Aerobic exercise and the lipid profile in type 1 diabetic men: a randomized controlled trial

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ABSTRACT

LAAKSONEN, D. E., M. ATALAY, L. K. NISKANEN, J. MUSTONEN, C. K. SEN, T. A. LAKKA, and M. I. J. UUSITUPA. Aerobic exercise and the lipid profile in type 1 diabetic men: a randomized controlled trial. *Med. Sci. Sports Exerc.*, Vol. 32, No. 9, pp. 1541–1548, 2000. **Purpose:** Despite the potential importance of favorable changes in the lipid profile produced by aerobic exercise, training-induced lipid profile changes in atherosclerosis-prone type 1 diabetes mellitus (DM) have not heretofore been adequately addressed. **Methods:** We assessed the effect of a 12- to 16-wk aerobic exercise program on cardiorespiratory fitness and the lipid profile in young men with type 1 DM. Generally active men aged 20–40 yr with type 1 DM ($N = 56$) were randomized into training ($N = 28$) and control (untrained, $N = 28$) groups after baseline measurements. Training consisted of 30–60 min moderate-intensity running 3–5 times a week for 12–16 wk. **Results:** For the 42 men finishing the study, peak oxygen consumption ($\dot{V}O_{2\ peak}$) increased significantly only in the trained group. Total and low-density lipoprotein (LDL) cholesterol and apolipoprotein (apo) B decreased and the high-density lipoprotein (HDL)/apo A-I ratio increased in the trained group. HDL and apo A-I increased in both groups. The exercise program brought about improvements in the HDL/LDL and apo A-I/apo B ratios and apo B and triglyceride levels when comparing the relative (%) changes in the trained versus control group. In the trained group, men with HDL/LDL ratios below the group median at baseline showed even more favorable changes in their lipid profile than those with higher initial HDL/LDL ratios. Body mass index, percent body fat and hemoglobin A_{1c} did not change during the training period in either group. **Conclusions:** Endurance training improved the lipid profile in already physically active type 1 diabetic men, independently of effects on body composition or glycemic control. The most favorable changes were in patients with low baseline HDL/LDL ratios, likely the group with the greatest benefit to be gained by such changes. **Key Words:** EXERCISE TRAINING, LDL CHOLESTEROL, HDL CHOLESTEROL, TRIGLYCERIDES, APOLIPOPROTEIN

Physical activity has been linked in prospective epidemiological studies to reduced cardiovascular mortality in both the type 1 (insulin-dependent) diabetes mellitus (DM) (20) and the general population (14,21). Part of the protective effect of physical exercise has been hypothesized to derive from antiatherogenic effects on lipid and lipoprotein metabolism.

Decreased high-density lipoprotein (HDL) and elevated low-density lipoprotein (LDL) cholesterol and high triglyceride levels are well-established cardiovascular risk factors in nondiabetic (12) and type 2 (non-insulin-dependent) DM individuals (8,36). Low apolipoprotein (apo) A-I and high apo B levels are also associated with increased risk for cardiovascular death (29). Much less, however, is known of the role of lipoprotein and apolipoprotein levels in the pathogenesis of the accelerated atherosclerosis (13) in type 1 DM. Even so, results from cross-sectional studies suggest that lipoprotein and apolipoprotein levels are also important cardiovascular risk factors in type 1 DM (19,44).

Results from mainly small and uncontrolled studies testing the effects of regular aerobic exercise on the lipid profile in type 1 DM individuals have been variable. The positive effects of regular exercise on lipid and glucose metabolism have been quite well documented in especially early type 2 DM and in other populations with manifestations of the metabolic syndrome, at least when weight loss occurs (16,31). The metabolic syndrome is characterized by hyperinsulinemia and insulin resistance, abdominal obesity, low HDL and high triglyceride levels and disturbances in glucose metabolism (24). The pathophysiology of type 1 DM is very different from that of type 2 DM, however, and is characterized by severe insulinopenia requiring exogenous insulin administration for survival. In contrast to type 2 DM, moderately or well-controlled type 1 DM patients are

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generally of normal weight and frequently have normal lipid and lipoprotein levels (but abnormal lipid metabolism, because glucose and lipid metabolism is tightly integrated and is regulated by insulin). For these reasons results from exercise intervention studies in type 2 DM or in nondiabetic subjects cannot be extrapolated to type 1 DM.

Regular exercise in nondiabetic subjects is best known to increase HDL and the HDL/total cholesterol ratio (e.g., (40,41); reviewed in (31)). Many well-designed studies have also shown that endurance training decreases LDL cholesterol and less frequently triglyceride levels (e.g., (30)). The role of weight loss or body composition changes in these lipid changes is still controversial (34,43), although studies have shown favorable effects of regular exercise on the lipid profile independent of weight loss (35). Antiatherogenic effects of physical exercise on apolipoproteins B and A-I in nondiabetic individuals have been less consistently observed but appear to have been related mainly to weight loss (4,5,26,27,42).

Beneficial changes in HDL cholesterol and triglycerides or LDL cholesterol have generally been most prominent in subjects having low HDL and high triglyceride levels or high total cholesterol at baseline (31). Other factors affecting results include gender, glycemic status, the degree of obesity and age of the subjects, the type and length of training protocol, and whether weight loss or changes in body composition occur.

Since DM markedly increases coronary heart disease morbidity and mortality, treatment of the diabetic patient involves minimization of cardiac risk factors in addition to optimizing glycemic control. Coronary risk increases with increasing LDL cholesterol and triglyceride levels and decreasing HDL levels and HDL/LDL ratios, even across "normal" ranges (3). Furthermore, the clinician is frequently faced with dyslipidemic type 1 DM patients in whom a low-fat diet is not enough or the HDL lowering effect often occurring with diet alone (11,45) would not be desirable. Despite the potential benefits of regular physical exercise on the lipid profile in type 1 DM patients, surprisingly few exercise intervention studies have been carried out in such persons. Some (15,37,46), but not all (38), studies have shown positive but inconsistent effects of regular exercise on lipoprotein levels. These studies were small, nonrandomized, and sometimes uncontrolled. To our knowledge, no randomized or even controlled study of adequate sample size assessing the effects of aerobic exercise training on the lipid profile in type 1 DM patients has been published. Information about the effect of exercise training on apolipoprotein levels in type 1 DM is sparse.

The main purpose of this randomized controlled trial was to test the hypothesis that a 12–16 wk aerobic exercise program would induce antiatherogenic changes in lipid, lipoprotein and apolipoprotein levels in men with type 1 DM. Further aims were to assess the role that changes in body fat, body mass or glycemic control may play in mediating the effect of regular exercise on those changes. We also evaluated whether baseline lipoprotein levels modify the response of lipoproteins to exercise.

METHODS

Subjects. Otherwise healthy men ($N = 56$) aged 20–40 yr with type 1 DM were recruited into the study after giving written informed consent (Table 1). Diabetic subjects were chosen from patients followed at the Kuopio University Hospital, the North Karelian Central Hospital, and the Joensuu Health Center in Eastern Finland. Subjects were in moderate glycemic control (mean Hb $A_{1c} = 8.3\%$, SD 1.2), without clinically evident atherosclerotic disease, microalbuminuria (overnight urinary albumin excretion < 20 μg/min and normal serum creatinine), or more than mild background retinopathy. Achilles reflexes were missing in three subjects. Patients were otherwise without signs or symptoms of neuropathy. Ten patients entering the study were current smokers. All underwent clinical examination, routine laboratory tests, and ECG to rule out significant diseases. Reasons for exclusion included any cardiovascular or pulmonary disease and chronic medication other than insulin, including lipid-lowering medications. The Ethics Committee of the University of Kuopio approved the study.

Anthropometric measurements. For anthropometric measurements the patients were without shoes and lightly clothed (shorts or warm-up pants). Height was measured to the nearest cm. Body weight was measured to the nearest kg. The body mass index (BMI; kg body weight·m^{-2} height) was calculated. For percent body fat, the sum of biceps, triceps, subscapular, and suprailiac skin folds was measured to the nearest mm with calipers by two trained sports medicine students. Skin-fold measurements for a given subject were taken by the same person both before and after the training period. The skin-fold measurements made by a given person were equally distributed between trained and control groups. Percent body fat was calculated according to age and gender norms (6).

Evaluation of physical activity. Physical activity was quantified at baseline using the 12-Month Leisure-Time Physical Activity Questionnaire (14), which was modified from the Minnesota Leisure-Time Physical Activity Questionnaire (33) for use in the Kuopio Ischemic Heart Disease Risk Factor Study. We also attempted to assess leisure-time physical activity during the study with diaries, but less than a quarter of the patients recorded physical activity sufficiently during the study.

Exercise testing. All subjects underwent a maximal exercise test to determine peak oxygen consumption ($\dot{V}O_{2\ peak}$, mL·kg^{-1}·min^{-1}) and peak exercise capacity (W_{peak}, W·kg^{-1}), using an electrically braked bicycle ergometer, breath-by-breath gas monitoring and continuous ECG. Testing began at 50 W and was increased by 25 W every 2 min. Peak effort was defined subjectively by the subjects' peak voluntary effort (heart rate was greater than 85% of predicted maximum heart rate in all cases). The tests were carried out before and after 12–16 wk of training. For some of the posttraining measurements, the oxygen gas analyzer malfunctioned, obviating the $\dot{V}O_{2\ peak}$ results for 20 patients (9 in the training group and 11 in the control group). W_{peak} was obtained for all type 1 DM men completing the study, however.

TABLE 1. Baseline and post-training anthropometric and biochemical data for the 42 training and control insulin-dependent diabetic men finishing the study.

		Training	Control
N		20	22
Age (yr)	Baseline	32.5 ± 5.7	29.5 ± 6.3
$\dot{V}O_{2peak}$ (mL·kg^{-1}·min^{-1})	Baseline	43.4 ± 8.0	42.0 ± 7.2
	After training	46.1 ± 6.6[a]	43.4 ± 7.2
W_{peak}[b] (W·kg^{-1})	Baseline	3.36 ± 0.65	3.31 ± 0.54
	After training	3.55 ± 0.67[c]	3.36 ± 0.52
Daily insulin dosage (U·kg^{-1})	Baseline	0.68 ± 0.19	0.71 ± 0.18
	After training	0.68 ± 0.20	0.70 ± 0.20
HbA_{1c} (%)	Baseline	8.2 ± 1.1	8.3 ± 1.3
	After training	8.0 ± 1.0	8.5 ± 1.6
Plasma glucose (mmol·L^{-1})	Baseline	10.5 ± 6.0	10.1 ± 4.3
	After training	12.1 ± 6.0	11.9 ± 5.8
BMI (kg·m^{-2})	Baseline	24.4 ± 1.9	24.4 ± 2.2
	After training	24.3 ± 1.9	24.5 ± 2.3
Percent body fat	Baseline	20.5 ± 4.1	18.5 ± 5.0
	After training	20.4 ± 4.7	18.2 ± 5.8
Serum total cholesterol (mmol·L^{-1})	Baseline	4.89 ± 0.97	4.71 ± 1.08
	After training	4.66 ± 0.94[d]	4.79 ± 1.18
LDL cholesterol (mmol·L^{-1})	Baseline	3.15 ± 0.81	2.99 ± 0.74
	After training	2.88 ± 0.75[e]	2.92 ± 0.80
HDL cholesterol (mmol·L^{-1})	Baseline	1.21 ± 0.28	1.21 ± 0.40
	After training	1.32 ± 0.28[f]	1.31 ± 0.45[g]
HDL/LDL	Baseline	0.41 ± 0.13	0.42 ± 0.12
	After training	0.49 ± 0.16[h]	0.46 ± 0.15[h]
Serum triglycerides (mmol·L^{-1})	Baseline	1.18 ± 0.50	1.12 ± 0.53
	After training	1.02 ± 0.50	1.25 ± 0.53
Apolipoprotein B (g·L^{-1})	Baseline	0.82 ± 0.20	0.78 ± 0.18
	After training	0.75 ± 0.19[i]	0.82 ± 0.20
Apolipoprotein A–I (g·L^{-1})	Baseline	1.42 ± 0.27	1.44 ± 0.34
	After training	1.50 ± 0.25[j]	1.54 ± 0.38[k]
HDL/Apolipoprotein A–I	Baseline	0.84 ± 0.08	0.84 ± 0.10
	After training	0.88 ± 0.07[l]	0.84 ± 0.10
Apo AI/apo B*	Baseline	1.83 ± 0.51	1.90 ± 0.47
	After training	2.09 ± 0.52[m]	1.96 ± 0.51

Data are means ± SD.
[a] $P = 0.023$, before vs. after training; [b] W_{peak}, peak exercise capacity; Apo A–I/apo B, apolipoprotein A–I/apolipoprotein B; [c] $P = 0.003$, before vs. after training; [d] $P = 0.001$, before vs. after training; [e] $P = 0.048$, before vs. after training; [f] $P = 0.012$, before vs. after training; [g] $P = 0.011$, before vs. after training; [h] $P < 0.001$, before vs. after training; [i] $P = 0.003$, before vs. after training; [j] $P = 0.014$, before vs. after training; [k] $P = 0.036$, before vs. after training; [l] $P = 0.042$, before vs. after training; [m] $P = 0.001$, before vs. after training.

Randomization. Diabetic men were divided into two groups based on median age. Subjects within the two groups were paired based on $\dot{V}O_{2\ peak}$ and randomized into training and control (untrained) groups. The training group underwent a 12–16 wk program of moderate-intensity endurance training. The untrained group was instructed to continue their normal level of physical activity. Of the 56 men participating in baseline measurements, 42 (training group $N = 20$, age 31.7 ± 5.8 yr [mean ± SD], duration of diabetes 13.8 ± 9.2 yr; control group $N = 22$, age 29.8 ± 6.4 yr, duration of diabetes 10.8 ± 5.8 yr) completed the study. All subjects were encouraged to finish the study regardless of adherence to the exercise goals of the group to which they were assigned. Reasons given by those not completing the study included time constraints imposed by work, major home repairs and moving out of the area. Of the six smokers finishing the study, two belonged to the training group and four to the control group.

Training. The training program consisted of 12–16 wk of moderate-intensity, sustained running. The first week consisted of 20–30 min running at about 50–60% $\dot{V}O_{2\ peak}$ mixed with walking as necessary three times a week. Training was gradually increased on an individualized basis, with a goal of 30–60 min running at 60–80% $\dot{V}O_{2\ peak}$ 4–5 times a week, although in practice only about one fourth of the training group participants achieved this level. The two sports medicine students guided the training program. Regular contact was maintained by telephone at 1–3 wk intervals or as necessary. Insulin dosage was adjusted as needed throughout the study based on regular home blood glucose monitoring and symptoms. All subjects were instructed to follow the American Diabetes Association recommendations for glycemic control during exercise for type 1 diabetic patients (1).

Dietary records. The patients kept a seven-day food record at baseline and after 6 and 12 wk. Because of poor compliance with keeping dietary records especially after baseline, however, dietary records after 6 and 12 wk were pooled. Food records were over seven consecutive days, during which the diet was considered representative by the subjects. Written and oral instructions were given for providing detailed information about the quantity and quality of all items consumed during the 7-d period. Nutrient intake (23) was calculated using the Micro-Nutrica software package for dietary analysis (Social Insurance Institution, Helsinki, Finland, 1993).

Blood sample collection and preparation. On a separate day from $\dot{V}O_{2\ peak}$ testing blood samples were taken both before and after the training period 1.5–4 h after eating a light carbohydrate-rich breakfast or lunch in the morning or mid-day. EDTA blood samples for later determination of HbA_{1c} levels were stored at 4°C and measured

within 4 d of being drawn. Samples for plasma glucose determination were drawn in NaFl/K-oxalate tubes and centrifuged for plasma. The plasma was stored at −74°C until determination within 2 wk of being drawn. Blood samples for serum lipoprotein, apolipoprotein, and triglyceride analyses were centrifuged for serum and stored at −74°C until determination after the completion of the study.

Blood HbA_{1c} and plasma glucose levels. Blood HbA_{1c} was measured using liquid cation exchange chromatography (normal range 4.0–6.0%). Plasma glucose levels were measured using a glucose oxidase method.

Serum cholesterol and triglyceride levels. Serum cholesterol and triglyceride levels were measured enzymatically (CHOD-PAP and GPO-PAP methods) with a Kone Specific Chemical Analyzer (Kone, Ltd., Espoo, Finland). The same method was also used for HDL after removal of LDL and VLDL by dextran sulfate/$MgCl_2$ (22). LDL was calculated according to Friedewald's formula (9), which has been validated in type 1 DM (39).

Serum apolipoprotein levels. Analyses of apo A-I and apo B were based on the measurement of immunoprecipitation enhanced by polyethylene glycol (PEG) at 340 nm (10) using a Kone Specific Chemical Analyzer (Kone Ltd.).

Statistical methods. SPSS/PC Windows software (SPSS, Chicago, IL) was used for statistical analyses. Variables are expressed as mean ± SD, except for percentages, which are expressed as median (95% confidence intervals [CI]). Differences in the measured variables before and after exercise were tested between groups using Student's unpaired *t*-test and within groups using ANOVA repeated measures after determining normality in distribution of the variables in question. The Mann-Whitney *U*-test was used to compare relative (%) changes in variables in trained and untrained groups over the training period. Correlation, partial correlation, and stepwise multiple regression analysis were used to assess the associations between selected variables at baseline. Statistical significance was defined at $P < 0.05$.

RESULTS

There were no significant differences with respect to glycemic control, cardiovascular fitness, or lipid profile between trained and control group before training (Table 1). The level of leisure-time aerobic (brisk walking, jogging, skiing, cycling, skating, and swimming) and conditioning (ball sports, weight lifting, and downhill skiing in addition to aerobic exercise) physical activity of the study participants for the 12 months before the study (Table 2) was for the most part in accordance with American Diabetes Association recommendations (1).

Total energy intake (training group 2324 ± 418 kcal·d^{-1}, control group 2287 ± 473 kcal·d^{-1}, $P = 0.36$), percent of total energy intake (E %) from fat (training group 33.5 ± 5.7 E %, control group 35.3 ± 8.0 E %, $P = 0.49$) and dietary polyunsaturated/saturated fatty acid ratio (training group 0.48 ± 0.17, control group 0.47 ± 0.17, $P = 0.86$) from the 32 men filling out dietary records were similar between training ($N = 18$) and control ($N = 14$) groups.

TABLE 2. Leisure-time aerobic and conditioning physical activity for the 12 months before baseline in the diabetic men.

	Training	Control	*P*
N	18	19	
Aerobic physical activity			
Energy expenditure (kcal·d^{-1})	224 ± 160	173 ± 228	0.43
Duration (h·wk^{-1})	2.8 ± 2.0	2.5 ± 2.9	0.96
Frequency (times·wk^{-1})	3.8 ± 2.7	2.7 ± 2.3	0.17
Conditioning physical activity			
Energy expenditure (kcal·d^{-1})	311 ± 230	254 ± 264	0.49
Duration (h·wk^{-1})	4.0 ± 2.8	3.7 ± 3.5	0.92
Frequency (times·wk^{-1})	4.8 ± 3.4	3.8 ± 2.6	0.28

Data are means ± SD.

Baseline associations of physical fitness, physical activity, and other clinical features with the lipid profile. $\dot{V}O_{2\ peak}$ ($r = -0.41$, $P = 0.002$) correlated inversely with age. W_{peak} also tended to correlate inversely with age ($r = -0.23$, $P = 0.089$). $\dot{V}O_{2\ peak}$ tended to be inversely related to total cholesterol ($r = -0.25$, $P = 0.073$) but not after controlling for age. Measures of cardiovascular fitness were not related to any other lipid profile index.

After adjusting for age, daily energy expenditure on leisure-time aerobic activity was associated with $\dot{V}O_{2\ peak}$ ($r = 0.33$, $P = 0.042$) and W_{peak} ($r = 0.57$, $P < 0.001$). After adjusting for percent body fat, daily energy expenditure on leisure-time aerobic activity correlated inversely with triglyceride levels ($r = -0.33$, $P = 0.049$) and positively with the apo A-I/apo B ratio ($r = 0.34$, $P = 0.048$). Daily energy expenditure on aerobic activity also tended to correlate with the HDL/total cholesterol ratio ($r = 0.29$, $P = 0.089$), but associations with other lipid or lipoprotein indices did not reach statistical significance. The correlation between daily energy expenditure on aerobic and conditioning activity and between daily energy expenditure on physical activity and duration of physical activity was high ($r > 0.90$). Consequently, substitution of conditioning physical activity for aerobic activity had little effect on the results. Substitution of duration of physical activity for physical activity energy expenditure also yielded similar results.

BMI and percent body fat correlated with LDL cholesterol ($r = 0.29$, $P = 0.033$ and $r = 0.45$, $P = 0.001$, respectively), total cholesterol ($r = 0.29$, $P = 0.033$ and $r = 0.46$, $P = 0.001$, respectively), and apo B ($r = 0.33$, $P = 0.015$ and $r = 0.43$, $P = 0.002$, respectively). No other associations with lipid or glycemic indices reached significance.

HbA_{1c} correlated with LDL ($r = 0.27$, $P = 0.050$), total cholesterol ($r = 0.30$, $P = 0.028$), and apo B ($r = 0.26$, $P = 0.058$) but not with BMI, percent body fat, or indices of cardiovascular fitness.

Determinants of baseline lipid, lipoprotein, and apolipoprotein measures. By using stepwise multiple linear regression with percent body fat, HbA_{1c}, and aerobic exercise daily energy expenditure as explanatory variables, percent body fat (partial β 0.46) was determinant of total cholesterol at baseline (adjusted $r^2 = 0.25$, $P = 0.0009$). HbA_{1c} approached significance (partial β 0.25, $P = 0.056$).

Also by using percent body fat, HbA_{1c}, and aerobic exercise daily energy expenditure as explanatory variables, percent body fat (partial β 0.44 and 0.42) explained 19% and 16% of the variation in LDL and apo B at baseline ($P = 0.001$ and 0.003). HbA_{1c} approached significance. BMI explained less of the variance when BMI was substituted for percent body fat. Daily energy expenditure on aerobic exercise (partial β −0.33) and percent body fat (partial β 0.36) explained 19% of the variation in triglyceride levels. Daily energy expenditure on aerobic exercise (partial β 0.34) was also determinant of the apo A-I/apo B ratio (adjusted $r^2 = 0.09$, $P = 0.046$). When substituted for aerobic exercise daily energy expenditure, neither peak exercise capacity nor $\dot{V}O_{2\ peak}$ significantly explained any of the variation in lipid levels.

Effect of endurance training. After 12–16 wk of endurance training, $\dot{V}O_{2\ peak}$ and W_{peak} increased significantly only in the training group (Table 1). In the training group, total and LDL-cholesterol and apo B decreased, and HDL, apo A-I, and the HDL/LDL and apo A-I/apo B ratios increased. In contrast, only HDL, apo A-I, and the HDL/LDL ratio increased in the control group. Results for all analyses are essentially identical when substituting HDL/total cholesterol for HDL/LDL. There were no significant changes in BMI, percent body fat, HbA_{1c} or daily insulin dosage in either group. For the 22 men completing the study who filled out dietary records after 6 or 12 wk, no changes in daily energy intake, fat intake, or dietary polyunsaturated/saturated fatty acid ratio occurred in either the trained ($N = 10$) or untrained ($N = 12$) group ($P > 0.3$ for all variables).

When comparing the relative changes brought about by the 12- to 16-wk endurance training program between the training and control groups, favorable changes in HDL/LDL, apo B, apo A-I/apo B, and triglyceride levels were significantly greater in the training group (Table 3). Of note, triglyceride levels increased 21% in the control group, although this change was not significant when comparing pre- and post-training levels.

Baseline HDL/LDL and the effect of endurance training on lipid levels. To examine the possible role of baseline lipid status in the response of the lipid profile to regular physical exercise, we divided the training and control groups into two subgroups based on the training group median HDL/LDL value (Table 4). As can clearly be seen, the relative changes in the HDL/LDL and apo A-I/apo B ratios produced by training are more prominent in type 1 DM men with low HDL/LDL levels at baseline. Smaller or no differences were found when dividing into subgroups based on median HDL or LDL baseline levels (data not shown). Apolipoprotein B decreased more with training in the men less physically active at baseline, but responses in other lipids, lipoproteins, and apolipoproteins was not clearly different. Physical fitness as measured by $\dot{V}O_{2\ peak}$ or W_{peak} did not modify the response to training (data not shown).

DISCUSSION

This study is to our knowledge the first randomized or even controlled study of sufficient sample size assessing the effect of regular aerobic exercise on the lipid profile in type 1 DM. The 12–16 wk endurance exercise program produced favorable changes in lipid, lipoprotein and apolipoprotein levels in type 1 diabetic men who for the most part already met the American Diabetes Association recommendations for physical exercise (1) at baseline. These changes were independent of effects on body mass or composition and glycemic control, and occurred despite a rather modest improvement in peak oxygen consumption.

The level of aerobic activity as measured by daily energy expenditure was associated inversely with triglyceride levels and directly with the apo A-I/apo B ratio, even after controlling for adiposity and glycemic control. Percent body fat correlated with total and LDL cholesterol, apo B, and triglyceride levels. Peak oxygen consumption was not associated with any of the lipid profile indices. This suggests that although physical activity and physical fitness are interrelated, physical activity has a greater bearing on lipid levels, independently of body composition. In contrast to our results, Austin et al. (2) found negative correlations between $\dot{V}O_{2\ peak}$ and total and LDL cholesterol and between BMI and HDL in 59 adolescent boys and girls with type 1 DM. The reason for the discrepancy in results may be in part due to the younger age group and inclusion of females in their study.

At the end of the exercise program the relative increase in HDL/LDL and especially apo A-I/apo B was greater in the training group, with no changes occurring in body

TABLE 3. Relative changes (%) in peak oxygen consumption, peak exercise capacity and lipid profile during the training period for the trained and control diabetic men.

Relative change	Training	Control	*P*
N	20	22	
$\dot{V}O_{2peak}$ ($mL \cdot kg^{-1} \cdot min^{-1}$, combined $N = 24$)	5.6 (−2.7–14.7)	3.2 (−5.8–13.1)	0.401
W_{peak}* ($W \cdot kg^{-1}$, combined $N = 44$)	8.3 (−2.2–16.1)	1.5 (−3.9–4.5)	0.124
Total cholesterol ($mmol \cdot L^{-1}$)	−6.2 (−3.9–−12.6)	2.5 (−6.9–4.9)	0.075
LDL cholesterol ($mmol \cdot L^{-1}$)	−11.1 (0.0–−16.8)	−0.9 (−10.3–2.7)	0.152
HDL cholesterol (mmol·L)	9.5 (−1.5–20.5)	6.9 (1.2–15.0)	0.559
HDL/LDL	20.4 (12.2–30.1)	12.6 (0.2–30.8)	0.044
Triglycerides ($mmol \cdot L^{-1}$)	−14.6 (−3.0–−26.8)	21.4 (−10.4–43.9)	0.015
Apolipoprotein B ($g \cdot L^{-1}$)	−11.6 (−6.9–−13.9)	1.3 (−2.9–11.0)	0.001
Apolipoprotein A–I ($g \cdot L^{-1}$)	5.7 (−2.5–14.1)	4.9 (−2.1–8.1)	0.919
HDL/Apolipoprotein A–I	3.4 (−0.9–11.0)	1.1 (−5.5–5.0)	0.212
Apo A–I/apo B[a]	16.4 (8.5–25.9)	2.8 (−3.4–9.0)	0.004

Data are medians (95% CI).
[a] Abbreviations as in Table 1.

TABLE 4. Relative changes (%) in exercise capacity and the lipid profile during the training period based on the median HDL/LDL baseline status in the training group; *P*-values are for training vs. control groups.

Relative Change		HDL/LDL < 0.42[a]	*P*[b]	HDL/LDL ≥ 0.42*	*P*[b]
W_{peak} (W)	Training	3.7 (−7.4–16.1)	0.89	9.2 (0.0–28.8)	0.045
	Control	1.2 (−9.2–16.1)		1.5 (−9.1–8.4)	
Total cholesterol (mmol·l^{-1})	Training	−10.0 (−14.3–6.8)	0.18	−6.0 (−9.9–5.5)	0.17
	Control	2.1 (−8.4–12.8)		3.7 (−3.9–14.9)	
LDL cholesterol (mmol·l^{-1})	Training	−12.3 (−20.3–2.4)	0.38	−11.7 (−16.5–2.5)	0.27
	Control	3.7 (−17.3–6.9)		−0.2 (−6.5–7.5)	
HDL cholesterol (mmol·l^{-1})	Training	10.9 (−6.7–12.4)	0.31	5.8 (−6.2–17.2)	0.82
	Control	9.6 (−8.2–29.1)		4.2 (−3.5–20.6)	
HDL/LDL	Training	29.7 (13.8–52.4)	0.05	14.3 (11.5–33.9)	0.27
	Control	13.8 (−2.9–29.1)		2.7 (−5.3–24.0)	
Triglycerides (mmol·l^{-1})	Training	−18.4 (−40.0–15.2)	0.06	−14.3 (−40.4–14.8)	0.15
	Control	17.7 (−17.3–58.4)		25.2 (−24.1–46.2)	
Apo B‡ (g·l^{-1})	Training	−14.9 (−20.3–−7.0)	0.005	−9.8 (−14.9–−2.0)	0.02
	Control	−2.5 (−10.7–25.0)		5.7 (−1.9–11.9)	
Apo A–I‡ (g·l^{-1})	Training	10.9 (−1.6–18.8)	0.44	9.8 (−6.7–12.4)	0.51
	Control	5.8 (0.9–16.5)		4.1 (−1.5–10.6)	
HDL/Apo A–I‡	Training	4.8 (−3.7–11.0)	0.23	2.5 (−7.2–14.2)	0.57
	Control	0.4 (−7.5–18.3)		4.0 (−9.8–7.1)	
Apo A–I/apo B‡	Training	24.1 (8.5–36.2)	0.01	11.7 (−6.6–23.9)	0.15
	Control	7.1 (−10.7–19.9)		1.8 (−7.7–7.1)	

Data are medians (95% CI).
[a] $N = 9$–11 in the training and control groups.
[b] Training vs. control group.
Abbreviations as in Table 1.

composition, body mass, glycemic control, dietary energy, and fat intake or insulin dosage. LDL and apo B also decreased significantly during the training period only in the training group, although only the relative change in apo B significantly differed from the control group. The 12- to 16-wk training program also significantly increased cardiovascular fitness, as demonstrated by modest gains in $\dot{V}O_{2\ peak}$ and W_{peak} in the training group.

In a small controlled but not randomized study, Yki-Jarvinen et al. (46) also found increases in the HDL/total cholesterol ratio, without significant changes in HDL or total cholesterol, BMI, or glycemic control after 6 wk of ergometer cycling exercise for 60 min 4 d·wk^{-1}. The relative change did not differ significantly between the trained and control groups; however, possibly because of the very small study size and short duration of training. In a very interesting but uncontrolled study investigating the effect of 3 months of regular exercise in 20 type 1 DM men and women 22–48 yr old, $\dot{V}O_{2\ peak}$ increased by only 6%, but LDL decreased by 14% and HDL increased by 10%, with concomitant weight loss and decreased percent body fat (15). Corresponding changes in apo B and apo A-I were also found. The weight loss and changes in body composition are clearly potential confounding factors in that study. A 16-wk program of 60 min mixed and aerobic exercise three times a week decreased total cholesterol without effects on HDL, triglycerides, body weight, or glycemic control in nine 25- to 46-yr-old men with type 1 DM in an uncontrolled study (37). The small study size, exercise frequency of only three times a week and use of mixed exercise could have affected the results. Twenty minutes of daily bicycle exercise had no effect on major lipid profile indices after 5 months in six 25- to 45-yr-old women with type 1 DM, although a small improvement in $\dot{V}O_{2\ peak}$ was noted (38). The rather short duration of exercise and small study size are obvious shortcomings of that study. Also, the lipid profile in mainly premenopausal nonobese women has usually been less responsive to regular exercise in studies in nondiabetic subjects (16,31). In the above-mentioned studies that were uncontrolled, seasonal variation in lipid and lipoprotein levels could either exaggerate or decrease the apparent effect of regular exercise on the lipid profile.

Patients with low HDL/LDL ratios at the beginning of the training program had the most favorable response to regular training. Of the various lipid indices, the HDL/LDL or HDL/total cholesterol ratio is the best single predictor of cardiovascular risk (3,29) and improvement of prognosis in response to lipid lowering therapy (3). More favorable changes in patients with low HDL/LDL levels are therefore clinically important because these are the patients standing to gain the most benefit by such changes.

Training furthermore increased the HDL/apo A-I ratio, with no change occurring in the control group. The HDL/apo A-I ratio is considered to be representative of the HDL_2/HDL_3 cholesterol ratio, because HDL_2 cholesterol has much less protein content than HDL_3 (7). Although controversial (29), HDL_2 is often held to be more antiatherogenic than HDL_3 cholesterol (7,25). Training in nondiabetic subjects most often has preferentially increased the HDL_2 subfraction (31). In contrast, Lehmann et al. (15) found increased HDL_3 cholesterol and unchanged HDL_2 levels with training in an uncontrolled exercise intervention in type 1 DM patients. No other studies have examined the effect of regular physical exercise on HDL subfractions in type 1 DM.

Of note is that in the present study HDL, apo A-I and the HDL/LDL ratio increased also in the control group, underscoring the need for a control group in lipid intervention studies. The reason for the increase in the control group is probably in part due to seasonal variability. The least favorable changes in HDL levels occur during cold months (17) (our study began in February and ended in June). We

also cannot rule out that the control group did not spontaneously increase the amount of physical activity during the spring.

The relative change in triglyceride levels was also more favorable in the trained men, although part of the difference between the trained and untrained men can be attributed to the increase in triglyceride levels in the untrained men. The antiatherogenic effect of training on triglyceride levels may be in part a spurious finding, since the samples were taken postprandially. Still, changes in HDL/LDL correlated inversely with changes in triglyceride levels, suggesting that training had a positive effect.

Mechanisms by which physical exercise may produce favorable changes in lipoprotein and lipid metabolism even in the absence of weight loss include increasing skeletal muscle lipoprotein lipase activity and decreasing hepatic triglyceride lipase activity (32,35). Furthermore, regular physical exercise may favorably affect reverse cholesterol transport by decreasing cholesterol ester transferase protein concentration or activity (28) and increasing lecithin: acylcholesterol transferase activity (18), preferentially increasing HDL_2 levels.

The present study also has some important limitations. Blood samples were taken only before exercise training and after exercise training. Percent body fat was estimated by skin fold measurements rather than by the more accurate but less practical underwater weighing technique. Compliance with completing food records was poor and obviates detection of subtle dietary changes and their possible impact during the exercise program. Furthermore, 14 of the 56 diabetic men enrolled in the study dropped out.

The present study can be considered to be the first controlled study of adequate sample size to assess the response in lipid, lipoprotein and apolipoprotein levels to aerobic exercise in type 1 DM patients. Twelve to 16 wk of moderately intense physical exercise decreased LDL cholesterol and apo B and increased the HDL/LDL and apo A-I/apo B ratios in type 1 DM men already meeting the American Diabetes Association recommendations for physical exercise, independently of effects on body weight, body composition or glycemic control. HDL and apo A-I levels increased also in the control group, emphasizing the need for controlled studies. The most favorable training induced changes in the HDL/LDL and apo A-I/apo B ratios were in patients with low baseline HDL/LDL levels, likely the group with the most benefit to be gained by such changes.

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