studies were repeated in the exercised and nonexercised (control) group at the end of 12 wk.

PROCEDURES

Euglycemic clamp. At the beginning of the clamp study, a continuous infusion of regular insulin was instituted at a rate of 100 mU/M²/min. This dose was found to be necessary to saturate the serum anti-insulin antibodies and obtain free insulin levels that inhibit hepatic glucose production. Blood glucose measurements were made at the bedside at 10-min intervals throughout the study. After blood glucose had fallen to =100 mg/dl, the variable glucose infusion was begun and adjusted to maintain glucose levels between 85 and 90 mg/dl. The adjustment in glucose infusion rate was directed by the algorithm15 programmed into a hand-held calculator such that the required glucose infusion rate in milligram per minute was converted to milliliter per minute using 10% dextrose in water. Once clamping was achieved, steady state was maintained for an additional 90 min before insulin infusion was discontinued. The variable glucose infusion rate necessary to maintain euglycemia was then gradually discontinued, decreasing in a stepwise manner over 60–90 min.

Maximal oxygen uptake. Maximal oxygen uptake (VO2 max) was measured during graded exercise to volitional exhaustion using a bicycle ergometer in the Cardiovascular Exercise Physiology Laboratory.16 Oxygen uptake was calculated from an analysis of O2 and CO2 in the expired breath with a mass spectrometer. VO2 max is the level at which the oxygen uptake fails to increase with continued increases in work.

Lean body mass. Lean body mass was determined by the hydrostatic weighing technique17 with correction for residual lung volume;18 percent body fat was computed by the Siri equation.19

Dietary intake. Each subject completed a 7-day dietary record during the week before admission to the CRC. While in the CRC, a trained nutritionist met with each subject to review the diet record and clarify information necessary for data coding. Food models were used to estimate quantities and types of foods consumed. Of the 7 days recorded, 3 days (one weekend and one weekday) were coded and subsequently computer analyzed for total calories.

Exercise training. The 12 wk of supervised exercise training consisted of three sessions per week, each lasting 45 min. In each session, performed between 1600 and 1700 h, there was a 10-min period of calisthenic warm-up, followed by 25 min of aerobic movement to music so that the pulse was maintained at ≥160 bpm; the pulse rate was measured by palpation at 5-min intervals. Finally, there was a 10-min period of cool-down. The training level of 160 bpm in heart rate represents 80–85% of maximum heart rate achieved during the baseline exercise tests. This level is known to produce improvement in cardiovascular fitness.20 To avoid hypoglycemia during and after acute exercise, subjects were instructed to consume 15–30 g carbohydrate 1 h before exercise. At the conclusion of each exercise session, 180 ml fruit juice (60–90 kcal; ≥20 g carbohydrate) was provided for each participant.

At the end of 12 wk and 48–72 h after the last acute exercise in the exercised group, all studies were repeated in the CRC. The control group was instructed not to change their usual routine, with respect to exercise and all studies were repeated 12 wk after the initial series. In both the exercised and control groups, no attempts were made to adjust daily prescribed insulin dose or dietary intake. All subjects were asked to maintain a log of hypoglycemic reactions and report severe reactions to the physician.

Laboratory methods. Whole blood glucose was measured immediately by the glucose oxidase method using a Yellow Springs Instrument Glucose Analyzer (Yellow Springs Instruments, Yellow Springs, Ohio). HbA1c determinations were performed by cation exchange chromatography as previously reported from this laboratory.21 Because insulin-treated diabetic subjects have variable degrees of insulin binding by endogenous anti-insulin antibodies, we measured free serum insulin levels during the clamp procedure in each patient. Free insulin was measured by radioimmunoassay after removal of antibody and antibody-bound insulin by polyethylene glycol precipitation.22 To reduce the potential influence of interassay vari-
ability (10–15%) in comparing insulin levels before and after the 12-wk period, two separate assays were performed, each incorporating all before and after samples from each group.

Statistical methods. The Student paired and unpaired t-tests were used to determine, respectively, statistical differences within each group before and after the 12 wk and between groups. Group differences were confirmed by analysis of covariance, with the baseline value of the dependent variable as covariate. Linear correlation coefficients were determined by the least-squares method. All data in the text and tables are shown as mean ± SEM.

RESULTS

Of the original seven control subjects, one was excluded from analysis because, despite agreeing not to augment physical activity, he had exercised vigorously (swimming, manual labor), as verified by increased physical fitness (increased VO$_2$ max) and lean body mass, both indices being >3 SD outside the mean of the control group. Among those who completed the study, age, body weight, duration of diabetes, and insulin dose did not differ between groups. No increase in hypoglycemic reactions was recorded or reported by subjects in either group; hypoglycemia did not occur in any subject during or after the exercise session. Mean daily insulin dosage did not change in the exercise group, remaining 1.07 ± 0.06 U/kg/day.

Glucose concentration was clamped between 85 and 90 mg/dl both before and after the 12-wk period in both groups. Actual glucose concentrations at steady state during the first and second clamp procedure were 85 ± 1 and 87 ± 1 mg/dl in the exercise group, with coefficients of variation of 5.9 ± 0.9% and 5.0 ± 0.5%. In the control group, glucose concentrations during the clamp were 89 ± 1% on both occasions, with coefficients of variation of 5.8 ± 0.9% and 5.4 ± 1.4% during the first and second clamps, respectively. The time from commencing insulin infusion to attaining steady-state glucose ranged from 102 ± 6 to 133 ± 11 min with no significant difference within or between groups. Since some of this time was required to lower blood glucose to ~100 mg/dl when the algorithm dictated glucose infusion, we examined the time from beginning glucose infusion to attaining steady state; this ranged from 60 ± 6 to 76 ± 10 min, with no significant differences within or between groups. Serum free insulin levels during the euglycemic clamp were consistent in each group before and after the 12-wk period. In the controls, free insulin levels were 147 ± 11 μU/ml before and 159 ± 16 μU/ml after, while in the exercised group, free insulin concentrations were 219 ± 11 μU/ml before and 206 ± 24 μU/ml after the 12-wk period.

Before the exercise training, the mean glucose utilization rates of both the control and exercised groups were similar, being 278 ± 40 mg/M$^2$/min and 274 ± 33 mg/M$^2$/min, respectively (Table 2). Whereas mean glucose utilization remained unchanged at 289 ± 42 mg/M$^2$/min in the control group, it rose to 338 ± 28 mg/M$^2$/min in the exercised group (Table 2). The change in the exercised group amounted to a mean increase of 64 ± 13.9 mg/M$^2$/min (P < 0.01), corresponding to a mean increase of 23 ± 5%.

That exercise resulted in increased physical fitness was evident from the change in VO$_2$ max during graded exercise testing (Table 2). The exercised group demonstrated a significant increase in VO$_2$ max from 36 ± 3 to 39 ± 3 ml/kg/min, representing a mean increase of 3 ± 0.8 ml/kg/min (P < 0.01) while the control group showed no significant change (39 ± 3.4 versus 37 ± 3.2 before and after 12 wk). Lean body mass increased from 45 ± 3 to 47 ± 3 kg in the exercised group, representing a mean increase of 1.94 ± 0.9 kg. In contrast, no change occurred in the control subjects (Table 2).

Despite clear-cut evidence for increased insulin sensitivity and evidence of increased physical fitness, as reflected in the increase in VO$_2$ max, overall metabolic control, as reflected in glycohemoglobin levels, did not change in either the exercised or control group. HbA$\sb{1c}$ levels remained at 12 ± 1% before and after the 12-wk period in both groups. Linear regression analysis failed to reveal any significant correlations between the increase in insulin sensitivity, as reflected in the glucose utilization rates during the euglycemic clamp and the increase in VO$_2$ max or lean body mass. By 7-day dietary rec-

### TABLE 2

Response before and after 12 wk

<table>
<thead>
<tr>
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<th>Exercise group (N = 9)</th>
<th>Control group (N = 6)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>Glucose utilization rate (mg/M$^2$/min)</td>
<td>274 ± 33</td>
<td>338 ± 28</td>
</tr>
<tr>
<td>Maximum oxygen uptake during graded exercise (ml/kg/min)</td>
<td>36.3 ± 3</td>
<td>39.3 ± 3</td>
</tr>
<tr>
<td>Lean body mass (kg)</td>
<td>45.3 ± 2.86</td>
<td>47.2 ± 2.29</td>
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All values are mean ± SEM.

*P < 0.05 as compared with pretraining.
ords, there was no significant change in caloric intake in either group.

**DISCUSSION**

This study demonstrates that a program of regularly supervised exercise training of modest intensity and duration can significantly augment physical fitness, as reflected in an increase in \( \text{VO}_2 \text{max} \) during exercise training, an increase in lean body mass, and an increase in insulin sensitivity, as assessed via the euglycemic clamp technique.

Glucose concentrations at steady state were clamped between 85 and 90 mg/dl in all our patients. The duration of insulin and glucose infusion and the coefficients of variation of glucose during steady state were similar to studies reported in adults. In adults, isotope dilution techniques with radioactive glucose combined with the clamp approach have documented complete suppression of hepatic glucose output at insulin levels >100 \( \mu \text{U/ml} \). Similarly, we demonstrated via the nonradioactive isotope 6,6-dideuterated glucose and gas chromatography–mass spectrometry that endogenous glucose production is totally suppressed in children at insulin concentrations of \( \approx 100 \mu \text{U/ml} \). Thus, available evidence supports the assertion that hepatic glucose production was negligible during our clamp studies where free insulin concentrations were 150–200 \( \mu \text{U/ml} \), concentrations associated with near-maximal rates of glucose utilization. Consequently, the significant increase in glucose utilization after exercise training reflects increased insulin sensitivity, attributable to the exercise program. The absence of any change in glucose utilization rates before and after 12 wk in control subjects further underscores that the observed changes were due to exercise training and not to psychological or other adjustments in undergoing the clamp procedure on two occasions.

Although the exercised group has a significantly higher free insulin concentration than the control group during the euglycemic clamp both before and after the 12-wk period, there was no significant change in either group when comparing the initial with the subsequent study run in the same assay. It must be emphasized that free insulin was determined in two separate assays, one for each group. If this difference in free insulin levels was responsible for the difference in glucose utilization rates, then such a difference should have been apparent at the time of the initial clamp before any individuals underwent exercise training. However, glucose utilization rates were remarkably similar in the exercise and control groups before the training period. Hence, the absence of change in free insulin levels achieved during the euglycemic clamp before and after 12-wk in both groups indicates again that the increased insulin sensitivity was due to the training of the exercised group. Since all subjects were infused with the same fixed dose of insulin at 100 mU/M\(^2\)/min, the significant difference in free insulin levels could reflect an interassay variation, a difference in insulin binding antibodies between the groups despite their being closely matched for duration of diabetes and daily insulin dose, or a difference in insulin clearance.

Muscle tissue has been demonstrated to be the site of increased glucose utilization after exercise and hyperinsulinemia in healthy adults. Several mechanisms contribute to this increased insulin sensitivity. In trained athletes, insulin binding to monocytes is increased due to an increase in receptor number, which is correlated to maximal aerobic power. In addition, postreceptor sensitivity is also increased by exercise training, as reflected in increased muscle glycogen synthase activity and muscle oxidative capacity. In the absence of changes in free insulin concentrations, it is likely that similar receptor and postreceptor mechanisms were responsible for the increased sensitivity in our patients. The absence of a correlation between the change in insulin sensitivity and the increase in maximal aerobic capacity contrasts with reports in normal adults. This relationship is independent of sex, although women have lower values for \( \text{VO}_2 \text{max} \) than men. The relatively small number of subjects studied may have obscured significant correlations between the increase in \( \text{VO}_2 \text{max} \) and the increase in insulin sensitivity in our study.

The overall findings of our study are highly similar to those reported in adults with type I diabetes. Although the subjects of that study were considerably older, had diabetes for almost twice as long, and exercised for 16 rather than 12 wk, their insulin sensitivity was increased by 20%, as determined by the insulin clamp technique, and \( \text{VO}_2 \text{max} \) by 8%, compared with, respectively, 23% and 8% in our study. Furthermore, as in our study, overall glycemic control, as reflected in glycohemoglobin levels, did not change. The discrepancy between the clear increase in insulin sensitivity, as measured by insulin-stimulated glucose metabolism during the clamp procedure, and absence of improvement in overall glycemic control, as reflected in glycohemoglobin levels, suggests that some compensatory mechanisms occurred during the 12-wk period. Since average daily insulin dose remained unchanged and no increase in hypoglycemic reactions was recorded, we speculate that our subjects increased daily caloric intake to compensate for the increase in insulin sensitivity. Although there was no significant increase in caloric intake, based on home dietary records, it is difficult to precisely quantify caloric intake over 12 wk under free living conditions in adolescents. Adults with type I diabetes who undergo exercise training have been shown to increase caloric intake by an average of 280 kcal per day. It is also possible that the increased insulin sensitivity demonstrated during the euglycemic clamp may not reflect in vivo conditions since in diabetic patients receiving once- or twice-daily s.c. injections, free insulin concentrations would not increase in response to a meal to levels that permit more efficient metabolism of glucose. Irrespective of the explanation, our study in adolescents and those previously reported in adults indicate that exercise, per se, in the absence of adjustments in insulin and diet will not improve overall glycemic control. However, the increased insulin sensitivity suggests that in the management of type I
diabetes, exercise training would be a valuable adjunct that may improve glycemic control providing there is additional adjustment of insulin and diet.

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REFERENCES


