The Relationship of Physical Fitness to Lipid and Lipoprotein(a) Levels in Adolescents With IDDM

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OBJECTIVE — Increased physical activity and physical fitness are recommended therapeutic modalities in addition to insulin and diet in the management of children with IDDM. The aim of this study was to assess the fitness levels of adolescents with IDDM compared with healthy control subjects and to evaluate the relationship between physical fitness and metabolic control.

RESEARCH DESIGN AND METHODS — We studied 59 patients with IDDM, 28 boys and 31 girls, age 15.6 ± 2.5 yr, duration of diabetes 7.6 ± 3.5 yr, HbA_1 10.6 ± 2.1% (mean ± SD), and compared them with 18 healthy, nondiabetic control subjects, 9 boys and 9 girls, matched for age, BMI, and Tanner stage. Physical fitness was measured by VO_{2max} during progressive bicycle ergometry. HbA_1 was used to determine glycemic control. Lipid profile included fasting total cholesterol, HDL, LDL, Lp(a), and TG levels.

RESULTS — Patients with IDDM had lower VO_{2max} levels than control subjects (33.7 ± 7.0 vs. 41.0 ± 10.4 $ml \cdot kg^{-1} \cdot min^{-1}$, $P = 0.001$). Males with IDDM had lower VO_{2max} than male control subjects, but diabetic and control females showed no difference. In IDDM patients, VO_{2max} correlated inversely with HbA_1, insulin dose, cholesterol, LDL, TGs, and Lp(a), but did not correlate with HDL, which correlated inversely with BMI.

CONCLUSIONS — We conclude that the state of physical fitness is an important correlate of lipid levels and Lp(a) in adolescents with IDDM. We speculate that higher physical fitness levels in adolescents with IDDM may decrease the risk of CVD through modulating lipid levels.

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LP(A), LIPOPROTEIN(A); IDDM, INSULIN-DEPENDENT DIABETES MELLITUS; BMI, BODY MASS INDEX; HDL, HIGH-DENSITY LIPOPROTEIN; LDL, LOW-DENSITY LIPOPROTEIN; TG, TRIGLYCERIDE; S_I, INSULIN SENSITIVITY; CVD, CARDIOVASCULAR DISEASE; RER, RESPIRATORY EXCHANGE RATIO; HPLC, HIGH-PERFORMANCE LIQUID CHROMATOGRAPHY; CDC, CENTERS FOR DISEASE CONTROL; ELISA, ENZYME-LINKED IMMUNOSORBENT ASSAY; CV, COEFFICIENT OF VARIATION; VLDL, VERY-LOW-DENSITY LIPOPROTEIN; APOA, APOLIPOPROTEIN A; NS, NO SIGNIFICANCE.

Physical training and increased physical fitness have been observed to improve insulin sensitivity in diabetic patients in several studies (1–3) and have been described as a beneficial adjunct to diet and insulin therapy. Despite the improvement in insulin action, however, longitudinal studies of long-term physical training programs have failed to improve glycemic and metabolic control in the majority of these patients (1,4). The reasons for this could be increased dietary intake or inappropriate decreases in insulin doses for fear of activity-related hypoglycemia.

In cross-sectional studies, physical fitness has been shown to be negatively related to glycemic control (5–7). Whether or not physical fitness has any relationship to lipid levels in adolescents with IDDM is not clear, however. Therefore, the aim of this study was to evaluate the physical fitness levels in a cross section of adolescents with IDDM and to assess its relationship to plasma lipid levels, specifically Lp(a), a lipoprotein strongly associated with early CVD (8–9). To our knowledge, no previous studies have addressed the natural relationships among these factors in a cross section of diabetic children and adolescents.

RESEARCH DESIGN AND METHODS

— We recruited 59 white patients with IDDM from among the patients followed at the Diabetes Center of Children's Hospital of Pittsburgh. The group consisted of 28 boys and 31 girls with a mean age of 15.6 ± 2.5 yr (range 9.5–19.3 yr). All of the patients were on twice-daily subcutaneous insulin injections consisting of combined intermediate (NPH or Lente) and short-acting (regular) insulin, with a mean daily insulin dose of 1.07 ± 0.28 $U \cdot kg^{-1} \cdot day^{-1}$, (range 0.80–1.35 $U \cdot kg^{-1} \cdot day^{-1}$). BMI calculated as weight (kg)/height (m^2) was 22.2 ± 3.2 kg/m^2 and Tanner developmental stages II-V. None of the patients had clinical evidence of chronic complications or other systemic diseases. Two patients were on thyroid replacement therapy for autoimmune thyroiditis and were euthyroid at the time of this evaluation.

The patient group was compared with a group of 18 healthy control subjects, 9 boys and 9 girls, matched for age (14.2 ± 2.1 yr), BMI (20.7 ± 3.4 kg/m^2) and Tanner stage. The control subjects were recruited by word of mouth from children of faculty, employees, and friends of the Division of Pediatric Endocrinology.

The procedures were approved by the Human Rights Committee of Children's Hospital of Pittsburgh. Research participants and their parents gave written consent to the procedures after they were fully explained. All studies were performed at the General Clinical Research Center at Children's Hospital of Pittsburgh.

Physical fitness was determined by VO_{2max} during progressive bicycle ergometry to exhaustion performed in the Cardiopulmonary Physiology Laboratory at Children's Hospital of Pittsburgh. The evaluation followed Godfrey's protocol (10), which consisted of a cycle ergometric test starting at 0 resistance and increasing the resistance minute by minute by increments based on body size (10 watts for subjects <125 cm; 15 watts for subjects 125–150 cm; and 20 watts for subjects >150 cm in height).

Minute ventilation, CO_2 production, O_2 consumption, and RER were determined via a Medical Graphics 2001 Metabolic Cart. Maximal effort was defined by a RER >1.10 and a heart rate that approached 100% of age-predicted maximal value. The day of the testing, fasting blood samples were obtained for HbA_1 and lipid level determinations. The patients received their usual subcutaneous insulin dose before breakfast, and the exercise test was performed 2 h after lunch. None of the patients experienced hypoglycemia during the test.

Biochemical analysis

HbA_1 was measured by HPLC (DIAMAT, Bio-Rad, Richmond, CA). Normal range was 5.1–7.8% in our laboratory. Cholesterol, HDL, and TG measurements were performed using CDC protocols. Cholesterol determinations were performed using Cholesterol High Performance-K enzymatic kit method (Boehringer Mannheim, Indianapolis, IN). For HDL measurements, serum was precipitated by dextran sulfate using HDL Cholesterol Determination (Seradyn, Indianapolis, IN). The supernatant then was measured for its cholesterol content as described earlier. TG levels were measured using Triglyceride-Glycerol blanked (Boehringer Mannheim). This method enabled us to give true TG measurements. LDL cholesterol was computed using cholesterol, HDL cholesterol, and TG levels. For Lp(a), we used ELISA methodology (Terumo Medical, Elton, MD). The method uses monoclonal anti-Lp(a) antibody technique with a sensitivity of 0.8 mg/dl. The intra-assay and interassay CVs are <6 and <10.3%.

Statistical analysis

Data were expressed as means ± SD. Two-tailed Student's *t* test compared the group of diabetic patients with control subjects. Least-squares linear regression analysis was applied to assess bivariate and multivariate relationships. Nonparametric statistics were applied when analyzing Lp(a) data that had a skewed distribution. Mann-Whitney test was used for comparison of two groups. Spearman rank order correlation was used for bivariate relationships. A nonparametric multiple regression was used with ranking of all observed data to assess multivariate relationships. Statistical significance is implied by $P < 0.05$.

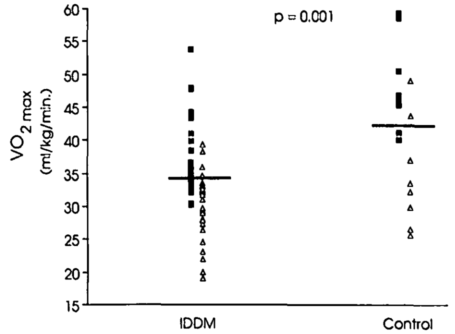

Figure 1—*Physical fitness levels of IDDM patients and control subjects, male (■) and female (△) subjects.*

RESULTS— Adolescents with IDDM had lower VO_{2max} levels than control subjects (33.7 ± 7.0 vs. 41.0 ± 10.4 $ml \cdot kg^{-1} \cdot min^{-1}$, $P = 0.001$), as shown in Fig. 1. VO_{2max} was lower in male patients with IDDM than in male control subjects (37.9 ± 5.8 vs. 48.2 ± 6.8 $ml \cdot kg^{-1} \cdot min^{-1}$, $P < 0.001$), but higher than in female patients with IDDM (37.9 ± 5.8 vs. 29.6 ± 5.4 $ml \cdot kg^{-1} \cdot min^{-1}$, $P = 0.001$). No significant difference occurred between female patients and control subjects (29.6 ± 5.4 vs. 33.8 ± 8.1 $ml \cdot kg^{-1} \cdot min^{-1}$, $P = 0.08$).

In the diabetic subjects, cholesterol was 3.8 ± 0.8 mM; LDL, 2.6 ± 0.7 mM; HDL 0.8 ± 0.2 mM; TG, 0.9 ± 0.1 mM; and VLDL, 0.3 ± 0.1 mM, with no significant differences between diabetic patients and control subjects (Table 1). The distribution of plasma Lp(a) concentrations was continuous but highly skewed in diabetic patients and control subjects (Fig. 2). Using the Mann-Whitney test for nonparametric statistics, we found no difference in Lp(a) levels between diabetic patients and control subjects (11 ± 16 vs. 8 ± 11 mg/dl). No gender-related differences were evident in lipid levels among dibetic patients or control subjects.

VO_{2max} correlated inversely with HbA_1, LDL, cholesterol, TGs, Lp(a), and insulin dose, but not with VLDL or HDL (Table 2). The latter was inversely related to BMI ($r = -0.32$, $P = 0.02$). To evaluate the relationship of VO_{2max} to lipid levels, independent of its relationship to HbA_1, we used partial correlation

Table 1—*Plasma lipid levels in diabetic patients and control subjects*

	IDDM patients	Control subjects	P
Cholesterol (mM)	3.8 ± 0.8 (2.1–6.1)	3.3 ± 0.6 (2.2–4.4)	NS
LDL (mM)	2.6 ± 0.7 (1.2–5.2)	2.4 ± 0.6 (1.3–3.4)	NS
TGs (mM)	0.9 ± 0.1 (0.4–2.0)	0.7 ± 0.3 (0.3–1.2)	NS
Lp(a) (mg/dl)	11 ± 16 (0.4–55)	8 ± 11 (0.1–33)	NS
HDL (mM)	0.8 ± 0.2 (0.5–1.5)	0.7 ± 0.1 (0.5–0.8)	0.05
VLDL (mM)	0.3 ± 0.1 (0.1–0.6)	0.3 ± 0.1 (0.1–0.4)	NS

Data are means ± SD, ranges are in parentheses. To convert from mM to mg/dl, divide by 0.02586 for cholesterol, LDL, HDL, and VLDL and by 0.01129 for TGs.

coefficient analysis. VO_{2max} remained significantly correlated with cholesterol ($r = -0.25$, $P = 0.05$), LDL ($r = -0.27$, $P = 0.04$), and Lp(a) ($r = -0.26$, $P = 0.03$).

Multiple regression analysis was used to assess the effects of age, sex, BMI, daily insulin dose, HbA_1, and VO_{2max} on lipid parameters at a significance level of 0.05. In a step-down regression analysis 18% ($R^2 = 0.179$) of the variance in LDL could be explained by VO_{2max} and HbA_1; 19% of the variance ($R^2 = 0.187$) in cholesterol could be explained by HbA_1 and VO_{2max}; 27% ($R^2 = 0.271$) of the variance in TGs could be explained by HbA_1, age, and daily insulin dose; and 12% ($R^2 = 0.123$) of the variance in Lp(a) could be explained by VO_{2max} and HbA_1.

CONCLUSIONS— Our evaluation of 59 adolescents with IDDM demonstrates an important inverse relationship between physical fitness and all parameters of metabolic control. The higher the physical fitness level, the better the outcome not only in glycemic control but also in plasma lipid profile, including Lp(a).

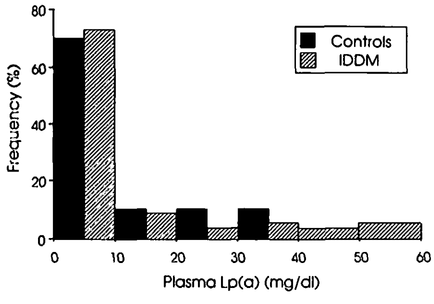

Figure 2—*The frequency distribution of Lp(a) in diabetic patients and control subjects.*

Exercise and improved physical fitness long have been advocated as an adjunct for the treatment of both IDDM and NIDDM patients. Acute exercise has the direct effect of enhancing muscle glucose uptake (11), and physical training has the sustained effect of augmenting S_I (12). In longitudinal studies of physical training in patients with IDDM, however, glycemic control has failed to improve despite improvements in physical fitness and S_I levels (1,4,13–15). This finding could be attributable to increased caloric intake during the training period or an inappropriate reduction in daily insulin requirements for fear of exercise-induced hypoglycemia.

On the other hand, Campagne et al. (16) showed a reduction in HbA_1 level with improved physical fitness after a 12-wk exercise training program in children with IDDM (16). Note that the patients were poorly controlled at the beginning of that study, and it does not reveal to what extent the improvement in glycemic control was caused by physical training per se versus stricter dietary adherence and closer physician supervision.

Our cross-sectional evaluation shows a clear inverse relationship between the state of physical fitness and GHb level. The present correlation coefficient is of similar magnitude to that observed by Marrero et al. (17) in 10 adolescents with IDDM, in whom phys-

Table 2—*Relationship of physical fitness to parameters of metabolic control in IDDM*

	VO_{2max} (ml · kg^{-1} · min^{-1})	HbA_1 (%)	BMI (kg/m^2)
HbA_1 (%)	r = −0.42 P = 0.002		r = 0.03 NS
LDL (mM)	r = −0.38 P = 0.005	r = 0.35 P = 0.01	r = 0.15 NS
Cholesterol (mM)	r = −0.36 P = 0.008	r = 0.41 P = 0.001	r = 0.06 NS
TGs (mM)	r = −0.30 P = 0.02	r = 0.35 P = 0.009	r = 0.15 NS
Lp(a) (mg/dl)	r = −0.28 P = 0.02	r = 0.50 P = 0.01	r = 0.11 NS
Insulin dose (U · kg^{-1} · day^{-1})	r = −0.28 P = 0.03	r = 0.31 NS	r = 0.03 NS
VLDL (mM)	r = −0.19 NS	r = 0.30 P = 0.02	r = −0.03 NS
HDL (mM)	r = 0.17 NS	r = 0.02 NS	r = −0.32 0.02
BMI (kg/m^2)	r = −0.10 NS	r = 0.03 NS	

ical training was associated with reduction in HbA_1 level.

A less studied benefit of exercise and fitness is its effect on lipid metabolism and atherosclerosis in patients with IDDM. Diabetic patients have an increased propensity to all types of vascular disease and cardiovascular mortality (18). Associated with this is an increase in coronary risk factors such as hyperlipidemia (19). A potentially more important role of physical training is the prevention or retardation of CVD and its complications in the diabetic patient. Cross-sectional studies of endurance athletes usually demonstrate lipid and lipoprotein patterns that would hypothetically lower their risk for coronary heart disease (20). The Lipid Research Clinics Program Prevalence Study found higher levels of self-reported activity were associated with slightly higher HDL levels (21). Data are scarce in IDDM patients. Our study demonstrates that the state of physical fitness is an important correlate of lipid levels in adolescents with IDDM. Thus, the higher the physical fitness level of patients, the lower the plasma total cholesterol and LDL levels, which would lower their risk for CVD. Previous studies of lipid levels in IDDM patients have shown an important effect of glycemic control on total and LDL cholesterol (22). In our study, after correcting for differences in glycemic control, the relationship between physical fitness and total and LDL cholesterol remains present.

Interest is increasing in Lp(a) because high levels have been associated with early atherosclerotic vascular disease in nondiabetic populations (8–9). In diabetic populations, especially in children and adolescents, data concerning Lp(a) levels are scarce. Most studies have focused on the influence of the degree of glycemic control on serum Lp(a) concentrations (23–26). Studies have shown Lp(a) levels are elevated in poorly controlled patients with IDDM (25) and decline with tight metabolic control (26). Furthermore, in a group of diabetic children and adolescents, Levitsky et al. (25) found significant racial differences, with higher levels of Lp(a) in black children compared with whites. In the latter group, Lp(a) levels were correlated directly with glycemic control, unlike the black patients in whom no relationship was present. Whether or not gender and puberty have an effect on Lp(a) levels in childhood is not known. Our findings do not reveal sex- or puberty-related differences in Lp(a) levels, although we did not study prepubertal patients.

Moreover, elevations in Lp(a) levels have been reported in diabetic patients with microalbuminuria and albuminuria in whom Lp(a) levels were comparable with patients with coronary artery disease (27–28). Whether elevated Lp(a) levels are a cause or a consequence of diabetic nephropathy is not known. Our study, for the first time, demonstrates an inverse relationship between physical fitness and plasma Lp(a) levels regardless of glycemic control. This could be another beneficial aspect of physical fitness in alleviating the risk of CVD in diabetes.

Another interesting post hoc observation from our study is the finding of two subpopulations among the diabetic patients in regard to Lp(a) distribution and relationship to daily insulin dose. Of the adolescents, ~70% with IDDM had Lp(a) levels <10 mg/dl. This group showed no relationship between Lp(a) and insulin dose. The remaining 30% of the patients had Lp(a) >10 mg/dl. In this group, daily insulin dose was a significant correlate of Lp(a) levels ($r = 0.72$, $P = 0.002$). Despite the drawbacks of such a post hoc analysis, it is tempting to speculate that a link exists between hyperinsulinemia and elevated levels of Lp(a), and that both may be risk factors for macrovascular disease.

Although 40% of the variability in Lp(a) concentrations is under genetic control explained by the genetic variability at the apoA locus (9), insulin may play a role in the modulation of high Lp(a) levels. Further studies are needed to research the relationship of Lp(a) to insulin in nondiabetic as well as diabetic populations.

In agreement with our findings, other studies have reported decreased physical fitness levels in children and adolescents with IDDM (6,7,29,30), with no clear explanations. The finding of an inverse relationship between glycemic control and physical fitness has led to the speculation that the poorly controlled diabetic state itself could affect fuel oxidation and be responsible for the inferior VO_{2max} levels (6). On the other hand, inadequate training and the adoption of a sedentary lifestyle could be responsible. Diabetic patients indeed might choose a more sedentary lifestyle for fear of exercise-related hypoglycemia and/or hyperglycemia.

In conclusion, this study demonstrates that higher physical fitness levels are associated with lower plasma lipid concentrations and Lp(a) and better outcome in cardiovascular risk factors in adolescents with IDDM.

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