The Effect of Physical Training on Glucose Tolerance and Plasma Lipids in Maturity-onset Diabetes

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In a general population, physical fitness is inversely associated with a variety of risk factors for coronary artery disease. These factors include heart rate, body weight, adiposity, systolic blood pressure, glucose tolerance and serum cholesterol, and triglycerides.[1–3] In much the same way, high-density lipoprotein cholesterol is elevated in physically fit individuals, and when low, is associated with an increased incidence of atherosclerotic vascular disease.[4,5]

In previously untrained subjects, physical training regimens have usually been shown to decrease plasma triglycerides[7–9] and cause a shift in cholesterol from low- to high-density lipoproteins.[10,11] Training programs produced only a modest improvement in glucose tolerance, if any; however, less insulin is required for improvement, thus suggesting enhanced insulin sensitivity.[7,12,13] It is not known whether training enhances insulin sensitivity in patients with diabetes and whether this results in a greater improvement in glucose tolerance than is reported in control subjects. In an attempt to answer these questions, we assessed the effects of physical training on glucose tolerance and serum insulin in several patients with maturity-onset diabetes. This report describes the effects of 3–6 months of physical training on a bicycle ergometer in six middle-aged men in whom diabetes was associated with fasting hyperglycemia and deficient insulin secretion. The effect of the training regimen on plasma triglycerides and cholesterol is also described.

METHODS

Patients. Six sedentary men with maturity-onset diabetes treated with diet alone were studied. None were on medication or were actively attempting to lose weight. BUN, creatinine, liver function studies, and an exercise electrocardiogram (double Masters test) were all within normal limits. The characteristics of the patients before and after training are noted in Table 1.

Exercise. After several instructional sessions in the use of a bicycle ergometer (Monark, Swinton Instruments, Seattle, Wash.; or Schwinn, Chicago, Ill.), maximal O_2 capacity (VO_2 max) was determined as described by Astrand.[14] Each subject was then given a bicycle ergometer to take home and was instructed to exercise according to a predetermined schedule at least 5 days per week. They were also told not to modify their usual diet. Exercise was progressively increased according to the patient's abilities and willingness. A typical subject pedaled 24–30 min per day at 300 kpm (8 to 10 3-min bouts of exercise interspersed with 3 min of rest) after 1 wk of training, 450 kpm by week 3, and at 600 kpm by week 6. Several patients were able to increase the workload to 750 kpm during the remainder of the program; others increased their pedaling time at the lower workload. The patients were seen by a physician, and VO_2 max was determined approximately every other week throughout the training program.

Tests. Intravenous glucose tolerance tests (25 g/patient) were carried out approximately 1 wk before the start of the exercise program and again six days and 2 wk after its completion. Oral glucose tolerance tests (100 g/patient) were performed before training and seven days after its cessation. Blood for cholesterol and triglyceride determinations was taken immediately before the glucose tolerance tests. Total body water was measured during the oral glucose tolerance tests.

Measurements. Triglycerides and cholesterol were determined in plasma with an AutoAnalyzer.[15] Glucose was determined in whole blood by a ferricyanide method on an AutoAnalyzer (Technicon Co., Tarrytown, New York). Total body water was determined with ^3H_2O as described by Morgan et al.,[16] and insulin was determined by a double antibody technique.[17]

Statistics. Statistical analyses were based on paired com-

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TABLE 1
Diabetic subjects undergoing physical training

Patient	Age	Duration of training (wk)	Height (cm)	Weight (kg) Initial	Weight (kg) Final	Body water (L) Initial	Body water (L) Final	VO_2 max (ml/kg/min) Initial	VO_2 max (ml/kg/min) Final
J.D.	57	20	180	89	88	43.5	43.3	21	22
L.F.	56	25	175	85	85	41.7	45.8	28	29
I.K.*	57	38	175	90	90	45	44.5	22	26
R.M.†	53	21	173	93	92	42.6	42.2	19	23
D.C.	38	14	172	81	80			27	34
J.V.	49	26	163	86	89	46.2	47.4	30	34
Mean ± SEM	52 ± 3	24 ± 4	176 ± 1.5	87.3 ± 1.7	87.3 ± 1.7	43.8 ± 0.8	44.6 ± 0.9	24.5 ± 1.8	28 ± 2‡

Final values were obtained approximately 1 wk post-training.
* Ceased training for 4 wk in middle of program.
† Patient had marked improvement in leg cramps that had disturbed him for many years.
‡ Significantly different from pretraining value, $P < 0.025$ (single-tailed, paired t test).

parisons in which the subject served as his own control. Significance was determined with the Student's t test.

RESULTS

Effect of training on physical characteristics. All of the subjects were moderately obese and were poorly conditioned, as judged from their initial VO_2 max. After 14–38 wk of training, VO_2 max was increased by approximately 15%. The values listed in Table 1 were obtained 6 days after the cessation of exercise. In measurements taken during the final week of the exercise program and 2 wk after its cessation, max VO_2's were 28.7 and 27.7 mg/kg/min, respectively, and were not significantly different from the value 6 days postexercise. The improvement in VO_2 max was not associated with changes in either body weight or total body water, indicating that the adipose mass was not diminished. Patient L.F. had an apparent increase in body water; however, he had the smallest increase in VO_2 max.

Intravenous glucose tolerance and insulin secretion (Table 2). All of the subjects had fasting hyperglycemia and an impaired ability to dispose of exogenous glucose. Before training, the mean rate of glucose disappearance (K) following intravenous glucose was 0.59%/min, and the increase in serum insulin observed in normal subjects after 3–5 min did not occur.[18,19] A significant increase in serum insulin (relative to the 3-min value) was not seen until 20 min.

Training improved glucose tolerance as shown by an increase in the K value to 0.75 6 days after the exercise program was halted. This improvement was not maintained in the absence of exercise, as another 8 days of inactivity led to a significant decrease in glucose disappearance, even though the improvement in VO_2 max was maintained (see above). Insulin levels before and 6 days after training were not different despite the improved glucose tolerance. On the other hand, between 6 and 14 days post-training, fasting serum insulin tended to increase, as did blood glucose. The increment in insulin 15 min and immediately before the administration of glucose was not significant; however, when values for two times were pooled, the increment in insulin of 4.2 ± 1.5 μU/ml was significantly greater than the 6-day postexercise value ($P < 0.025$).

Oral glucose tolerance (Table 3). In contrast to the findings when glucose was administered intravenously, there were no clear-cut effects of physical training on glucose tolerance or insulin secretion following an oral glucose load. In keeping with the findings of others in patients with relatively severe maturity-onset diabetes,[18] the early phase of insulin secretion was very blunted, and maximal insulin levels occurred at 120–180 min.

Plasma lipids. Plasma triglycerides and cholesterol were determined on several occasions before and after training. For the purposes of statistical analysis, the means of these values were used. It was possible to do this, as there was no change in triglyceride and cholesterol levels between 1 and 2 wk postexercise. As shown in Table 4, physical

TABLE 2
Effect of physical training on intravenous glucose tolerance

	Fasting glucose (mg/dl)	Glucose disappearance (K)	Time (min) −15	0	3	5	10	20	30	60	90	120
Insulin, μU/ml												
Pretraining	149 ± 16	0.59 ± 0.12	15 ± 2	17 ± 3	12 ± 2	12 ± 2	11 ± 2	21 ± 4	23 ± 5	20 ± 4	20 ± 4	20 ± 3
Post-training (6 days)	145 ± 16	0.75 ± 0.12*	16 ± 3	13 ± 2	10 ± 3	12 ± 2	14 ± 3	20 ± 2	27 ± 3	27 ± 4	20 ± 4	17 ± 2
Post-training (14 days)	157 ± 16	0.65 ± 0.13	18 ± 2†	19 ± 2†	16 ± 4	17 ± 5	17 ± 4	27 ± 4	29 ± 6	28 ± 5	23 ± 4	20 ± 2

Results are means ± SEM. Insulins were measured on only five subjects.
* Significantly different from pretraining value, $P < 0.02$.
† Different from value 1 wk post-training, $0.05 < P < 0.10$.

TABLE 3
Effect of physical training on oral glucose tolerance

Time (min)	0	15	30	60	90	120	180
Insulin, μU/ml							
Pretraining	17 ± 5	26 ± 10	31 ± 8	54 ± 14	72 ± 14	96 ± 28	96 ± 26
Post-training 7 days	13 ± 3	20 ± 4	33 ± 7	61 ± 16	69 ± 17	67 ± 15	76 ± 12
Glucose, mg/dl							
Pretraining	135 ± 15	163 ± 20	223 ± 22	275 ± 23	296 ± 33	263 ± 32	216 ± 35
Post-training 7 days	155 ± 15	182 ± 13	227 ± 17	279 ± 11	299 ± 14	305 ± 45	242 ± 29

Results are means ± SEM of five values. Patient J.V. was not studied.

training caused a decrease in plasma triglycerides from 144 to 122 mg/dl. Plasma cholesterol decreased by 20–30 mg/dl in four of five individuals (mean decrease ± SEM, 26 ± 2.5, $P < 0.001$); in the fifth individual, it increased by 20 mg/dl, however. Seasonal variation in cholesterol[20] would have diminished the decrease in cholesterol. All of the patients except D.C. had their initial cholesterol determinations done in the summer and early autumn and their final determination in the winter. According to the results published by Thomas et al.,[20] seasonal variation should have produced an average increment of serum cholesterol of 20 mg/dl in the five subjects studied.

DISCUSSION

The data suggest that physical training of a previously inactive patient with maturity-onset diabetes enhances his ability to dispose of an intravenous glucose load. Serum insulin was not simultaneously increased, suggesting that training either enhanced sensitivity to endogenous insulin or diminished some anti-insulin factor. Whatever the basis for it, the effect of training was short lived. Within 2 wk of the cessation of exercise, fasting glucose and insulin levels had tended to increase and glucose tolerance had deteriorated significantly. The reason physical training did not cause a comparable improvement in the oral glucose tolerance test remains to be determined.

There have been few reports dealing with the effect of physical training on glucose and lipid metabolism in the diabetic. In a group of five extremely obese subjects (mean weight 129 kg) with glucose intolerance without marked hyperinsulinism, Björntorp et al.[21] achieved a 5–10% increase in VO_2 max with an 8-wk training regimen. Neither oral nor intravenous glucose tolerance was improved; fasting plasma insulin and insulin levels during the intravenous glucose tolerance test were both diminished. In contrast, the insulin response to oral glucose was not altered.

More recently, Saltin and his co-workers (this symposium) evaluated the effect of 6 months of physical training (60 min twice a week) on glucose tolerance in a group of normal weight patients (mean 79.7 kg) with maturity-onset diabetes. The patients were detected during a screening program and were less severely diabetic than the subjects studied in this investigation. Training increased VO_2 max from 2.2 to 2.75 L/min. In contrast to the findings of Björntorp et al.[21] and those reported here, some improvement in oral glucose tolerance (performed 4 days after last exercise) associated with a diminished insulin response was observed. Interestingly, the improvement in glucose tolerance was most evident 120 min after the glucose load and was either not seen or was less impressive at earlier times. In neither this study nor that reported by Björntorp and his co-workers have plasma lipids been reported.

The reasons for the different effects of physical training on glucose tolerance and circulating insulin in these three studies remain to be determined. The patients differed as to the severity of their diabetes, the degree of obesity, and the intensity and duration of their training regimens. Also, the time elapsed between the cessation of exercise and performance of glucose tolerance tests may have been a factor, as studies in nondiabetic obese subjects suggest that enhanced insulin sensitivity may persist in some individuals for 4–6 days.[22]

A second finding of note is the decrease in plasma triglycerides. A decrease in plasma triglycerides after various periods of physical training was first noted in man by Holloszy and his co-workers[7] and has since been observed by many others.[9] Training regimens and even brief periods of exercise have also been shown to lower plasma triglycerides in patients with endogenous hypertriglyceridemia.[23,24] The basis for this effect of exercise is not known, although recent studies in the rat suggest that physical training diminishes hepatic triglyceride secretion.[25]

The effect of physical training on total plasma cholesterol is less clear. Several groups have reported decreases and others no change.[9,11] In general, decreases in cholesterol, where observed, were modest, and the possibility that they

TABLE 4
Effect of physical training on plasma triglycerides and cholesterol

	Triglyceride		Cholesterol	
	Pre-training	Post-training	Pre-training	Post-training
Patient	(mg/dl)		(mg/dl)	
J.D.	131 (4)	106 (6)	187 (6)	154 (6)
I.K.	188 (6)	168 (6)	262 (6)	282 (6)
L.F.	81 (4)	64 (6)	164 (4)	141 (6)
D.C.	176 (2)	149 (6)	230 (4)	206 (6)
R.M.	176 (4)	476 (6)	196 (4)	175 (6)
	144 ± 24	122 ± 23*	208 ± 17	192 ± 25†

Numbers of determinations before and after training used to calculate mean values are in parentheses. Subject R.M. had hyperlacticacidemia and possibly alcohol-induced hypertriglyceridemia. Because of this and because of the wide swings in his individual triglyceride values, he is not included in the statistical analysis.

* Significantly different from pretraining values, $P < 0.01$, when patient R.M. omitted.

† Significantly different from pretraining values, $P < 0.001$, when patient I.K. was omitted (see text).

were related to changes in adipose mass were not ruled out. To some extent, the variable response of total plasma cholesterol may be related to the fact that a decrease in cholesterol in low-density and very low-density lipoprotein is partially compensated for by an increase in cholesterol in the high-density lipoprotein fraction.[10,11] Also, in most studies, seasonal variations[20] were not taken into account.

In the present study, four subjects experienced a decrease in cholesterol that averaged 26 mg/dl and was not associated with a change in body weight or water. The fifth subject in whom cholesterol was determined had an increase of 20 mg/dl after training, even though his plasma triglycerides had diminished. The increment in plasma cholesterol in this individual, in part, may have been related to seasonal variation, as his initial determinations were done during the summer and his later determinations in March, when plasma levels may be in excess of 20 mg/dl higher.[20]

The results suggest that the role of physical training in the therapy of diabetes requires further consideration. Additional studies are needed to define the intensity and frequency of exercise needed to produce and maintain biochemical improvement in the diabetic. Also, it remains to be determined if certain patients will benefit more than others. Individuals with deficient insulin secretion were reported here. As training seems to enhance insulin sensitivity, it may well be that maturity-onset diabetics with hyperinsulinism and insulin resistance[26] would show even greater improvement.

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