The Association of Lipoprotein(a) Plasma Levels With Prevalence of Cardiovascular Disease and Metabolic Control Status in Patients With Type 1 Diabetes

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OBJECTIVE

To investigate the association of the cardiovascular risk factor lipoprotein (Lp)(a) and vascular complications in patients with type 1 diabetes.

RESEARCH DESIGN AND METHODS

Patients with type 1 diabetes receiving regular care were recruited in this observational cross-sectional study and divided into four groups according to their Lp(a) levels in nmol/L (very low <10, low 10–30, intermediate 30–120, high >120). Prevalence of vascular complications was compared between the groups. In addition, the association between metabolic control, measured as HbA_{1c}, and Lp(a) was studied.

RESULTS

The patients ($n = 1,860$) had a median age of 48 years, diabetes duration of 25 years, and HbA_{1c} of 7.8% (61 mmol/mol). The median Lp(a) was 19 (interquartile range 10–71) nmol/L. No significant differences between men and women were observed, but Lp(a) levels increased with increasing age. Patients in the high Lp(a) group had higher prevalence of complications than patients in the very low Lp(a) group. The age- and smoking-status–adjusted relative risk ratio of having any macrovascular disease was 1.51 (95% CI 1.01–2.28, $P = 0.048$); coronary heart disease, 1.70 (95% CI 0.97–3.00, $P = 0.063$); albuminuria, 1.68 (95% CI 1.12–2.50, $P = 0.01$); and calcified aortic valve disease, 2.03 (95% CI 1.03–4.03; $P = 0.042$). Patients with good metabolic control, HbA_{1c} <6.9% (<52 mmol/mol), had significantly lower Lp(a) levels than patients with poorer metabolic control, HbA_{1c} >6.9% (>52 mmol/mol).

CONCLUSIONS

Lp(a) is a significant risk factor for macrovascular disease, albuminuria, and calcified aortic valve disease in patients with type 1 diabetes. Poor metabolic control in patients with type 1 diabetes is associated with increased Lp(a) levels.

Lipoprotein(a) [Lp(a)] is an established cardiovascular risk factor that is receiving increasing attention (1). Lp(a) is an LDL particle to which an apolipoprotein(a) is covalently bound to the apolipoprotein B. LDL and Lp(a) particles are both atherogenic, but the strong capacity of Lp(a) to carry oxidized phospholipids has been proposed as an additional proatherogenic property compared with LDL-cholesterol (LDL-C) (2). Plasma levels of Lp(a) have a skewed distribution that ranges up to three orders of magnitude

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and are highly influenced by genetic inheritance (3) and ethnicity (4) but to a much lesser extent affected by age, sex, and lifestyle (5). The plasma level of Lp(a) is not affected by food intake, and fasting is not required before blood sampling (6).

The Lp(a) particle size has a great heterogeneity that represents a challenge for the laboratory assessment of its plasma level. Historically, plasma levels of Lp(a) have been expressed as mass (mg/dL), but today, several routine immunoassays measure the molar concentration (nmol/L). Hence, comparison of results from studies using different methods for Lp(a) measurement is problematic, and the use of standardized methods, traceable to an international reference material, are desirable (7).

The evidence for Lp(a) as a cardiovascular disease (CVD) risk factor has accumulated over the years. Lp(a) has been shown to correlate with CVD in different types of studies, including genome-wide association and Mendelian randomization (8,9), population-based cohorts (10), and in a large meta-analysis (11). In the latter, which consisted of seven placebo/statin clinical trials ($n = 29{,}000$) including a mix of patients in primary and secondary CVD prevention, a nearly linear relation between Lp(a) and CVD could be shown regardless of whether the patients had received statin treatment or not. Several studies have identified Lp(a) plasma levels >80th percentile, corresponding to 50 mg/dL (~120 nmol/L), as a threshold for a significantly increased risk for coronary heart disease (CHD) (11–13), calcified aortic valve disease (12), and peripheral artery disease (14). The data for cerebrovascular disease (CVL) are not as convincing, and whether Lp(a) is a risk factor is still debated (15).

Young adults with type 1 diabetes still experience an increased vascular morbidity and mortality rate despite an improved vigilance in CVD risk factor management in clinical practice over the years (16). A recent registry study identified LDL-C as an important predictor for excess risk of death and cardiovascular outcomes in type 1 diabetes alongside HbA_{1c}, albuminuria, diabetes duration, and systolic blood pressure (17). The knowledge about Lp(a) in type 1 diabetes is very limited. A small prospective study showed Lp(a) was a predictor for CVD at levels >30 mg/dL (~75 nmol/L) (18). Plasma levels of Lp(a) in children with type 1 diabetes have been shown to correlate with HbA_{1c} (19) and also display a positive trend with albuminuria (20). In contrast, strong evidence has just emerged demonstrating Lp(a) as an important risk factor in patients with type 2 diabetes with stable coronary artery disease (21). The study reported an Lp(a) level >50 mg/dL (~120 nmol/L) resulted in a 3.5-fold higher risk for a cardiovascular event than for patients without diabetes and a low Lp(a) (<10 mg/dL or ~24 nmol/L).

The purpose of our cross-sectional study with 1,860 patients was to evaluate Lp(a) as a vascular risk factor in type 1 diabetes. Our results underline the importance of Lp(a) as a significant risk factor for macrovascular complications and calcified aortic valve disease. In addition, they reveal an association between Lp(a) levels and metabolic control of the disease.

RESEARCH DESIGN AND METHODS

Study Design and Inclusion and Exclusion Criteria

In this observational cross-sectional registry study, patients with type 1 diabetes receiving regular care at the outpatient clinic, Endocrinology Unit, Karolinska University Hospital, Stockholm, were recruited during the period August 2017 to October 2018. A total of 2,191 patients were eligible for inclusion. All patients with a planned visit during the inclusion period and an Lp(a) measurement were included in the study. Exclusion criteria were patients without Lp(a) or HbA_{1c} measurements. Laboratory data were extracted from a database at the Karolinska University Laboratory. Clinical data and information about diabetic complications, risk factors, and medication were collected by manual review of the electronic medical record at Karolinska University Hospital. The study was approved by the Stockholm Region Ethical Board (2017/872–31/4).

Laboratory Parameters and Definitions of Vascular Complications

Blood sampling was performed after at least 10 h of fasting. Lp(a) was measured with the certified clinical routine assay at Karolinska University Laboratory, a particle enhanced turbidimetric immunoassay (Tina-quant Lipoprotein[a] Gen 2; Roche Diagnostics) that expresses Lp(a) concentration in nmol/L and is standardized to the International Federation of Clinical Chemistry reference material (SRM 2B). Lp(a) values <10 nmol/L are reported as <10 nmol/L from the laboratory, and in the statistical calculation they were defined as the very low Lp(a) group. Lp(a) in 5.1% ($n = 96$) of the patients was measured in other laboratories using an alternative certified laboratory assay (Sentinel Lp(a) Ultra Diagnostics [Beckman Coulter] or Lp(a) ADVIA XPT [Siemens Healthcare]) that reports values in mg/dL. Before statistical analysis, all values were converted to nmol/L by using a conversion factor [Lp(a) nmol/L = 2.4 × Lp(a) mg/dL] suggested by Roche Diagnostics and Brown et al. (22). HbA_{1c}, creatinine, cholesterol, HDL-C, and triglycerides (TGs), and urine sampling (albumin-to-creatinine ratio) were analyzed with certified routine assays at Karolinska University Laboratory, Karolinska University Hospital. LDL-C was calculated using the Friedewald formula when TG was ≤4.5 mmol/L. The estimated glomerular filtration rate was calculated from creatinine using the Lund-Malmö revised formula (23).

Antiplatelet treatment was ≥75 mg acetylsalicylic acid or 75 mg clopidogrel daily, and lipid lowering was defined as statin or ezetimibe usage daily, or both. No patient received proprotein convertase subtilisin/kexin type 9 inhibition treatment.

Macrovascular complications were defined according to the ICD-10. CVD was a composite of CHD and CVL. CHD included a history of angina pectoris (I20), myocardial infarction (I21, I25.2), presence of coronary angioplasty implant (Z95.5), or coronary artery bypass graft (Z95.1). CVL included transient ischemic attack (G45.9) or ischemic stroke (I63.4, I63.5). Aortic stenosis was defined if the diagnosis (I35.0, I35.2) was noted in the patient's electronic medical record or if the patient had undergone a transthoracic heart ultrasound specifically indicating aortic valve sclerosis or stenosis. All patients not fulfilling any of these criteria were deemed without signs of calcified aortic valve disease. The presence of microvascular complications was defined as a history of the following: retinopathy by fundus photography of the retina verified by an ophthalmologist, albuminuria as a urine albumin-to-creatinine ratio >3 mg/mmol, or peripheral neuropathy in feet by loss of pinprick sensation in a monofilament test performed by the clinician. Diabetic foot

disease was defined as a history of recurrent ulcerations, revascularization interventions due to atherosclerosis (percutaneous transluminal or bypass), or partial/complete limb amputation due to ischemia.

Statistical Analysis

The patients' characteristics are summarized in Table 1 with counts and percentages for the categorical variables and with means (SDs) and medians (interquartile ranges) for the numeric variables. Men and women were compared by using the two-sample *t* test for differences in means, the Wilcoxon rank sum test for medians, and the Pearson χ^2 test for proportions. Missing values were <2.5% for laboratory parameters, except from Lp(a) and HbA_{1c}, and <3.5% for clinical data. The crude and adjusted relative risks reported in Table 2 are from multinomial logistic regression models (24). The four-level categorical variable denoting the Lp(a) groups was the dependent variable in all of the regression models. For the crude relative risk ratios (RRRs), the independent variable in each model was the binary indicator of the complication being considered. For the adjusted RRRs, the models also included age as a numeric covariate and smoking status as a categorical covariate introduced by means of dummy variables. We estimated the median and the 80th and 90th percentiles reported in the figures with quantile regression. The numeric dependent variable was Lp(a), and the independent variables were the age groups through dummy variables (Fig. 1*B*) and HbA_{1c} levels through dummy variables (Fig. 2*A*). We tested for differences in the percentiles across age and HbA_{1c} groups with Wald tests. We set the level of the test at 5%. We performed the analyses with Stata version 15 software (StataCorp, College Station, TX).

Table 1—The type 1 diabetes study sample

	Sample (N = 1,860)
Sex	
Men, *n* (%)	1,042 (56.0)
Women, *n* (%)	818 (44.0)
Age, years	48 (16)
Smoking status	
Never, *n* (%)	1,285 (69.1)
Previous, *n* (%)	336 (18.1)
Current, *n* (%)	232 (12.5)
Diabetes	
Age at diagnosis, years	23 (15)
Diabetes duration, years	27 (15)
Multiple daily injections, *n* (%)	1,438 (77.3)
Insulin pump, *n* (%)	422 (22.7)
HbA_{1c}, %	7.8 (1.3)
HbA_{1c}, mmol/mol	62 (14)
Creatinine, μmol/L	80 (40)
eGFR, mL/min/1.73 m^2	83 (20)
Blood pressure	
Systolic, mmHg	128 (15)
Diastolic, mmHg	75 (9)
Lipids	
TGs, mmol/L	0.8 (0.6–1.2)
Cholesterol, mmol/L	4.7 (1.0)
HDL-C, mmol/L	1.7 (0.5)
LDL-C, mmol/L	2.5 (0.8)
Lp(a), nmol/L	19 (10–72)
Additional treatment	
Platelet inhibition, *n* (%)	291 (15.6)
Lipid lowering, *n* (%)	741 (39.8)
Hypertension, *n* (%)	758 (40.7)
Macrovascular complications	
CHD, *n* (%)	128 (6.9)
CVL, *n* (%)	63 (3.4)
Microvascular complications	
Albuminuria, *n* (%)	255 (13.7)
Retinopathy, *n* (%)	1,254 (67.4)
Neuropathy, *n* (%)	390 (21.0)
Diabetic foot disease	
Ulceration, *n* (%)	77 (4.1)
Calcified aortic valve disease	
Sclerosis/stenosis, *n* (%)	88 (4.7)

Data are presented as the mean (SD), the median (interquartile range), or as indicated otherwise. eGFR, estimated glomerular filtration rate.

RESULTS

Type 1 Diabetes Sample and Lp(a) Distribution

The study included 1,860 patients from a total of 2,191 eligible patients at the clinic. The patients' characteristics are summarized in Table 1. The median age and diabetes duration were 48 and 25 years, respectively, and the median metabolic control measured as HbA_{1c} was 7.7% (61 mmol/mol). The insulin pump–to–multiple daily injections ratio was 0.29. The total prevalence of CVD was 9.0%, divided as 6.9% CHD and/or 3.4% CVL.

The skewed distribution of Lp(a) is visualized in Fig. 1*A*. The values spread between <10 nmol/L, corresponding to the 33rd percentile of the sample, and 1,100 nmol/L. The median, 80th, and 90th percentiles were 19, 98, and 176 nmol/L, respectively. No significant differences in Lp(a) levels were observed between men and women when comparing their median (18 and 21 nmol/L), 80th percentile (95 and 105 nmol/L), and 90th percentile (166 and 193 nmol/L) values. Increasing levels of Lp(a) were observed across age quartile groups: quartile (Q) 1: 18–35, Q2: 36–48, Q3: 49–59, and Q4: 60–90 years. The Lp(a) (nmol/L) for the respective quartiles were at median (Q1: 14, Q2: 20.0, Q3: 22, Q4: 21), 80th percentile (Q1: 73, Q2: 85, Q3: 112, Q4: 111), and 90th percentile (Q1: 145, Q2: 152, Q3: 212, Q4: 215) (Fig. 1*B*). Compared with the lowest respective quartile, each age quartile increase was associated with a significantly higher Lp(a) level ($P < 0.05$ for all comparisons except for Q2).

Table 2—Vascular complications in relation to Lp(a) levels

		Lp(a) levels, nmol/L			
	All	Very Low <10	Low 10–30	Intermediate 30–120	High >120
All, *n* (%)	1,860	621 (33.3)	502 (27.0)	434 (23.2)	303 (16.3)
Macrovascular					
CVD, *n* (%)	168	38 (6.1)	54 (10.7)	38 (8.7)	38 (12.5)
RRR (95% CI)		1	1.85 (1.20–2.85)**	1.47 (0.92–2.35)	2.20 (1.37–3.52)**
RRR, adjusted‡ (95% CI)		1	1.54 (0.98–2.43)	1.22 (0.79–1.99)	1.59 (0.96–2.61)
CHD, *n* (%)	128	27 (4.3)	44 (8.8)	27 (6.2)	30 (9.9)
RRR (95% CI)		1	2.11 (1.29–3.46)**	1.46 (0.84–2.52)	2.42 (1.41–4.15)**
RRR, adjusted (95%CI)		1	1.73 (1.04–2.92)*	1.18 (0.67–2.10)	1.70 (0.97–3.00)
CVL, *n* (%)	63	16 (2.6)	18 (3.6)	16 (3.7)	13 (4.3)
RRR (95% CI)		1	1.41 (0.71–2.93)	1.45 (0.71–2.93)	1.69 (0.80–3.57)
RRR, adjusted (95% CI)		1	1.16 (0.58–2.34)	1.21 (0.59–2.47)	1.22 (0.57–2.60)
Microvascular					
Albuminuria, *n* (%)	255	63 (10.1)	66 (13.1)	73 (16.8)	53 (17.5)
RRR (95% CI)		1	1.33 (0.92–1.92)	1.78 (1.24–2.56)**	1.87 (1.26–2.78)**
RRR, adjusted (95% CI)		1	1.23 (0.85–1.78)	1.69 (1.17–2.44)**	1.68 (1.12–2.50)*
Retinopathy, *n* (%)	1,294	406 (65.4)	363 (72.3)	311 (71.6)	214 (70.6)
RRR (95% CI)		1	1.39 (1.07–1.80)*	1.38 (1.05–1.81)*	1.28 (0.95–1.74)
RRR, adjusted (95% CI)		1	1.30 (1.00–1.69)*	1.30 (0.99–1.72)	1.13 (0.83–1.54)
Neuropathy, *n* (%)	390	133 (21.4)	105 (20.9)	87 (20.0)	65 (21.4)
RRR (95% CI)		1	0.95 (0.71–1.27)	0.92 (0.68–1.25)	1.01 (0.72–1.42)
RRR, adjusted (95% CI)		1	1.08 (0.80–1.46)	1.05 (0.76–1.44)	1.27 (0.89–1.80)
Diabetic foot disease					
Ulceration, *n* (%)	77	25 (4.0)	20 (4.0)	16 (3.7)	16 (5.3)
RRR (95% CI)		1	0.96 (0.53–1.76)	0.90 (0.47–1.72)	1.33 (0.69–2.54)
RRR, adjusted (95% CI)		1	1.04 (0.56–1.91)	0.98 (0.51–1.86)	1.51 (0.79–2.91)
Composite CVD§	240	62 (10.0)	72 (14.3)	54 (12.4)	52 (17.2)
RRR (95% CI)		1	1.51 (1.05–2.17)*	1.28 (0.87–1.89)	1.87 (1.26–2.78)**
RRR, adjusted (95% CI)		1	1.34 (0.92–1.94)	1.31 (0.76–1.68)	1.51 (1.01–2.28)*
Calcified aortic valve disease					
Sclerosis/stenosis, *n* (%)	88	16 (2.6)	27 (5.4)	23 (5.3)	22 (7.3)
RRR (95% CI)		1	2.15 (1.14–4.04)*	2.12 (1.11–4.06)*	2.96 (1.53–5.72)**
RRR, adjusted (95% CI)		1	1.73 (0.90–3.31)	1.73 (0.88–3.38)	2.03 (1.03–4.03)*

‡Adjusted for age and smoking status. §Composite CVD: macrovascular complications, including CHD (including history of angina pectoris, myocardial infarction, presence of coronary angioplasty implant, or coronary artery bypass graft), CVL (including transient ischemic attack or ischemic stroke), and diabetic foot ulcerations as a clinical sign of peripheral artery disease. *$P < 0.05$; **$P < 0.01$.

Lp(a) Levels and Prevalence of Vascular Complications

Lp(a) levels in our sample were defined as very low <10 ($n = 621$), low 10–30 ($n = 502$), intermediate 30–120 ($n = 434$), and high >120 ($n = 303$) nmol/L. The division into four groups was based on prior knowledge of Lp(a) risk levels for CVD (13). The prevalence of vascular complications and statistical comparisons between the groups are summarized in Table 2. Patients with high Lp(a) levels, compared with those with very low levels, had an RRR for CVD of 2.20 (95% CI 1.37–3.52, $P = 0.001$). This effect on CVD was mainly influenced by coronary events, with an RRR of 2.42 (95% CI 1.41–4.15, $P = 0.001$). Also, in a comparison of a composite CVD variable including any macrovascular complication (CHD, CVL, and diabetic foot ulcerations as a clinical sign of peripheral artery disease), the RRR was 1.87 (95% CI 1.26–2.78, $P = 0.002$). When comparisons were adjusted for age and smoking status, the corresponding RRRs were 1.59 for CVD (95% CI 0.96–2.61, $P = 0.071$), 1.70 for CHD (95% CI 0.97–3.00, $P = 0.063$) and 1.51 for composite CVD (95% CI 1.01–2.28, $P = 0.048$). Similar age- and smoking-adjusted RRR comparisons for microvascular complications showed an influence of high Lp(a) only on albuminuria of 1.68 (95% CI 1.12–2.50, $P = 0.01$) but not for retinopathy or neuropathy. Patients with high levels of Lp(a) showed an RRR of 2.96 (95% CI 1.53–5.72; $P = 0.001$) compared with very low Lp(a) levels for having signs of calcified aortic valve disease (adjusted RRR 2.03, 95% CI 1.02–4.01, $P = 0.043$).

Lp(a) Levels in Relation to Metabolic Control of Diabetes

The relationship between diabetes metabolic control and plasma Lp(a) was studied by dividing the sample into three groups according to their HbA_{1c}%, with a group of good <6.9% (<52 mmol/mol; $n = 385$), intermediate 6.9–8.6% (52–70 mmol/mol; $n = 1,008$), and poor >8.6% (>70 mmol/mol; $n = 467$) control. Lp(a) levels were inversely related to metabolic control, with median values at 17, 18, and 24 nmol/L, 80th percentile values at 78, 104, and 104 nmol/L, and 90th percentiles values at 126, 184, and 220 nmol/L, in the three groups, respectively (Fig. 2*A*). After age adjustment and using the group with good metabolic control as a reference, the median levels of Lp(a) were significantly higher in the group with poor metabolic control but

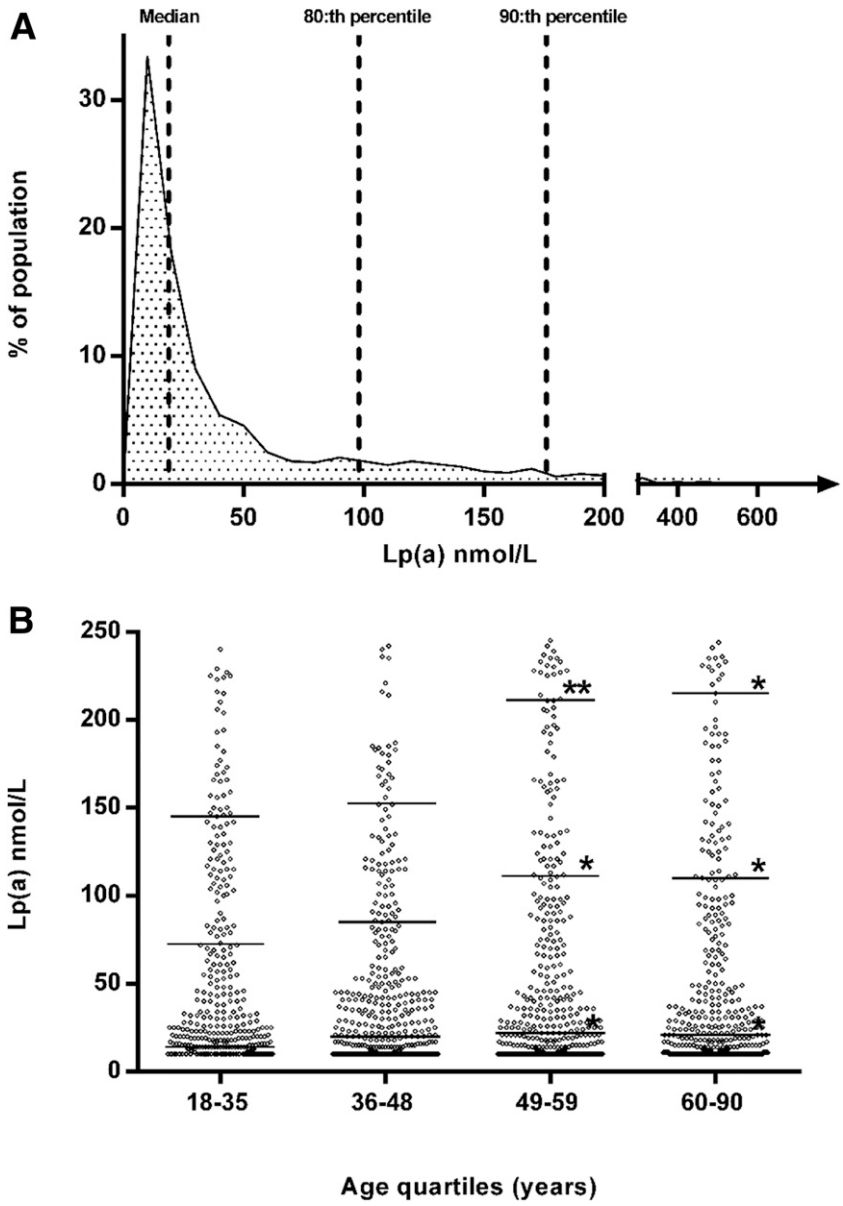

Figure 1—*A*: Distribution of plasma Lp(a) levels in patients ($n = 1,860$) with type 1 diabetes. *B*: Comparison of Lp(a) levels between age quartiles at median, 80th, and 90th percentile levels against the lowest respective quartile. Lp(a) axes are truncated (highest value 1,100 nmol/L), and median, 80th, and 90th percentiles are indicated with black lines. *$P < 0.05$; **$P < 0.01$.

not in the group with intermediate metabolic control. At the 80th percentile level, Lp(a) was significantly higher in the intermediate but not in the poor metabolic control group, and at the 90th percentile level, it was significantly higher in both groups. The Lp(a) level of patients with good control was significantly lower than for patients with poorer control (HbA_{1c} >6.9% or 52 mmol/mol) compared at both the 80th ($P = 0.031$) and 90th ($P < 0.001$) percentile levels. The addition of use of an insulin pump as a covariate in the comparisons did not significantly alter the relationship between Lp(a) and metabolic control (data not shown). Finally, the age-adjusted RRR of patients with Lp(a) >120 nmol/L compared with patients with very low Lp(a) levels (<10 nmol/L) increased to 1.49 (95% CI 1.01–2.18, $P = 0.043$) for patients in with intermediate metabolic control and to 1.78 (95% CI 1.15–2.76, $P = 0.01$) for patients with poor metabolic control (Fig. 2*B*).

CONCLUSIONS

In this cross-sectional study, we demonstrate a significant relationship between Lp(a) levels and vascular complications in patients with type 1 diabetes. To the best of our knowledge, this is the largest type 1 diabetes study of Lp(a) and its impact on CVD. High Lp(a) levels (>120 nmol/L) are associated with a 1.5-fold increase in CVD RRR, which is mainly driven by coronary events, and a 2-fold increase in the RRR for calcified aortic valve disease. The European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) lipid guidelines identify Lp(a) >50 mg/dL (~120 nmol/L) as a clinically pertinent risk level (25). Thus, our study affirms this level as relevant also in the vulnerable population with type 1 diabetes.

The skewed distribution of Lp(a) found in this sample of patients with type 1 diabetes is typical for the lipoprotein. No significant difference in plasma Lp(a) levels was observed between the men and women. However, a larger sample size is needed to exclude the possibility of an interaction of sex. The 80th percentile (98 nmol/L) level is slightly lower than the results found in two general population studies: the Copenhagen population study (50 mg/dL or ~120 nmol/L) (10) and the Bruneck study (45 mg/dL or ~110 nmol/L) (26). Lp(a) levels vary between ethnic groups, where Caucasians display lower levels than people of African and Asian descent (4). However, ethnicity cannot explain the difference because both studies only included white Caucasians, and the proportion of non-Caucasians in the current study is estimated to be <1% (to the best of our knowledge). In comparison with type 2 diabetes, a meta-analysis of clinical trial data (11) showed that patients without CVD (Collaborative Atorvastatin Diabetes Study [CARDS] trial) and patients on hemodialysis (Die Deutsche Diabetes Dialyse Studie [4D] trial) had a median (interquartile range) Lp(a) level of 22 nmol/L (12–101) and 29 nmol/L (12–101), respectively. The recent study that compared Lp(a) levels in an ethnic homogenous Chinese population (21) found only a very small difference in median Lp(a) levels between patients without diabetes (15.2 mg/dL) and those with type 2 diabetes (14.7 mg/dL). It is evident that caution must be taken when comparing Lp(a) levels from studies that used different Lp(a) measurement methods, and it is too early at this point to conclude that patients with diabetes have lower Lp(a) levels than the general population.

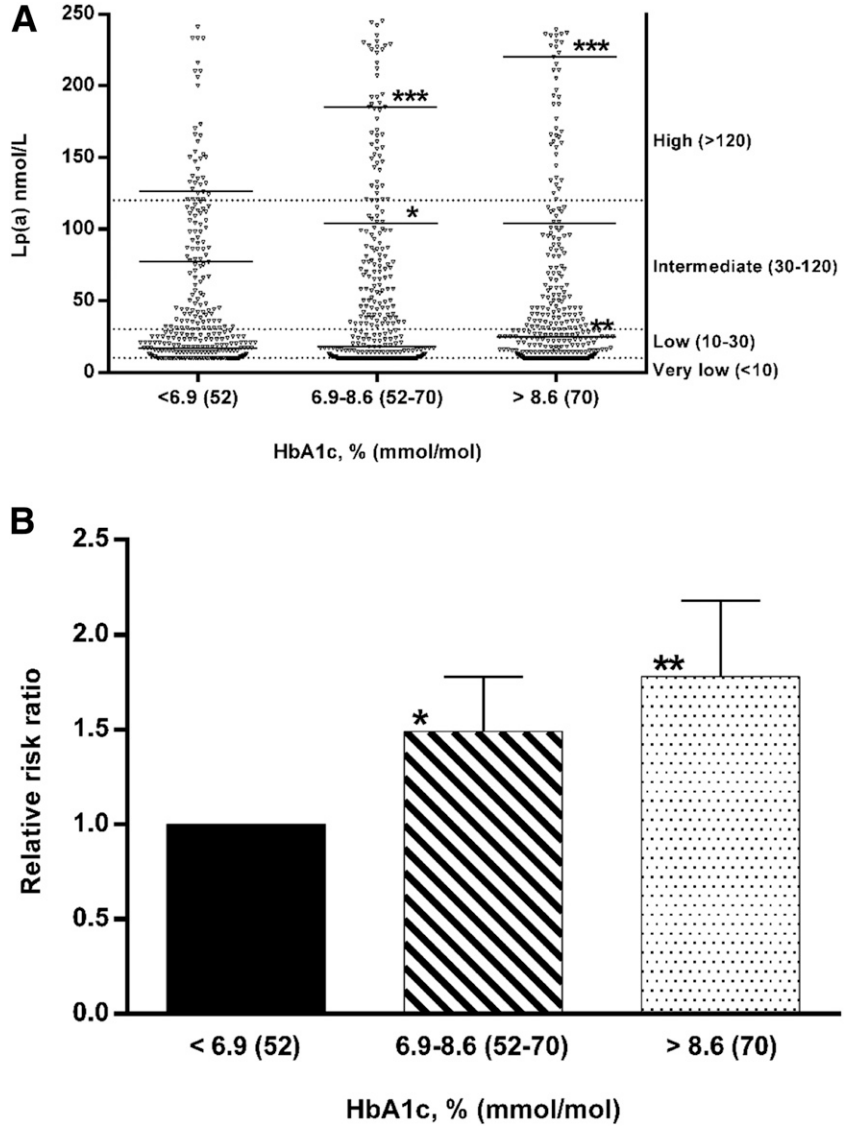

Figure 2—Association between diabetic metabolic control and Lp(a) levels. The study sample was subdivided by HbA_{1c}% (mmol/mol) into three groups with good, <6.9% (<52) (n = 385); intermediate, 6.9–8.6% (52–70) (n = 1,008); or poor, >8.6% (>70) (n = 467) control. *A*: Absolute values of Lp(a) in each HbA_{1c} group with medians, 80th, and 90th percentiles indicated. The left *y*-axis is truncated at 250 nmol/L, and the right *y*-axis shows corresponding levels for the Lp(a) subgroups. *B*: RRR to have a high vs. low Lp(a) level (>120 vs. <10 nmol/L) in relation to each HbA_{1c} group. Error bars, SE. Comparisons between HbA_{1c} groups (age adjusted) using the good metabolic control group as reference. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

The lipoprotein profiles in plasma differ considerably between patients with type 1 and type 2 diabetes, where the former is similar to healthy individuals, whereas the lipid profile of patients with insulin resistant type 2 diabetes is characterized by an increase of TG-rich lipoproteins and small, dense LDLs, and a low HDL-C concentration (27). However, much less is known about Lp(a). The liver is the key organ for Lp(a) metabolism, controlling both its synthesis and catabolism. A recent publication (28) indicates that plasma Lp(a) levels are mainly controlled by its rate of synthesis, at least in healthy normolipidemic men. Our finding that patients with good diabetic metabolic control have lower Lp(a) levels would suggest that insulin may affect the hepatic synthesis of Lp(a). Interestingly, insulin levels in type 2 diabetes have been shown to correlate inversely to the residual plasma Lp(a) level (i.e., the proportion of Lp(a) that is not regulated by the inherent genetic control) (29). Cross-sectional studies of patients with type 1 diabetes have found similar association between HbA_{1c} and Lp(a) (30), whereas others have not (31,32). The question has also been addressed in prospective intervention studies where metabolic control has been improved with intensified insulin therapy during a shorter time period (3 weeks–3 months), again yielding conflicting results (33,34). Common for both studies was that the number of participants with Lp(a) above the clinically significant level of 120 nmol/L (~50 mg/dL) was very low (n = 2–7). The current study has a large proportion (16%, n = 303) above this critical level, which could help explain why we were able to find a possible shift in Lp(a) between groups with different metabolic control. In a foreseeable future, it will be possible to evaluate the insulin effect on the liver Lp(a) synthesis with a prospective study design by comparing time-in-range glucose data for patients with continuous glucose monitoring to determine whether the hyperinsulinemia or the metabolic control per se is decisive.

The catabolic pathway of Lp(a) in the liver is not well understood. It seems to be differentiated from the LDL-C particles but plays only a minor part for the determination of Lp(a) plasma levels (28,35). In addition, the kidney seems to have a role in Lp(a) catabolism (36), and Lp(a) is increased in chronic kidney disease (CKD) (37). Furthermore, Lp(a) is proposed to have a causal role in CKD development, and the levels of Lp(a) predict the new onset of CKD in patients with type 2 diabetes (38). In the 10-year follow-up, patients with increased Lp(a) levels (range 32–65 mg/dL or ~75–155 nmol/L) had a twofold increased risk of onset of CKD stage 3 compared with patients with low levels (<9 mg/dL or ~<22 nmol/L). The importance of cholesterol and apolipoprotein B for the development of albuminuria has also been shown for type 1 diabetes (39). Our study suggests that Lp(a) may also have a causal role in the development of renal impairment in patients with type 1 diabetes since we observed a nearly twofold increase in the relative risk for albuminuria for patients with Lp(a) >120 nmol/L.

A limitation of the study is its observational design. Consequently, we cannot provide evidence for a causative role of Lp(a) for the vascular complications in patients with type 1 diabetes. It is also limited in size, and only 9% of the participants exhibited overt CVD, restricting the possibility to proficiently compare

incrementing Lp(a) risk levels. In the adjusted RRR model, sex and diabetes duration were not incorporated as covariates because we did not find an association to Lp(a) levels (sex) or a high collinearity with age (diabetes duration). Also in this study, two alternative laboratory methods were used in 5% of the cases to measure Lp(a), and the conversion of Lp(a) values between different units is problematic because the accuracy is dependent on apolipoprotein(a) size and the laboratory method used.

In summary, our study supports the concept of Lp(a) as a risk factor for CVD also in patients with type 1 diabetes. The identified CVD risk level for Lp(a) of 120 nmol/L and the association between Lp(a) and aortic valve disease are novel findings for this patient group. Introducing measurement of plasma Lp(a) levels in the routine management of these patients could potentially improve their risk factor assessment and provide the basis for intensified conventional treatment. Lp(a) is also emerging as a clinically important target, with new pharmacological treatments with antisense oligonucleotides currently being developed to significantly reduce Lp(a) levels (40). They would, if proven effective and safe, possibly be a treatment option for this patient group with high inherent CVD risk.

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