Diabetologia (1986) 29: 53–57

Diabetologia

Long-term physical training in female Type 1 (insulin-dependent) diabetic patients: absence of significant effect on glycaemic control and lipoprotein levels

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Summary. No objective evidence has been presented to support the beneficial effect of physical training on glycaemic control in Type 1 (insulin-dependent) diabetic patients trained two to three times a week for several months. In the present study we examined the possibility that a daily exercise programme would be more suitable for improving glycaemic control. Thirteen patients completed a 5-month study; 6 were randomized to exercise training (20 min daily bicycle exercise) and 7 served as non-exercising controls. The training resulted in an 8% increase in maximal oxygen uptake ($p < 0.05$). No change in glycaemic control occurred during the study period in either group. In addition, serum lipid and lipoprotein levels were followed. Total cholesterol decreased during the study period irrespective of training. No effect was noted on the levels of LDL, VLDL, HDL and HDL_2 cholesterol. A significant training effect was obtained in the HDL_3 subfraction (-10%, $p < 0.05$). Total triglycerides were unchanged, but a decrease in the level of LDL triglycerides was observed with training (-12%, $p < 0.01$). It is concluded that, in female Type 1 diabetic patients, daily physical training for several months does not improve glycaemic control and results only in minor changes in serum lipoprotein profiles.

Key words: Type 1 (insulin-dependent) diabetes, maximal oxygen uptake, exercise, serum triglycerides, serum cholesterol, glycaemic control.

It is generally recognized that physical exercise is of importance in the therapy of patients with Type 1 (insulin-dependent) diabetes. However, no objective evidence has as yet been presented to support a supposed beneficial effect of physical training on glycaemic control. On the contrary, when training was performed 3 times a week for 2–5 months, glycaemic control was unaffected [1–4]. Still, one may speculate whether glycaemic control in this patient group can be improved if exercise is performed daily.

It is well known that diabetic patients are predisposed to macroangiopathy [5] and elevated mortality from cardiovascular disease [6], especially female Type 1 diabetic patients [7]. The underlying mechanism is unclear, but much attention has been paid to the roles of hyperlipoproteinaemia and HDL cholesterol [8]. Altered plasma lipid and lipoprotein levels have been observed in Type 1 diabetic patients [9, 10]; however, other reports show normal serum cholesterol [11]. At the same time, physical fitness seems to be associated with favourable serum lipoprotein profiles. In cross-sectional studies, physically well-trained women [12, 13] have been shown to have higher HDL-cholesterol levels than inactive women. Furthermore, the HDL_2 subfraction has been demonstrated to increase with physical training [14, 15].

Consequently, the aims of the present study were to examine the effects of daily physical exercise on glycaemic control and on serum lipids and lipoprotein levels in a group of female Type 1 diabetic patients. To be able to differentiate between effects of training and effects of increased hospital contact, patients were randomized to exercise-training or a non-exercising control group.

Subjects and methods

Participants

The participants were recruited from female Type 1 diabetic patients aged 25 to 45 years, with diabetes duration of at least 5 years, regularly attending the outpatient clinic of the Department of Medicine, Huddinge Hospital, Stockholm, Sweden. Patients with proliferative retinopathy, diabetic neuropathy, nephropathy, hypertension or any other diseases were excluded. Forty-six patients were randomly assigned to a training group (T) or a control group (C). The nature, purpose and possible risks of the study were carefully explained to the patients before they gave their consent to paricipate. Twenty-one patients agreed to participate; 11 in the T and 10 in the C group. Three patients from each group failed to complete the study period. The reasons for

Table 1. Pre-study data for the female Type 1 diabetic patients

Patient	Age	Body mass index	Duration of diabetes (years)	Insulin dose (U/d)	Injections per day	Type(s) of insulin[a]	HbA_1 %	Background retinopathy
Training								
1	26	24.1	24	32	2	I	11.1	+
2	32	20.7	9	26	2	I	12.1	−
3	38	18.6	5	36	2	I	9.7	−
4	38	20.6	11	32	2	S+I	8.4	−
5	39	23.9	27	40	2	I	12.0	−
6	42	22.4	6	28	2	I	9.0	−
Mean ± SEM	36 ± 2	21.7 ± 0.9	14 ± 4	32 ± 2			10.4 ± 0.6	1/6
Non-training								
1	26	23.7	12	68	2	S+I	10.8	−
2	31	22.0	7	38	2	S+I	9.7	−
3	32	21.8	11	40	2	I	9.5	−
4	34	20.8	23	38	2	I	12.0	+
5	36	21.2	11	48	2	I	13.7	−
6	41	21.7	8	34	3	S+I	9.3	−
7	43	22.7	18	32	1	I	9.5	−
Mean ± SEM	35 ± 2	22.0 ± 0.4	13 ± 2	43 ± 5			10.6 ± 0.6	1/7

[a] S = soluble insulin, I = intermediate acting insulin

Table 2. Weekly physical activity, maximal oxygen uptake and submaximal heart rate in training and non-training groups of female Type 1 diabetic patients during a 5-month period.

Patient	Mean weekly physical activity[a]		$\dot{V}O_2$ max $ml \cdot kg^{-1} \cdot min^{-1}$			Submaximal heart rate at 100 Watts, beats/min	
	Before	During	Before	After	Change in %	Before	After
Training							
1	0	2.8	32.3	32.5	0.6	147	146
2	0	5.8	33.5	33.9	1.2	160	146
3	1.0	6.1	27.5	32.6	18.5	150	136
4	1.0	5.7	34.4	37.3	8.4	142	125
5	0	4.5	20.8	23.0	10.6	146	145
6	0	6.2	32.9	36.7	11.6	160	152
Mean ± SEM	0.3 ± 0.2	5.2 ± 0.5[b]	30.2 ± 2.1	32.7 ± 2.1[c]	8.5 ± 2.8	151 ± 3	142 ± 4[c]
Non-training							
1	0	0	31.6	32.5	2.8	160	167
2	1.0	1.0	26.2	27.6	5.3	137	148
3	2.0	2.0	25.8	27.1	5.0	165	158
4	0	0	28.5	26.3	−7.7	134	150
5	0	0	27.8	28.8	3.6	140	138
6	0	0	29.7	27.9	−6.1	145	140
7	0	0	26.4	25.7	−2.7	160	156
Mean ± SEM	0.4 ± 0.3	0.4 ± 0.3	28.0 ± 0.8	28.0 ± 0.8	0.03 ± 2.1	149 ± 5	151 ± 4

[a] Sessions per week; [b] $p < 0.001$ vs. before; [c] $p < 0.05$ vs. before

the dropouts were lack of time (two subjects), illness (one subject), changed physical activity level (two subjects in the C group) and unspecified reasons (one subject). Furthermore, two participants in the training group were not able to complete the training programme satisfactorily due to orthopaedic problems during the study (average number of training sessions per week: 2.4 and 2.2, respectively). They were therefore withdrawn from the analysis. Thus six patients in the training group and seven in the control group completed the study.

Pre-training determinations

For one month prior to the training, baseline values for clinical control of diabetes, including home monitoring of blood glucose and measurements of haemoglobin A_1, were followed. During the second half of this control period, physical work capacity [two measurements of maximal oxygen uptake ($\dot{V}O_2$ max) and submaximal heart rate] and measurements of serum lipids, lipoproteins and lipoprotein fractions were performed.

Clinical and laboratory data for the patients are presented in Table 1. Two participants (one in each group) had detectable C-peptide levels in plasma (> 0.05 nmol/l) in the basal state. There was no difference between the groups in the degree of physical activity in the year prior to the study. Two patients in the T group and three in the C group were cigarette smokers and did not change their smoking habits during the study.

Training period

In the training group, physical training was performed for 5 months (from January to June), and consisted of 20 min of daily bicycle exercise at home. A bicycle ergometer was lent to each participant. The daily training programmes were constructed individually, based on

the pretraining maximal oxygen uptake of the patients. Training consisted of a 5-min low intensity warm-up and 15 min high intensity cycling (60–70% of $\dot{V}O_2$ max the first month, 70–80% the second and third months and 75–90% of $\dot{V}O_2$ max during the last 2 months of training). Training diaries, including the intensity and duration of all training sessions, were carefully kept by the patients and collected every month. Once a month a submaximal bicycle test was performed and a new training programme was constructed on the basis of the pre-training $\dot{V}O_2$ max. Weight and blood pressure were noted and blood samples for HbA_1 were obtained during these monthly controls. Furthermore, home monitored blood glucose registrations were collected and individually evaluated by a physician; insulin doses were adjusted when necessary. Between the monthly controls at the hospital, each patient was contacted by telephone once a week (to ensure that training was going well and that there were no problems with glycaemic control).

The control group received the same treatment as the training group except for the daily 20 min training sessions and the monthly submaximal bicycle tests. Participants in both groups were instructed not to change their habitual physical activities during the study, except for the training sessions in the training group. The average number of exercise sessions per week increased from 0.3 ± 0.2 to 5.2 ± 0.5 in the training group, while the control subjects did not change their physical activity (0.4 ± 0.3 sessions per week both before and during the study period) (Table 2). Samples for serum lipids and lipoproteins were drawn before and after 2.5 and 5 months of training.

Post-training determinations

Post-study measurements included two maximal oxygen uptake determinations, registration of submaximal heart rate and collection of blood samples for HbA_1, serum lipids, lipoproteins and lipoprotein subfractions.

Maximal oxygen uptake determinations

Maximal oxygen uptake was determined on a bicycle ergometer (Elema Schönander, Stockholm, Sweden) at 60 rpm both before and after the training period. The mean value of the two measurements was used. The exercise was started at 40 W and the work load was increased by 30 W every 5 min until exhaustion. Expired air was collected in Douglas bags and analyzed by a mass spectrometer. For criteria of $\dot{V}O_2$ max, see Åstrand and Rodahl [16]. In addition, submaximal heart rate at 100 W was recorded electrocardiographically under steady state conditions (6 min of exercise) before the study, once every month (for the training group) and after the study.

Glycaemic control

Pretraining glycaemic control was assessed from home monitored blood glucose 2 days per week for 4 weeks prior to the training period and from two measurements of haemoglobin A1 (HbA_1). During the training period the patients were asked to monitor their blood glucose four times a day 2 days per week. Haemoglobin A1 was measured once a month during the training period and 48–72 h after the last training session.

Haemoglobin A1 as a percentage of total haemoglobin in blood was determined at constant room temperature (23 °C) by a microchromatographic technique, using a commercial kit (Bio-Rad Laboratories, Richmond, Ca., USA). The normal value for HbA_1 in our laboratory is less than 8% (intra-assay variability 4.6%, inter-assay 9.5%). Details on the procedure for home monitoring of blood glucose have been described elsewhere [2]. During the study a total of 1706 blood glucose measurements were made at home (824 and 882 measurements in the training and control group respectively). The home monitored blood glucose values were used for calculation of the mean blood glucose level.

C-peptide in plasma was determined by radioimmunoassay using antibody M 1230 [17]. Synthetic human C-peptide was used as standard and 125I-Tyr-C-peptide as tracer.

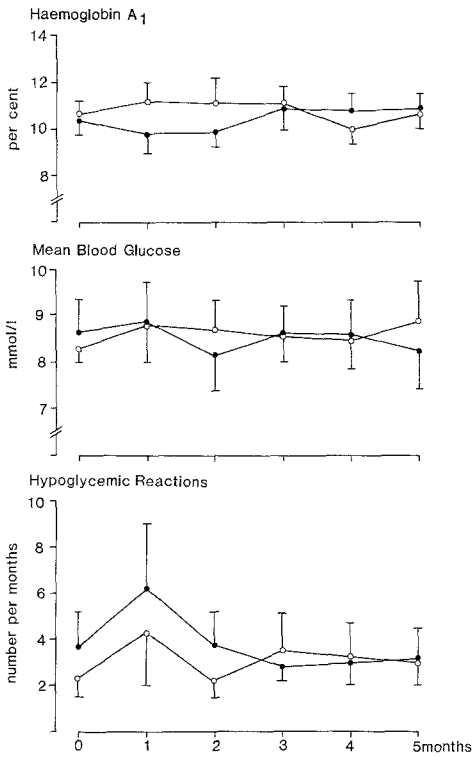

Fig. 1 Haemoglobin A_1, mean blood glucose and hypoglycaemic reactions in female Type 1 diabetic patients during a 5-month period of physical training (●). A non-exercising control group of female diabetic patients (○) was also monitored. Mean blood glucose was calculated from 1706 home monitored blood glucose values (824 and 882 measurements in the training and the control group respectively). Results are expressed as mean ± SEM

Serum lipoproteins

Serum samples were obtained in the morning after an overnight fast before injection of the morning insulin dose. Serum lipoproteins were determined by combined preparative ultracentrifugation and agarose gel electrophoresis as described by Carlson [18]. After centrifugation at $d = 1.006$, heparin-manganese chloride was added to the infranatant, which precipitated the apo-B containing low density lipoprotein (LDL) fraction. The triglyceride and cholesterol concentrations were determined in the top fraction (very low density fraction, VLDL) and in the bottom fraction both before and after precipitation by means of the Ultrolab system, measuring high and low density lipoproteins (HDL + LDL) and HDL respectively [19, 20]. The triglyceride and cholesterol concentrations in LDL were then determined by subtraction. The recovery ranged from 90–110%. Agarose gel electrophoresis was carried out according to Noble [21]. The lipoprotein bands were analyzed in whole serum, in the top fraction after separation at $d = 1.006$ (VLDL) and in the bottom fraction (VLDL + HDL).

The cholesterol concentration in the HDL subfractions HDL_2 and HDL_3 were determined according to Kirstein [22]. HDL_3 was measured as cholesterol in the bottom fraction after preparative ultracentrifugation of whole serum at $d = 1.125$ for 48 h at 40000 rpm in a 40.3 rotor. HDL_2 cholesterol was calculated as the difference between total HDL-cholesterol and HDL_3 cholesterol.

Since alcohol consumption was difficult to ascertain for both patients and controls, alanine-aminotransferase and aspartate-aminotransferase in serum (S-ASAT and S-ALAT) were measured at the same time as the lipid samples were obtained; all tests were normal.

Statistical calculations

Results are given as mean ± SEM. Student's t-test for paired and unpaired data was used when applicable. Analysis of variance (ANO-

Table 3. Serum lipids and lipoproteins in female Type 1 diabetic patients. Values are given in mmol/l

Lipid fraction	Training			Non-training			ANOVA for training effect
	Before	2.5 months	5 months	Before	2.5 months	5 months	
Triglycerides, total	0.93 ± 0.05	0.87 ± 0.10	0.88 ± 0.08	0.94 ± 0.13	0.85 ± 0.08	0.81 ± 0.10	NS
VLDL triglycerides	0.31 ± 0.03	0.34 ± 0.06	0.28 ± 0.05	0.42 ± 0.12	0.33 ± 0.05	0.33 ± 0.08	NS
LDL triglycerides	0.41 ± 0.04[a]	0.32 ± 0.04	0.36 ± 0.04	0.31 ± 0.03	0.32 ± 0.02	0.33 ± 0.03	$p < 0.01$
HDL triglycerides	0.18 ± 0.02	0.20 ± 0.01	0.18 ± 0.02	0.18 ± 0.02	0.17 ± 0.01	0.16 ± 0.02	NS
Cholesterol, total	6.04 ± 0.27	5.59 ± 0.32	5.44 ± 0.32	5.43 ± 0.30	5.24 ± 0.14	5.10 ± 0.33	NS[b]
VLDL cholesterol	0.24 ± 0.03	0.27 ± 0.04	0.21 ± 0.05	0.27 ± 0.06	0.24 ± 0.04	0.21 ± 0.05	NS
LDL cholesterol	3.67 ± 0.33	3.36 ± 0.33	3.25 ± 0.22	3.19 ± 0.30	3.21 ± 0.24	3.11 ± 0.29	NS
HDL cholesterol	2.09 ± 0.27	1.98 ± 0.27	2.06 ± 0.27	1.79 ± 0.18	1.83 ± 0.15	1.82 ± 0.22	NS
HDL_2 cholesterol	1.44 ± 0.32	1.36 ± 0.27	1.44 ± 0.28	1.07 ± 0.14	1.06 ± 0.13	1.06 ± 0.21	NS
HDL_3 cholesterol	0.69 ± 0.06	0.63 ± 0.05	0.62 ± 0.04	0.72 ± 0.06	0.78 ± 0.05	0.76 ± 0.04	$p < 0.05$

[a] $p < 0.05$ vs non-training (Student's t-test); [b] significant decrease ($p < 0.05$) over time irrespective of training

VA) was used for the evaluation of the lipid results. These data were analysed for effect of training and effect of time (irrespective of training).

Results

Physical work capacity

Maximal oxygen uptake was similar in the two groups before the start of the training programme - 30.2 ± 2.1 and 28.0 ± 0.8 $ml \cdot kg^{-1} \cdot min^{-1}$ in the training and the control group respectively (NS, Table 2). After 5 months of physical training there was an 8% increase in $\dot{V}O_2$ max to 32.7 ± 2.1 $ml \cdot kg^{-1} \cdot min^{-1}$ ($p < 0.05$), and a decrease in submaximal heart rate from 151 ± 3 to 142 ± 4 beats/min ($p < 0.05$) in the training group. During the same period no change occurred in the control group. $\dot{V}O_2$ max remained the same, 28.0 ± 0.8 $ml \cdot kg^{-1} \cdot min^{-1}$, and submaximal heart rate was 149 ± 5 beats/min before and 151 ± 4 beats/min after (NS).

Glycaemic control

No change in glycaemic control, as assessed by HbA_1, occurred in the training group during the period of physical exercise (Fig. 1). The non-training control group also showed no significant changes in this respect. The HbA_1 values for the two groups did not differ significantly on any of the sampling occasions. The mean blood glucose, calculated from home monitored values, did not change significantly in either group (Fig. 1). The number and severity of registered hypoglycaemic reactions were unchanged during the study in the training as well as in the control group (Fig. 1). The daily insulin dose was unchanged in both groups during the study period. Body mass index remained unchanged in both groups throughout the study period.

Serum lipoproteins

None of the patients was hyperlipaemic. Prestudy levels of total serum triglycerides and cholesterol did not differ between the two groups (Table 3). Similarly, the groups had similar contents of the different lipoprotein fractions, except for LDL triglycerides, which were higher in the training group ($p < 0.05$). However, 2.5 months of training resulted in a significant decrease in the LDL triglyceride fraction (−12%, $p < 0.01$, ANOVA), bringing it to level similar to that in the control group.

Total cholesterol levels for the total group decreased during the study period irrespective of training ($p < 0.05$, ANOVA). No significant changes occurred in the VLDL, LDL or HDL cholesterol fractions. However, training had a significant effect on the HDL_3 cholesterol subfraction, which was significantly lower than in the control group after 2.5 and 5 months of training ($p < 0.05$, ANOVA). The HDL_2 subfraction was unchanged in both groups.

Discussion

Although physical training is generally recommended for patients with Type 1 diabetes as part of their regular treatment, no firm evidence has been presented to support the presumed beneficial effect on glycaemic control. Several recent studies have failed to show an improvement in glycaemic control after 2–5 months of physical training [1–4]. In all these studies the training frequency was 3 times/week. We have examined the possibility that a daily exercise programme could be more suitable for improving glycaemic control in Type 1 diabetic patients. However, the 5 months of almost daily exercise in the present study did not elicit any improvement in blood glucose control, as assessed by home monitoring of blood glucose and monthly HbA_1 measurements (Fig. 1). It should be noted that all patients tolerated the training well and that no adverse reactions were seen; the frequency and intensity of hypoglycaemic reactions did not change during the study period.

Total cholesterol decreased significantly during the study period (Table 3), but this effect cannot be ascribed to the training since a decrease also occurred in the non-

training group. This type of seasonal variation, with a decrease in serum cholesterol levels from winter to spring, has been demonstrated by Doyle et al. [25]. Thus, effects on serum cholesterol in training studies without an appropriate control group should be evaluated with caution.

In the present study the HDL cholesterol fraction did not change with training, while the HDL_3 cholesterol subfraction decreased and the HDL_2 subfraction was unaffected. HDL_2 has been thought to be the more variable subfraction of the two [14], but recently the HDL_3 fraction was shown to fluctuate more than previously assumed [24], a finding which is supported by the present study. In healthy women, cross-sectional studies have shown that long-distance runners have a significantly higher concentration of HDL cholesterol compared to sedentary controls [12, 13]. The lack of effect on HDL and HDL_2 cholesterol in the present study may be explained by the fact that the pre-study levels in our patients were relatively high compared to other female Type 1 diabetic patients [23].

There was no change in total triglycerides in either group. However, our finding of a small decrease in the LDL triglycerides fraction is in accordance with the observation that healthy runners have significantly lower LDL triglycerides compared to sedentary control subjects [12].

In summary, long-term physical training of moderate intensity in female Type 1 diabetic patients resulted in minor changes in lipid profiles, whereas no effect was detected on glycaemic control. Thus, based on this and recent studies [1-4], regular physical exercise does not seem to help in achieving improved glycaemic control in Type 1 diabetes.

Acknowledgement. The present study was supported in part by the Swedish Diabetes Association, the Karolinska Institute, the Swedish Society of Medical Sciences, and the Swedish Medical Research Council (Project No. 3108). It was presented in part at the 19th Annual Meeting of the European Association for the Study of Diabetes, Oslo, Norway, September 14-17, 1983.

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Received: 7 May 1985
and in revised form: 28 October 1985

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