

## Studies on the mechanism of improved glucose control during regular exercise in Type 2 (non-insulin-dependent) diabetes

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**Summary.** The effects of 6 weeks of thrice weekly training on glycaemic control were assessed in 20 sedentary Type 2 (non-insulin-dependent) diabetic patients and 11 control subjects matched for previous physical activity. Maximal oxygen uptake was lower in the diabetic patients than in control subjects before training ( $26.2 \pm 1.1$  versus  $32.6 \pm 1.7$  ml·kg<sup>-1</sup>·min<sup>-1</sup>;  $p < 0.001$ ). Glycosylated haemoglobin levels decreased in the diabetic patients during the training programme ( $12.2 \pm 0.5$  to  $10.7 \pm 0.4\%$ ;  $p < 0.02$ ). Oral and intravenous glucose tolerance determined 72 h after the last exercise period showed only minimal improvement. Plasma glucose levels were, however,

significantly lower at 12 h than 72 h after exercise in eight subjects tested at both time points. These data suggest that an exercise programme can produce a significant decrease in glycosylated haemoglobin levels in Type 2 diabetic males probably due, in great measure, to the cumulative effect of transient improvements in glucose tolerance which follow each individual period of exercise.

**Key words:** Exercise, Type 2 diabetes, physical training, maximal oxygen uptake, exertion, insulin sensitivity.

Type 2 (non-insulin dependent) diabetes mellitus is associated with an increased morbidity and mortality from atherosclerotic and microvascular disease [1, 2]. Physical training is believed to improve a number of the factors which may predispose to these complications, including abnormalities in plasma lipids and lipoproteins [3–5], hyperglycaemia and hyperinsulinaemia [6–10]; for this reason it has been recommended in the treatment of Type 2 diabetes [11, 12]. Despite this, information concerning the effectiveness of physical training in Type 2 diabetes is limited and it is unclear whether observed benefits are due to acute effects of exercise or to improved physical fitness. Likewise the optimal frequency, duration, and intensity of training sessions and the specific risks of exercise in Type 2 diabetes are uncertain.

We have assessed the effects of physical training on a group of 20 Type 2 diabetic patients and 11 control subjects matched for age, weight and previous physical activity. This study describes the effects of 6 weeks of moderately intense training on glucose tolerance, glycosylated haemoglobin (HbA<sub>1c</sub>) and plasma insulin.

### Subjects and methods

#### Subjects

All patients were sedentary males within 20% of ideal body weight according to the Metropolitan Life Insurance tables and had Type 2 dia-

betes according to the criteria of the National Diabetes Data Group [13]. None had a history or physical findings suggestive of cardiovascular, pulmonary or renal disease, hypertension or peripheral vascular insufficiency. All were treated by diet alone and none was receiving medication known to affect glucose tolerance.

Age-, sex- and weight-matched control subjects, with normal glucose tolerance by the above criteria, were also studied. Their athletic histories, i.e. participation in team sports and recreational physical activity performed at least once a week over the decade before entry to the programme were similar to those of the patients and, like the patients, none engaged in an occupation requiring heavy physical activity during the year preceding the study.

Individuals with a weight gain or loss of more than 2.5 kg in the preceding 6 months were excluded. All subjects were placed on a weight-maintaining diet providing 50%–60% of calories as carbohydrate, 15% as protein and 25%–35% as fat for at least 6 weeks before the initial testing and throughout the study period. Two patients and one control were cigarette smokers and maintained this habit throughout.

All studies were approved by the Institutional Review Board of Rutgers Medical School and written informed consent was obtained from each subject prior to participation.

#### Evaluation of subjects

All subjects were studied before and after 6 weeks of physical training. Maximal oxygen uptake (VO<sub>2 max</sub>) was determined after they had the opportunity to become familiar with the laboratory equipment and personnel. All patients and control subjects reported to the exercise laboratory at 08.00 h, following a 10–12 h overnight fast. A standard graded exercise test with ECG monitoring was performed on a Monarch bicycle ergometer (Quinton Instruments, Seattle, Washington). The exercise test consisted of a 5-min warm-up period at a workload of 25 W, followed by increments of 25 W at 3-min inter-

vals until voluntary exhaustion. A second session took place 7–10 days following the initial test. At the second visit, patients started exercise at 50% of their previously estimated  $\text{VO}_2 \text{ max}$  and worked to voluntary exhaustion as before.

Expired gas was collected over the last 60 s of each work level and allowed to equilibrate to room temperature. Oxygen concentration was determined by an Applied Electronics oxygen meter (Applied Electrochemistry, Sunnyvale, California) and carbon dioxide concentration by a Godart-Statham Capnograph carbon dioxide meter (Godart-Statham, Bilthoven, The Netherlands). The criterion for  $\text{VO}_2 \text{ max}$  was a plateau of  $\text{VO}_2$  in the face of an increasing absolute work load.

Evaluation of the autonomic nervous system was performed on two occasions before training by evaluating beat to beat variation of heart rate during five deep breaths. A variation of < 10 beats/min was considered evidence of autonomic dysfunction [14].

$\text{HbA}_1$  was measured after an overnight fast on three occasions one week apart before training. During training,  $\text{HbA}_1$  was determined at the end of weeks 5 and 6 and once during the first post-training week. During and following training,  $\text{HbA}_1$ , oral and IV glucose tolerance were determined 72 h after the last period of exercise.

Oral glucose tolerance tests were performed at 08.00 h, following a 10–12 h overnight fast. Subjects ingested 100 g of glucose as Glucola (R) (Ames Division, Miles Laboratories, Elkhart, Indiana) and blood was obtained at 0, 30, 60, and 120 min. Every subject was tested before and after 6 weeks of training. IV glucose tolerance tests were performed within 7–10 days of the oral tests at 08.00 h, following an overnight fast. Subjects received an IV dose of glucose (0.375 g/kg body weight) and blood samples were obtained at 0, 2, 4, 6, 10, 20, 30, 45 and 60 min.

Eight diabetic patients who, after the initial 6-week training period, exercised twice a week for at least 3 months to maintain their improved  $\text{VO}_2 \text{ max}$  (data not shown), were studied both 12 and 72 h following an exercise bout. The subjects first exercised for 30 min at their usual training intensity (70% of initial  $\text{VO}_2 \text{ max}$ ) on a bicycle ergometer at 08.00 h. They then remained sedentary for 72 h and an oral glucose tolerance test was performed. That same evening at 19.00 to 20.00 h (1 h after supper) they underwent a second training session, identical to the first. A second glucose tolerance test was performed the next morning approximately 12 h after exercise.

### Training

All subjects underwent 6 weeks of physical training in the exercise laboratory under the direct supervision of the exercise physiologist. Three times a week, they exercised major muscle groups on metered equipment (bicycles, arm ergometers, treadmills, rowing machines, etc.) for eight 4-min periods interrupted by 1.5 min of rest. The intensity of the work was set at 50% of  $\text{VO}_2 \text{ max}$  initially and was increased to 70%–75% of initial  $\text{VO}_2 \text{ max}$  over the first 2 weeks. Exercise was prescribed and monitored on the basis of heart rate. The appropriate heart rate was estimated from the determination of  $\text{VO}_2 \text{ max}$  and confirmed on a subsequent day by determining the oxygen uptake during work at the prescribed rate. Following the successful completion of 6 weeks of training, glucose tolerance,  $\text{VO}_2 \text{ max}$  and other measurements were repeated. Every subject attended all three sessions each week.

### Methods of analysis

$\text{HbA}_1$  was determined by ion exchange chromatography (Bio-Rad Laboratories, Richmond, California) [15]. Plasma glucose was measured enzymatically [16] and insulin was determined by radioimmunoassay (Pharmacia Diagnostics, Piscataway, New Jersey, USA) [17]. Samples obtained before and after 6 weeks of training were stored at  $-20^\circ\text{C}$  and determinations were carried out in the same assay for each subject. For IV glucose tolerance, the rate of blood glucose disappearance ( $K_g$ ) was determined from the slope of the linear regression of the log of blood glucose between 10 and 60 min after glucose injection [18]. To analyse further the insulin response to IV

glucose, the baseline value of insulin was subtracted from the values at subsequent time points and the sum of these differences was used to reflect the area under the curve. The values from 0 to 10 min were used to estimate the early insulin response and the values between 10 and 60 min the late response [18]. Body fat was estimated using a Lange skinfold caliper (Cambridge Scientific Industries, Cambridge, Maryland, USA). Measurements were made at the biceps, triceps, supra-iliac, and subscapular areas and the sum of these measurements was used to estimate body density and percentage body fat [19, 20].

### Statistical analysis

Measurements obtained at entry and at later visits were entered into an IBM 370/168 computer and analyzed using Statistical Analysis Systems [21]. Inter-group and intra-group comparisons were performed using analysis of variance or, where appropriate, the paired or unpaired Student's t-test. Pearson's correlation coefficients were determined to establish relationships between variables. Results are expressed as mean  $\pm$  SEM.

## Results

### Clinical characteristics

Work and recreational histories were similar in control and diabetic subjects. Estimated percentage body fat was also comparable between the two groups (Table 1). Two of the 20 patients had background retinopathy detected by direct ophthalmoscopy and 11 had symmetrical loss of distal vibratory and temperature sensation over the lower extremities. None of the patients complained of impotence, and blood pressure changes from lying to standing were < 10 mmHg in all subjects. An R-R interval variation of < 10 beats/min was found in four of the 20 diabetic patients, all of whom also had sensory neuropathy. Neurological abnormalities were not found in any control subjects. Body weight and estimated percentage body fat were not altered by training in either group.

### $\text{VO}_2 \text{ max}$

The diabetic patients initially had a significantly lower  $\text{VO}_2 \text{ max}$  than the control subjects ( $26.2 \pm 1.1$  versus  $32.6 \pm 1.7 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ;  $p < 0.001$ , Table 1). This was not related to the slightly older age of the diabetic patients. Even when the eight oldest patients were eliminated to equalize the mean age of the two groups ( $48 \pm 1$  versus  $46 \pm 4$  years), the difference in  $\text{VO}_2 \text{ max}$  persisted ( $25.6 \pm 1.3$  versus  $32.6 \pm 1.7 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ;  $p < 0.001$ ). No association was apparent between  $\text{VO}_2 \text{ max}$  and abnormal R-R interval variation. A significant increase in  $\text{VO}_2 \text{ max}$  and a decrease in heart rate at the same absolute submaximal workload (100 W) was observed in both groups after 6 weeks of physical training. The improvement in  $\text{VO}_2 \text{ max}$  was less in the diabetic than the control subjects, but the difference was not statistically significant. After training the  $\text{VO}_2 \text{ max}$  remained lower in the diabetic subjects.

**Table 1.** Patient characteristics before and after 6 weeks of training

	Control subjects (n = 11)		Diabetic patients (n = 20)	
	Untrained	Trained	Untrained	Trained
Age (years)	46 ± 4	–	51 ± 2	–
Weight (kg)	81.6 ± 3.1	80.6 ± 3.6	78.2 ± 1.5	79.6 ± 1.6
Estimated percentage body fat	24.3 ± 1.4	24.7 ± 1.1	24.7 ± 0.6	24.4 ± 0.6
VO <sub>2</sub> max (ml · kg <sup>-1</sup> · min <sup>-1</sup> )	32.6 ± 1.7	37.5 ± 2.3 <sup>c</sup>	26.2 ± 1.1 <sup>d</sup>	28.4 ± 1.0 <sup>a, d</sup>
Heart rate at 100 W (beats/min)	132 ± 5	124 ± 8 <sup>b</sup>	138 ± 4	124 ± 4 <sup>b</sup>

Results are expressed as mean ± SEM. VO<sub>2</sub> max is given for conditions of standard temperature and pressure. <sup>a</sup> *p* < 0.05, <sup>b</sup> *p* < 0.02, <sup>c</sup> *p* < 0.01 for trained versus untrained subjects; <sup>d</sup> *p* < 0.01 for diabetic versus control subjects

### Glycosylated haemoglobin

Levels of HbA<sub>1c</sub> decreased significantly in the diabetic patients after 6 weeks of training, suggesting overall improvement in glucose homeostasis (Table 2). There was no significant correlation between the decrease in HbA<sub>1c</sub> and body weight, age, duration of diabetes, initial VO<sub>2</sub> max, or improvement in VO<sub>2</sub> max. The 13 patients with fasting plasma glucose levels < 11.1 mmol/l (200 mg/dl) at entry had a threefold greater decrease in HbA<sub>1c</sub> than the patients with glucose levels > 11.1 mmol/l, although because of patient variability the difference was not statistically significant (1.8 ± 0.5 versus 0.6 ± 0.4%).

### Glucose tolerance measured 72 h post-exercise in trained subjects

Despite the decrease in HbA<sub>1c</sub> in the diabetic patients after 6 weeks of training, oral glucose tolerance showed only a minimal improvement, which attained statistical significance only at 30 min. A similar pattern was seen in the control subjects. As a group, the diabetic patients had modest fasting hyperinsulinaemia. However, their insulin response to oral glucose was impaired and did not change after 6 weeks of training (Table 3).

Training appeared to result in a small improvement in IV glucose disposal but the difference did not attain statistical significance in either group. The diabetic patients had a severe deficiency in the early insulin response (0–10 min) to IV glucose, but the late response (10–60 min) was similar to controls. Training had little effect on these insulin levels in the diabetic patients while in the control subjects the early insulin response tended to decrease, while late insulin responses were enhanced (Table 4).

**Table 2.** Effect of physical training on glycosylated haemoglobin

	Glycosylated haemoglobin A <sub>1c</sub> (%)	
	Control subjects (n = 11)	Diabetic patients (n = 20)
Untrained	7.7 ± 0.2	12.2 ± 0.5
Trained	7.5 ± 0.2	10.7 ± 0.4 <sup>a</sup>

Results are expressed as mean ± SEM. Measurements were carried out before and after training three times a week for 6 weeks. <sup>a</sup> *p* < 0.02 for trained versus untrained subjects

**Table 3.** Effect of physical training on oral glucose tolerance

Time (min)	Control subjects (n = 11)		Diabetic patients (n = 20)	
	Untrained	Trained	Untrained	Trained
Glucose (mmol/l)				
0	5.3 ± 0.2	5.1 ± 0.2	9.9 ± 0.5	9.6 ± 0.6
30	9.7 ± 0.6	7.9 ± 0.3 <sup>a</sup>	14.4 ± 0.6	12.8 ± 0.7 <sup>a</sup>
60	8.3 ± 0.8	7.8 ± 0.4	17.8 ± 0.6	16.5 ± 0.8
120	6.1 ± 0.4	6.1 ± 0.4	18.7 ± 0.9	18.0 ± 0.9
Insulin (mU/l)				
0	13 ± 2	10 ± 1	16 ± 2	16 ± 2 <sup>c</sup>
30	47 ± 9	56 ± 11	30 ± 4 <sup>b</sup>	28 ± 3 <sup>c</sup>
60	56 ± 8	57 ± 6	39 ± 5	39 ± 4 <sup>b</sup>
120	47 ± 7	45 ± 7	42 ± 4	51 ± 5

Results are expressed as mean ± SEM. Glucose tolerance tests were performed 72 h after the last training session. <sup>a</sup> *p* < 0.05 trained versus untrained subjects; <sup>b</sup> *p* < 0.02, <sup>c</sup> *p* < 0.01; diabetic versus control subjects

**Table 4.** Effect of physical training on IV glucose tolerance

	Control subjects (n = 11)		Diabetic patients (n = 20)	
	Untrained	Trained	Untrained	Trained
K <sub>g</sub> (%/min)	1.81 ± 0.22	1.94 ± 0.20	0.57 ± 0.05 <sup>b</sup>	0.67 ± 0.06 <sup>b</sup>
Insulin response				
0–10 min (mU/l)	163 ± 58	138 ± 32	14 ± 5 <sup>b</sup>	18 ± 6 <sup>b</sup>
10–60 min (mU/l)	78 ± 14	110 ± 19 <sup>a</sup>	66 ± 13	68 ± 7 <sup>b</sup>

Results are expressed as mean ± SEM. Tests were performed 72 h after an exercise session. K<sub>g</sub> was calculated from the slope of linear regression of the log of glucose concentration between 10–60 min after the glucose injection. Values for the insulin response were obtained by subtracting the insulin concentration at time 0 from those at subsequent times and adding the differences. <sup>a</sup> *p* < 0.02; trained versus untrained subjects; <sup>b</sup> *p* < 0.01; diabetic versus control subjects

**Table 5.** Comparison of oral glucose tolerance 12 and 72 h post-exercise in eight trained diabetic subjects

Time (min)	Plasma glucose (mmol/l)	
	12 h	72 h
0	10.0 ± 1.1	11.2 ± 1.1 <sup>a</sup>
30	13.3 ± 1.5	15.1 ± 1.3 <sup>a</sup>
60	17.3 ± 1.6	18.8 ± 1.3 <sup>b</sup>
120	17.3 ± 1.7	19.2 ± 1.4 <sup>b</sup>

Results are expressed as mean ± SEM. <sup>a</sup> *p* < 0.05, <sup>b</sup> *p* < 0.02; 12 versus 72 h

### *Glucose tolerance and plasma insulin in trained individuals 12 and 72 h after exercise*

To determine whether glucose tolerance was improved at a time earlier than 72 h post-exercise, oral glucose tolerance tests were performed at both 12 and 72 h after the last period of exercise in eight trained diabetic patients. Plasma glucose levels were significantly lower at 12 h at all time points (Table 5). There were no differences in plasma insulin. The four patients who showed the largest improvement at 12 h compared with 72 h, had a mean fasting plasma glucose of  $9.3 \pm 1.5$  versus  $13.1 \pm 0.6$  mmol/l for the other four subjects.

### *Complications during training*

Two patients developed symptomatic, but transient, orthostatic hypotension following maximal exercise in the untrained state. Only one of these individuals had an abnormal R-R interval variation (7.6 beats/min). Six patients had asymptomatic post-exercise orthostatic hypotension. All the hypotensive episodes occurred in the summer months and it is our impression that Type 2 diabetic patients are less tolerant to exercise in warm weather. No orthostatic changes occurred in either group following training. One patient had a significant increase in background retinopathy during the study. However none experienced clinically evident visual, renal, or neurological deterioration. No patient had an episode of hypoglycaemia.

### **Discussion**

We have studied a well-defined group of mildly obese, male Type 2 diabetic patients with moderate glucose intolerance, mild fasting hyperinsulinaemia and a sedentary lifestyle. Despite similar recreational and work histories, the diabetic patients had a lower  $VO_2$  max than did the control subjects. While  $VO_2$  max declines with age [22] and the diabetics were slightly older, this did not account for the difference as it persisted after correcting for this variable. Low values for  $VO_2$  max in Type 2 diabetes have been reported previously [23, 24]; at present there is no adequate explanation for this finding. In insulin-dependent-diabetes, it has been associated with dysfunction of the autonomic nervous system [25, 26] but none of our patients had orthostatic hypotension and only four had a clearly abnormal R-R interval variation. However, subtle autonomic dysfunction and unappreciated differences in lifestyle or cardiac or skeletal muscle function cannot be excluded as explanations.

Training at the prescribed levels was under the direct supervision of an exercise physiologist and resulted in an increased  $VO_2$  max and a decrease in heart rate at the same submaximal workload in both diabetic and control subjects. The diabetic patients appeared to have

a smaller increment in  $VO_2$  max than controls, possibly because the intensity of the training regimen was based on an individual's initial  $VO_2$  max and was thus lower for these subjects. Similar increases in  $VO_2$  max during training regimens of modest intensity have been reported by others [27–30].

Following 6 weeks of training there was a significant decrease in the levels of HbA<sub>1c</sub> in the diabetic patients, suggesting improvement in overall glycaemic control. It is unlikely that this improvement was the result of subtle dietary alterations. Subjects were carefully instructed on maintaining a constant diet and were given 6 weeks of dietary equilibration prior to the study. Food intake was estimated weekly by the nurse during the study and no significant changes were noted in caloric intake or diet composition. In addition, body weight and adiposity remained constant. However, maintenance of a constant weight throughout the training period suggests that a small increase in caloric intake (in the range of approximately 100 calories a day) probably occurred. It is also unlikely that exercise-induced haemolysis lowered HbA<sub>1c</sub> levels, since a similar decrease was not observed in the exercising control group, and haematocrits remained stable throughout training.

Several studies have demonstrated enhanced glucose tolerance in endurance athletes and an apparent increase of insulin sensitivity during physical training in normal and diabetic subjects [7, 8, 30–33]. Whether the improvements in glucose tolerance were the result of the summed effects of individual exercise bouts or of the trained state has not been addressed by these studies. Improved glucose disposal following a single period of exercise has been demonstrated repeatedly [6, 34–36]. Whether the duration or magnitude of this acute response is altered by training is unknown, although recent studies by Goldberg et al. [37] suggest this may be the case. Rapid deterioration of glucose tolerance following the cessation of exercise in trained individuals has also been noted [5, 33, 38], although changes in  $VO_2$  max and muscle enzyme profiles associated with improved fitness persist for weeks [39]. These findings are consistent with the hypothesis that much of the improvement noted in glucose disposal during physical training is related to the summed effects of individual bouts of exercise. Our studies are also consistent with this hypothesis. Thus, the improvement in HbA<sub>1c</sub> in the trained diabetic patients occurred without major alterations in adiposity. It was also unrelated to the initial  $VO_2$  max or the improvement in  $VO_2$  max suggesting that it had little relationship to the level of fitness. Most importantly glucose tolerance was significantly better at 12 h than at 72 h after an acute period of exercise; in fact, at the latter time, it was similar to that in the pre-trained state. At the practical level, these findings suggest that in Type 2 diabetes exercise of the type and intensity used here should be performed three or more times a week to achieve a continuous improvement in glycaemic control.

Berger et al. [40] and Wahren et al. [41] have reported that exercise acutely lowers the blood glucose levels in most diabetic patients with a fasting plasma glucose concentration less than 11.1 mmol/l (200 mg/dl), whereas in patients with higher fasting glucose concentrations blood glucose may increase. Fasting glucose levels prior to training tended to fall in our diabetic and normal subjects during 30 min of bicycle exercise at 70%  $VO_2$  max ( $-0.8 \pm 0.6$  versus  $-0.3 \pm 0.2$  mmol/l; NS). These small changes did not correlate with improved glucose control. However, our own observation that diabetic patients with a fasting glucose level less than 11.1 mmol/l showed a stronger tendency to diminish their HbA<sub>1c</sub> than did diabetic patients with higher glucose levels is consistent with this concept. Similarly, the four patients showing the greatest difference between 12 h and 72 h post-exercise glucose tolerance were those with the lowest fasting plasma glucose levels. Extension and confirmation of these findings may prove useful in identifying diabetic patients particularly likely to benefit from programmes of regular exercise.

In general, the patients tolerated the exercise programme well and there were no major complications. Our observation of post-exercise orthostatic hypotension in patients without clinical evidence of autonomic neuropathy suggests the need to monitor post-exercise blood pressure in the untrained diabetic initiating an exercise programme, especially in warm weather. Physical training appears to ameliorate this problem. The relationship between post-exercise hypotension and subclinical neuropathy or myocardial disease requires further investigation.

In conclusion, the data suggest that a programme of regular physical training in Type 2 diabetes can be safely and effectively utilized as part of the overall treatment plan. Patients with milder diabetes with a fasting plasma glucose of less than 11 mmol/l may be particularly likely to benefit. Because the short-term improvements appear to result mainly from the summed effects of the individual bouts of exercise, the frequency of the exercise may be an important determinant of the response. Our studies were limited to male subjects and further studies should be performed to determine whether these results can be applied to female subjects.

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