Association Between Lipoprotein(a) and Insulin-Like Growth Factor I During Puberty and the Relationship to Microalbuminuria in Children and Adolescents With IDDM

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OBJECTIVE — To study pubertal changes in serum lipoprotein(a) [Lp(a)] and insulin-like growth factor I (IGF-I) in insulin-dependent diabetes mellitus (IDDM) and the relationship to microalbuminuria.

RESEARCH DESIGN AND METHODS — Seventy-nine children and adolescents (59 with normoalbuminuria, 20 with microalbuminuria) with ≥5 years of IDDM were investigated together with 54 healthy control subjects in a cross-sectional study. Fasting serum Lp(a); apolipoprotein (apo) A-1 and B; total, low-density lipoprotein (LDL), and high-density lipoprotein cholesterol; triglycerides; and IGF-I were analyzed as were HbA_{1c} and overnight albumin excretion rate (AER). Pubertal development was assessed by Tanner staging.

RESULTS — Lp(a), apoB, triglycerides, and total and LDL cholesterol were higher ($P < 0.001$) and apoA-1 was lower ($P = 0.03$) in normoalbuminuric IDDM patients than in healthy control subjects. Lp(a) was increased during puberty (stages 2–4) in IDDM patients but not in healthy subjects, whereas IGF-I was significantly increased during puberty in healthy control subjects only. In IDDM patients Lp(a) correlated to insulin dose, total cholesterol, and LDL cholesterol, but not to IGF-I, HbA_{1c}, systolic and diastolic blood pressure, diabetes duration, age, or sex. In multiple regression analysis with Lp(a) as the dependent variable, puberty was the only significant contributor to the regression ($r^2 = 0.33$, $P = 0.008$). Microalbuminuria was seen only in the pubertal stage 4–5. Lp(a) tended to be higher ($P = 0.06$) as did apoB, whereas IGF-I was lower ($P < 0.001$) in this group than in normoalbuminuric patients of the same pubertal stages. In multivariate analysis, with log AER as the dependent variable, apoB/apoA-1, systolic blood pressure, age, and IGF-I but not Lp(a) added to the regression ($r^2 = 0.47$, $P < 0.0001$).

CONCLUSIONS — Lp(a) is elevated during puberty in normoalbuminuric subjects with IDDM, independent of metabolic control and IGF-I. Lp(a) tends to be further increased in microalbuminuria but does not seem to be a contributing determinant of log AER whereas low IGF-I does. Prospective studies are required to establish the temporal relationship between increased Lp(a) and microalbuminuria in children and adolescents with IDDM.

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ACE, angiotensin-converting enzyme; AER, albumin excretion rate; apo, apolipoprotein; CVD, cardiovascular disease; GH, growth hormone; IDDM, insulin-dependent diabetes mellitus; IGF-I, insulin-like growth factor I; LDL, low-density lipoprotein; Lp(a), lipoprotein(a); NIDDM, non-insulin-dependent diabetes mellitus; SHBG, sex hormone–binding globulin.

An elevated lipoprotein(a) [Lp(a)] level (>0.30 g/l) is regarded as an independent risk factor for atherosclerosis and cardiovascular disease (CVD) in nondiabetic adult white subjects (1). The development of CVD is closely related to nephropathy in insulin-dependent diabetes mellitus (IDDM) (2,3), and lipoprotein as well as coagulation disturbances, predictive for CVD, are found in patients with incipient nephropathy (4,5). However, conflicting data regarding the relationship between Lp(a) levels and incipient or established late complications in adults with IDDM have been presented in cross-sectional studies (6–9).

Microalbuminuria is rare before puberty (10,11) and metabolic as well as hormonal changes may partly be responsible for the increasing albumin excretion. Lower increments in insulin-like growth factor I (IGF-I) than normally seen during puberty (12) and increasing insulin requirements may indicate a growth hormone resistance in IDDM adolescents that may possibly contribute to the onset of microalbuminuria. The only study, so far, of serum Lp(a) during puberty in IDDM reported higher pubertal, but not prepubertal levels in IDDM patients than in healthy control subjects (13). Whether increased Lp(a) is an independent predictor of microalbuminuria is unknown, as prospective studies are missing. Furthermore, the interaction between Lp(a) and endogenous levels of growth factors, such as growth hormone (GH) and IGF-I, have not been studied in adolescents with IDDM. However, administration of pharmacological levels of GH to healthy subjects were shown to increase serum Lp(a) (14). In contrast, recombinant human IGF-I lowered serum lipids, including Lp(a), when given to non-insulin-dependent diabetes mellitus (NIDDM) patients (15).

The object of the present study was to examine *1*) the interrelation between serum Lp(a) and IGF-1 during pubertal development in normoalbuminuric

Table 1—*Clinical characteristics of the study patients*

	Patients with IDDM		
	Normoalbuminuric	Microalbuminuric	Healthy control subjects
n	59	20	54
Age (years)	15.6 (14.6–16.6)	19.0 (17.9–20.2)	14.4 (13.2–15.7)
Sex (M/F)	32/27	9/11	21/33
Pubertal stage			
1	13	—	15
2	6	—	5
3	3	—	4
4	9	5	12
5	28	15	15
Body mass index (kg/m^2)	20.8 (14.9–26.7)	23.7 (22.3–25.1)	19.3 (18.4–20.2)
Age at onset of diabetes (years)	5.8 (4.9–6.8)	8.5 (6.4–10.7)	—
Duration of diabetes (years)	9.5 (8.4–10.5)	11.1 (8.9–13.3)	—
Insulin dose ($U \cdot kg^{-1} \cdot$ body wt^{-1})	0.96 (0.86–1.04)	1.00 (0.91–1.07)	—
HbA_{1c} (%)	8.1 (7.6–8.5)	8.6 (7.6–9.5)	4.1 (3.9–4.3)
AER ($\mu g/min$)	4 (3–4)	30 (19–47)	3 (3–4)
Glomerular filtration rate ($ml \cdot min^{-1} \cdot 1.73\ m^{-2}$)	141 (133–148)	130 (113–146)	—
Blood pressure (mmHg)			
Systolic	115 (111–118)	125 (119–132)	113 (109–116)
Diastolic	68 (65–70)	74 (68–79)	67 (65–70)

Data are means or geometric means for AER (95% confidence interval).

subjects with IDDM and 2) the relative contribution of Lp(a) and IGF-1 on the occurrence of microalbuminuria.

RESEARCH DESIGN AND METHODS

— Fifty-nine children and adolescents with ≥5 years of IDDM duration, consecutively attending the diabetic ward at St. Göran's Children's Hospital in Stockholm between November 1992 and November 1993, were included in the study. The patients were admitted for a routine clinical control including investigations of renal function and early signs of late diabetic complications. In addition, 20 patients with microalbuminuria (i.e., with an albumin excretion rate [AER] 15–200 μg/min in at least two of three consecutive overnight urinary samples, tested every 3rd month) recruited from the pediatric departments at St. Göran's, Sachs, and Danderyds Hospitals in Stockholm were included. Of the patients with IDDM (8 with microalbuminuria), 15 had simplex retinopathy defined as one or more microaneurysms and/or hemorrhages, and 3 (with microalbuminuria) had proliferative changes. The control group was 54 nondiabetic healthy subjects with similar age and sex distributions as the IDDM patients with normoalbuminuria. Clinical data for the groups are presented in Table 1.

Patients with diabetes were on a regimen of three to five subcutaneous insulin injections daily, except for one patient who received a subcutaneous continuous insulin infusion. Five patients with microalbuminuria and two without were treated with enalapril (10–20 mg/day) for 3–24 months and two with microalbuminuria received metoprolol (50–100 mg/day) for the last 6 months. No patient was taking lipid-lowering medication. Two girls in the normo- and microalbuminuric group, respectively, were taking low-dose estrogen/gestagen contraceptives (containing 30 μg ethinyl estradiol). Healthy control subjects received no continuous medication except for low-dose oral contraceptives in two women. Seven normoalbuminuric subjects, 4 patients with microalbuminuria, and 10 healthy control subjects were smokers. No subject had any renal disease unrelated to diabetes. Six patients with IDDM and two of the healthy control subjects had a family history of hypertension, but none of premature CVD in first-degree relatives.

All subjects and parents had given their informed consent for participation in the study, which was approved by the regional ethics committee at Karolinska Institute.

Chemical analyses

Blood samples for lipid, lipoprotein, and IGF-I analyses were taken after an overnight fast before insulin administration. Samples were stored at −70°C until analyzed. Lipids were measured at the accredited (EN 45001-1285) laboratory at the Karolinska Hospital in Stockholm. Cholesterol and triglycerides were measured using Kodac Ektachem 700 (Rochester, NY). High-density lipoprotein cholesterol was measured after precipitation

Table 2—*Fasting serum lipid, lipoprotein, and IGF-I levels in 59 normoalbuminuric patients with IDDM and in 54 healthy control subjects*

	Normoalbuminuric patients with IDDM	Healthy control subjects	*P* value
Lp(a) (g/l)	0.13 (0.10–0.18)	0.06 (0.04–0.09)	<0.001
ApoB (g/l)	1.03 (0.95–1.10)	0.81 (0.75–0.86)	<0.001
ApoA-1 (g/l)	1.42 (1.36–1.49)	1.53 (1.45–1.60)	0.03
ApoB/apoA-1	0.67 (0.63–0.76)	0.59 (0.54–0.63)	0.001
Total cholesterol (mmol/l)	4.7 (4.5–5.0)	4.2 (4.0–4.4)	0.001
HDL cholesterol (mmol/l)	1.29 (1.21–1.37)	1.34 (1.24–1.43)	NS
LDL cholesterol (mmol/l)	2.88 (2.65–3.11)	2.50 (2.32–2.65)	<0.001
Triglycerides (mmol/l)	1.04 (0.91–1.19)	0.81 (0.73–0.90)	<0.001
IGF-I (μg/l)	304 (272–341)	330 (288–383)	NS

Data are means or geometric means for Lp(a), triglycerides, and IGF-I (95% confidence interval).

with dextrane sulfate and low-density lipoprotein (LDL) cholesterol was calculated by the formula of Friedewald's et al. (16). Lp(a) and apolipoprotein (apo) A1 and apo B were measured using reagents from Beckman (Fullerton, CA) and a nephlometric immunoassay. Measurements were calibrated using reference material from the kit manufacturer. The DAKO rabbit anti-human Lp(a) antibody (DAKOPATTS, Stockholm, Sweden) used in the Lp(a) analysis reacts with human apo(a), and traces of contaminating antibodies have been removed by solid-phase absorption with human plasma proteins. No cross-reactivity is detected with apoB tested up to 5 g/l or with plasminogen up to 1 g/l. The intra- and interassay coefficients for Lp(a) were 3.5 and 4.2%, respectively, and the lowest detection limit was 0.02 g/l.

IGF-I in serum was analyzed by radioimmunoassay after ethanol extraction (17). The lowest detection limit was 9 μg/l and the intra- and interassay coefficients were 7.5 and 15.3%.

HbA_{1c} was evaluated by high-performance liquid chromatography (Auto-A, Kyoto-Diaiichi, Kagaku, Kyoto, Japan; reference level 4–6%).

Timed overnight AER was analyzed by an immunoturbidimetric method (18) on fresh specimens.

Leucocyturia and hematuria were excluded by using the Ecur4-Test and ketonuria was excluded by the Keto-Diabur Test (Boehringer Mannheim, Mannheim, Germany).

Clinical examinations

Pubertal development was assessed by Tanner staging of pubic hair development. The scoring was performed by one of four pediatricians. Pubertal stage was not obtained in three healthy control subjects.

Systolic and diastolic blood pressures were measured in the supine position after a 15-min rest using an automatic device (DINAMAP, Critikon, Johnson & Johnson, Tampa, FL). Each value was recorded as the mean of two measurements.

Signs of retinopathy were recorded by stereoscopic fundus photography and also by fluoroangiography in patients with proliferative changes and were analyzed by an ophthalmologist.

Glomerular filtration rate was measured by Crom 51 EDTA clearance (2 μCi ^{51}Cr per kg body wt), using the two-compartment analysis (19).

Statistical analysis

Skewed distributions of variables were log-transformed before calculations. Comparisons between normoalbuminuric IDDM and healthy subjects were performed by the unpaired Student's *t* test as were means between microalbuminuric patients and the subgroup of normoalbuminuric patients of similar pubertal development (stages 4–5). Group mean comparisons of Lp(a) and IGF-I, respectively, of different pubertal stages were assessed by one-way analysis of variance followed by the Student's *t* test when a statistical difference was indicated. Differences in sex and puberty distributions were analyzed by the Kolmogorov-Smirnov two-sample test. Single correlations were performed by the Pearson method. Multiple regression analyses were used to study the relative contribution of independent variables on log-transformed Lp(a) and log AER levels separately. All values are expressed as means or geometric means and 95% confidence intervals. $P < 0.05$ was considered statistically significant.

RESULTS — Overall, Lp(a) levels were skewedly distributed with a predominance of low levels. Of healthy control subjects, 19% had values >30 g/l compared with 29% among normoalbuminuric and 42% among microalbuminuric subjects with IDDM.

Lp(a) and IGF-I in normoalbuminuric IDDM subjects and the relation to puberty

Patients with IDDM had higher serum levels of Lp(a), apoB, total- and LDL cholesterol, and triglycerides and lower levels of apoA-1 as compared with healthy control subjects (Table 2). Lp(a) was related to the pubertal stage in IDDM but not in healthy control subjects. Geometric means and 95% confidence intervals of Lp(a) at different stages are given in Fig. 1. In IDDM subjects, Lp(a) was increased during pubertal stages 2–4 compared with prepubertal levels ($P = 0.01$). At Tanner stage 5, the difference in Lp(a) compared with stage 1 did not reach statistical significance. IGF-I increased with pubertal development in healthy subjects (stage 1 vs. stages 2–4 and 5 respectively, $P < 0.001$) but only tended to do so in patients with IDDM (Fig. 2). Lp(a) or IGF-I levels did not differ between sex in

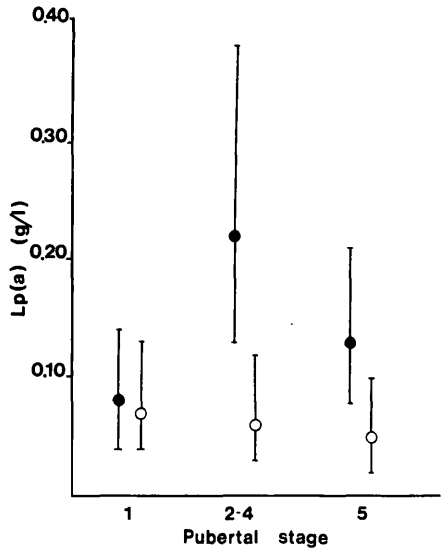

Figure 1—*Lp(a) levels according to pubertal development in normoalbuminuric patients with IDDM ● and healthy control subjects ○. Values are given as geometric means and 95% confidence intervals.*

patients with IDDM or in healthy control subjects. Therefore, the relations between pubertal stage and Lp(a) and IGF-I, respectively, were analyzed for both sexes together.

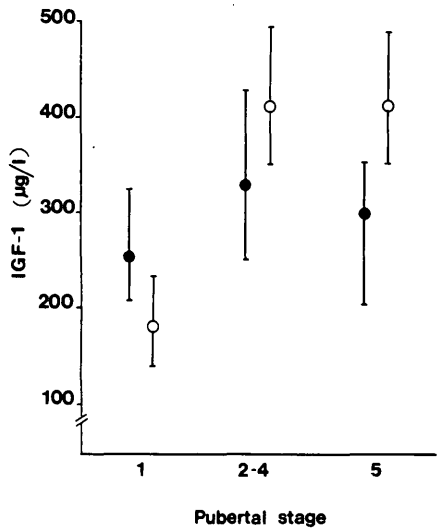

Figure 2—*IGF-I in serum according to pubertal development in normoalbuminuric patients with IDDM ● and healthy control subjects ○. Values are geometric means and 95% confidence intervals.*

Table 3—*Fasting serum lipid, lipoprotein, and IGF-I levels in 20 microalbuminuric and 37 normoalbuminuric patients with IDDM in pubertal stage 4–5*

	Microalbuminuric	Normoalbuminuric	*P* value
Lp(a) (g/l)	0.22 (0.16–0.40)	0.13 (0.09–0.20)	0.06
ApoB (g/l)	1.44 (1.18–1.80)	1.08 (0.97–1.18)	0.01
ApoA-1 (g/l)	1.40 (1.25–1.53)	1.49 (1.37–1.56)	NS
ApoB/apoA-1	1.11 (0.85–1.36)	0.76 (0.67–0.84)	0.01
Total cholesterol (mmol/l)	5.0 (4.7–6.7)	4.8 (4.4–5.2)	NS
HDL cholesterol (mmol/l)	1.24 (1.00–1.48)	1.25 (1.15–1.36)	NS
LDL cholesterol (mmol/l)	3.61 (2.68–4.73)	2.89 (2.58–3.22)	NS
Triglycerides (mmol/l)	1.39 (1.04–2.03)	1.13 (0.98–1.31)	NS
IGF-1 (µg/l)	208 (272–366)	315 (272–366)	<0.001

Data are means or geometric means for Lp(a), triglycerides, and IGF-I (95% confidence interval).

HbA_{1c} was not increased in patients with IDDM in Tanner stages 2–4 compared with those of stage 1 (8.2 [7.3–9.1] vs. 7.7 [6.7–8.8]%) whereas the insulin dose was higher in Tanner stages 2–4 (1.04 [0.97–1.17] vs. 0.92 [0.69–1.11] U/kg, $P = 0.009$).

In normoalbuminuric IDDM patients, single correlation analysis showed that log Lp(a) was correlated to insulin dose ($r = 0.21$, $P = 0.02$) and total and LDL cholesterol ($r = 0.38$; $r = 0.43$, $P = 0.01$) but not to IGF-I, apoB, apoA-1, triglycerides, HbA_{1c}, systolic or diastolic blood pressure, duration of diabetes, body mass index, age, or sex. In multiple regression analysis with log Lp(a) as the dependent variable and pubertal stage and the above-mentioned variables interrelated with Lp(a) as independent variables, puberty emerged as the only variable independently associated with Lp(a) ($r^2 = 0.33$, $P = 0.008$).

ApoB was also related to pubertal stage. This was seen independent of, but together with, HbA_{1c} and insulin dose, using multiple regression ($r^2 = 0.31$, $P = 0.002$).

Lp(a) and IGF-I in relation to microalbuminuria

Microalbuminuric patients were all in Tanner stages 4–5; thus, comparisons with normoalbuminuric patients were restricted to these pubertal stages. ApoB and apoB/apoA-1 were higher and Lp(a) tended to be so in the microalbuminuric group, whereas IGF-I was significantly lower (Table 3). In multivariate analysis, including all IDDM subjects, with continuous log AER values as the dependent variable, apoB/apoA1, systolic blood pressure, age, and IGF-I added to the regression, although age and IGF-I with marginal significance. Lp(a), HbA_{1c}, diastolic blood pressure, or diabetes duration did not add to the regression (Table 4).

Lp(a) and IGF-I in subjects with retinopathy

Patients with retinopathy ($n = 18$) had similar levels of Lp(a) as those without: 0.15 (0.10–0.22) vs. 0.13 (0.07–0.23) g/l, $P = 0.8$. No correlation between the occurrence of retinopathy and Lp(a) levels was seen ($r = 0.01$, $P = 0.94$). IGF-I

Table 4—*Regression coefficients in order of entrance into the regression, with log-transformed AER values as the dependent variable*

	Standardized regression coefficient	Two-tailed *P* value
ApoB/apoA-1	0.37	<0.001
Systolic blood pressure	0.31	0.01
Age	0.21	0.06
IGF-I	−0.16	0.11

$r^2 = 0.47$, $P < 0.001$.

was lower in patients with retinopathy: 232 (128–505) vs. 318 (156–748) μg/l, $P = 0.01$.

CONCLUSIONS — Onset of IDDM before 20 years of age increases the risk for nephropathy (20). Still, postpubertal duration of diabetes seems to carry a higher risk than total duration time (21). This suggests that puberty may be crucial for the initiation of renal affection in young IDDM patients. In this study all patients with microalbuminuria were in late puberty. Several studies have previously demonstrated that microalbuminuria seldom develops at prepubertal ages (10,11,22). In line with a widespread clinical impression, this has partly been ascribed to impaired glycemic control during puberty (22). However, somewhat unexpectedly, we found that current HbA_{1c} concentration was not independently associated with AER levels.

Puberty is also a state of raised GH levels, associated with insulin resistance, which has been implicated in the genesis of diabetic microangiopathy (23,24). IGF-I is, at least in part, the mediator of GH actions. Still, in spite of reports of more marked GH secretion in pubertal subjects with IDDM than without (25), we found no significant pubertal IGF-I increase in IDDM subjects. Such disproportionally low IGF-I levels were earlier described during puberty in IDDM patients (12). This may reflect an enhanced clearance of IGF-I due to abnormal regulation of IGF-I binding proteins (26), but has also been suggested to imply a GH resistance due to post-GH receptor defects (12).

We also found lower IGF-I levels in microalbuminuric than in normoalbuminuric IDDM patients. Furthermore, IGF-I was inversely associated with AER in the multivariate analysis, indicating that low IGF-I may possibly contribute to microalbuminuria. To date, the association between serum IGF-I levels and microalbuminuria in adolescents with IDDM is unclear. In experimental diabetes, a rise in renal IGF-I precedes mesangial growth (27). In subjects with overt proteinuria IGF-I was found to be increased (28), but this was suggested to reflect decreased renal degradation of IGF-I due to kidney damage. These results do not necessarily contradict the fact that low IGF-I in serum, as a possible indicator of GH resistance, may be associated with microalbuminuria in young IDDM patients. We also noted decreased IGF-I in subjects with retinal changes. Previous results regarding this association have been contradictory. Dills et al. (28) found an inverse trend between IGF-I and the risk for proliferative retinopathy. In contrast, earlier studies in adults with retinopathy presented elevated IGF-I levels (29,30) and in children and adolescents no relationship was seen (31). These different results may partly be ascribed to methodological variations.

In agreement with an Australian study (13), we found increased Lp(a) levels, independent of glycemic control, during puberty in IDDM patients but not in healthy control subjects. We also analyzed the relative contribution of endogenous serum IGF-I levels on elevated Lp(a), and no such association could be found. This is in contrast to earlier findings in NIDDM patients, in whom administration of recombinant human IGF-I decreased Lp(a) in serum (15), as suggested to be due to GH suppression. The lack of an association between Lp(a) and IGF-I in our study does not contradict the possibility that GH resistance may affect the Lp(a) levels during puberty in IDDM patients. Increased Lp(a) was earlier shown after administration of pharmacological doses of GH in healthy subjects (14). It has also been suggested that exogenous insulin may influence Lp(a) metabolism (32). Increased insulin requirements during puberty and a positive correlation between insulin dose and Lp(a) were not independent of pubertal stage in our study.

The pubertal rise in sexual steroids could be a plausible regulator of Lp(a) levels. Sex hormones were not measured in the present study, but androgenicity in IDDM female adolescents in late puberty (as indicated by a low sex hormone–binding globulin [SHBG] and high testosterone/SHBG ratio) was not associated with increased Lp(a) in a recent study of ours (S.R., B.P., unpublished data). On the other hand, testosterone levels in nondiabetic men were positively correlated to Lp(a) serum (33), whereas estrogen therapy reduced Lp(a) in men with prostatic carcinoma (34) and in postmenopausal women (35).

Plasma levels of Lp(a) are mainly genetically determined (36). In healthy subjects ~40% of the plasma variability of Lp(a) is dependent on apo(a) polymorphism (37). Normoalbuminuric IDDM patients seem to have similar apo(a) phenotypes as healthy control subjects (38). Thus, Lp(a) may only partly be influenced by environmental factors. However, the pubertal increase seen in IDDM patients suggest the existence of specific triggering factors for a rise in Lp(a) in diabetes. Such factors, responsible for the nongenetic variability of Lp(a), could not be identified in the present study and warrant further prospective studies.

Elevated Lp(a) may be pathogenetically linked to diabetic nephropathy because of its homology with plasminogen and participation in thrombus formation (39). In addition, Lp(a) may be incorporated into the arterial walls and accumulate in atherosclerotic plaques, in proportion to plasma levels (40). A coupling of Lp(a) to glycosaminoglycans could also be a contributing pathogenic mechanism (41). To our knowledge, this study is the first to present Lp(a) levels in IDDM adolescents with microalbuminuria. Consistent with most (7,8) but not all (9) cross-sectional studies in adults with IDDM, we found that Lp(a) tended to be elevated in microalbuminuria, independent of the degree of metabolic control. The increased Lp(a) during puberty in normoalbuminuric patients may implicate elevated Lp(a) levels as a precursor for the rise in urinary albumin excretion. This contention was not supported by our cross-sectional study as Lp(a) levels had

no independent influence on log AER in the multivariate analysis. Lp(a) is also increased in renal diseases unrelated to diabetes (42) and may vary with the degree of albumin loss in the nephrotic syndrome (43). Albumin leakage may trigger the liver production of lipoproteins (44). Albeit only low-grade microalbuminuria was present in our patients, elevated Lp(a) could thus be an accompanying feature of incipient nephropathy. Only prospective studies can determine the temporal relationship between elevated Lp(a) and microalbuminuria. Such studies should also consider the apo(a) phenotype to control for the high and genetically determined individual variation.

Neither systolic nor diastolic blood pressure correlated to Lp(a) in patients with IDDM. A few patients, mainly in the microalbuminuric group, were treated with an angiotensin-converting enzyme (ACE) inhibitor that may reduce Lp(a) (45). Thus, if ACE inhibition affected the Lp(a) levels in our study, these ought to be lower than expected in the microalbuminuric group. Two patients with microalbuminuria were taking β-blockers, known to impair plasma lipid- and lipoprotein profiles (46). However, exclusion of these patients did not alter the statistical results. Neither did exclusion of the girls receiving oral contraceptives that may decrease serum Lp(a) (35).

In general, a more atherogenic lipid and lipoprotein profile was seen in IDDM children and adolescents than in healthy control subjects. This tended to be more pronounced in microalbuminuric subjects, but significantly so only for apoB and the apoB/apoA-1 ratio, which had an independent influence on AER levels. In contrast to an earlier report in children and adolescents (13), we also found apoB to be related to pubertal stage. Taken together, this may indicate that lipid alterations already seen in very young subjects with IDDM may add to the risk for incipient nephropathy.

In summary, Lp(a) is increased during puberty in IDDM patients, independent of metabolic control or IGF-I levels. Lp(a) tends to be increased in adolescents with microalbuminuria, which may be an epiphenomenon, whereas suppressed IGF-I levels during puberty may contribute to increased urinary albumin excretion. Prospective studies with larger numbers of patients are needed to clarify the influence of Lp(a) and growth factors on the development of microalbuminuria in children and adolescents with IDDM.

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