Lipoprotein(a) as a Predictor of Cardiovascular Disease in a Prospectively Followed Cohort of Patients With Type 1 Diabetes

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Lipoprotein(a) [Lp(a)] concentrations are genetically determined (1,2), and numerous epidemiological studies in the general population have identified elevated Lp(a) levels as a risk factor for atherosclerotic disorders (3,4). However, this association is not as clearly defined in patients with type 1 diabetes (5), since large prospective studies are missing. We therefore analyzed the role of Lp(a) for the incidence of cardiovascular disease (CVD) complications.

RESEARCH DESIGN AND METHODS

— The 429 consecutive, unrelated type 1 diabetes patients included in this observational study were from the Hospital Lainz-Vienna. Inclusion criteria described recently (6) were regular attendance at the outpatient clinic in the last year and stable metabolic control. For patient characteristics, see Table 1. The recruitment period lasted from 1993 to 1999. Regular follow-ups were performed every 3–6 months. Yearly follow-ups included detailed history, laboratory parameters, measurement of peripheral and autonomic neuropathy, staging of retinopathy, and feet inspection.

Previous CVD complications were obtained by self reports verified from hospital records. Patients' blood was drawn after an overnight fast. Lp(a) quantification was carried out, as described in detail (7). Apolipoprotein(a) phenotyping was performed by SDS agarose gel electrophoresis (8). Glomerular filtration rate (eGFR) was calculated from the Modification of Diet in Renal Disease equation (9).

A composite CVD end point during follow-up was defined as coronary artery disease, cerebrovascular disease, and peripheral arterial disease.

Univariate comparisons of variables were performed using unpaired *t* test, Mann-Whitney *U* test, and Pearson's χ^2 test. To investigate the influence of various variables on the risk of CVD complications, multiple Cox regression models were calculated.

RESULTS

— Sixty of the 429 patients suffered a CVD event during the observation period of up to 10.7 years (average 5.8). These events included cases of coronary artery disease (10 myocardial infarctions, 2 coronary artery bypass grafts, 10 percutaneous transluminal angioplasties, and 4 coronary stenoses >50%), cerebrovascular disease (1 transient ischemic attack, 6 ischemic strokes, and 2 carotid endarterectomies), and 25 cases with peripheral arterial disease. Univariate comparisons of patients with and without CVD events and results of the multiple Cox regression analysis are provided in Table 1. Cox regression analysis revealed previous CVD complications, eGFR, Lp(a) >30 mg/dl, diabetes duration, HbA_{1C} (A1C), and triglyceride levels as significant predictors of CVD complications. Previous CVD complications showed the strongest association with CVD event-free survival (hazard ratio [HR] 7.74 [4.18–14.34], $P < 0.0001$). Lp(a) >30 mg/dl was associated with a more than twofold higher risk for CVD events (2.23 [1.28–3.87], $P = 0.004$). Neither a concomitant elevation of LDL cholesterol nor a decrease of HDL cholesterol or both influenced the association of Lp(a) >30 mg/dl with CVD.

Since kidney disease is an important predictor of CVD and to exclude that the increased risk by high Lp(a) in patients with kidney impairment (10–13) is only a secondary effect of Lp(a) increasing kidney impairment, we performed three sensitivity analyses. First, we excluded patients with end-stage renal disease (ESRD) at study entry ($n = 21$); second, we excluded 110 patients either proteinuric or with microalbuminuria and/or with ESRD; and third, we excluded 40 patients with an eGFR <60 ml/min per 1.73 m^2 and/or ESRD. These analyses increased the estimates for Lp(a) to 2.41 (1.35–4.30, $P = 0.003$), 3.31 (1.38–7.95, $P = 0.007$), and 2.96 (1.38–6.34, $P = 0.005$), respectively.

CONCLUSIONS

— This prospective study is the largest study in type 1 diabetes demonstrating Lp(a) >30 mg/dl as a strong and independent predictor of CVD complications (HR 2.23). Only a few studies have investigated this question in type 1 diabetic patients and reported inconsistent results. This can probably be explained by differences in study design, sample size and population, short observation periods, definition of inclusion criteria and clinical end points, and the method used to measure Lp(a). The only available 4-year prospective nested case-control study (14) in 22 patients did not identify Lp(a) as a predictor of events. Similarly, most small cross-sectional

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Abbreviations: CVD, cardiovascular disease; eGFR, glomerular filtration rate; ESRD, end-stage renal disease; Lp(a), lipoprotein(a).

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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Table 1—*Baseline clinical characteristics and variables associated with cardiovascular outcome during follow-up of 429 patients with type 1 diabetes*

		Univariate comparison of patients			Cox regression analysis*	
Clinical characteristics	Entire group (n = 429)	Without CVD complications during follow-up (n = 369)	With CVD complications during follow-up (n = 60)	P value†	HR (95% CI)	P value
Sex (M/F)	245 (57.1)/184 (42.9)	206 (55.8)/163 (44.2)	39(65.0)/21 (35.0)	0.18		
Age (years)	39.8 ± 13.1	38.3 ± 12.8	49.4 ± 10.7	<0.0001		0.18‡
Diabetes duration (years)	22.1 ± 13.2	20.4 ± 12.8	32.5 ± 10.0	<0.0001		
Diabetes duration >22 years (median) (years)	208 (48.5)	155 (42.0)	53 (88.3)	<0.0001	3.72 (1.55–8.93)	0.003
A1C (%)	8.5 ± 1.4 (7.6/8.3/9.1)	8.4 ± 1.3 (7.6/8.2/9.0)	9.0 ± 1.6 (7.9/8.7/9.7)	0.005	1.19 (1.02–1.39)	0.03
BMI (kg/m²)	24.4 ± 3.2	24.4 ± 3.2	24.4 ± 3.2	0.90		
Current smoking	127 (30.2)	106 (29.3)	21 (35.6)	0.55		
Hypertension§	175 (40.8)	130 (35.2)	45 (75.0)	<0.0001		0.16‡
eGFR (ml/min per 1.73 m^2)	83 ± 25 (70/84/98)	86 ± 22 (72/86/100)	62 ± 27 (46/68/83)	<0.0001	0.985 (0.974–0.996)	0.006
Urinary protein excretion				overall <0.0001		
No microalbuminuria	331 (77.3)	303 (82.3)	28 (46.7)			
Microalbuminuria 30–300 mg/day	45 (10.5)	35 (9.5)	10 (16.7)		0.40‡	
Proteinuria 300–3,500 mg/day	39 (9.1)	25 (6.8)	14 (23.3)		0.59‡	
Nephrotic syndrome	13 (3.0)	5 (1.4)	8 (13.3)		0.28‡	
Previous cardiovascular events	41 (9.6)	14 (3.8)	27 (45.0)	<0.0001	7.74 (4.18–14.34)	<0.0001
Total cholesterol (mg/dl)	187 ± 43	186 ± 41	195 ± 53	0.16		0.16‡
LDL cholesterol (mg/dl)	134 ± 37	113 ± 36	120 ± 42	0.15		
HDL cholesterol (mg/dl)	51.6 ± 17.2	52.4 ± 17.5	46.4 ± 14.5	0.03		0.26‡
Triglycerides (mg/dl)	108 ± 87 (57/84/127)	103 ± 77 (56/82/122)	143 ± 128 (73/109/167)	0.001	1.003 (1.000–1.006)	0.037
Lp(a) (mg/dl)	20.3 ± 27.5 (3.7/9.1/24.3)	19.3 ± 26.9 (3.6/8.7/21.7)	25.5 ± 30.5 (4.7/13.2/38.0)	0.09		
Lp(a) >30 mg/dl	93 (21.8)	72 (19.7)	21 (35.0)	0.008	2.23 (1.28–3.87)	0.004
LMW apo(a) phenotypes‖	115 (27.6)	101 (28.2)	14 (23.7)	0.475		

Data are means ± SD, means ± SD (25/50/75th percentile) (since the variable is nonnormally distributed), or n (%). *Only variables that showed a P value <0.20 in the unadjusted Cox regression analysis were offered to the multiple Cox regression analysis. HRs (95% CI) are provided only for the variables that turned out to be significant in a stepwise selection procedure of the multiple Cox regression analysis. †For comparison of patients with and without CVD complications. ‡P values for variables which did not significantly contribute to the Cox regression model. §Hypertension was defined as a systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg and/or the current use of blood pressure–lowering drugs. ‖Low–molecular weight (LMW) apolipoprotein(a) [apo(a)] phenotypes included all subjects with at least one apo(a) isoform with 11–22 K-IV repeats.

studies were also negative (15–17). Wollesen et al. (18) found Lp(a) to be related to toe systolic blood pressure but not to CVD. Another negative study (19) investigated a priori asymptomatic patients, which is again different from our and other studies. Preexisting CVD turned out to be one of the most important predictors of future CVD events in our study. Since many variables, including high Lp(a) levels, are also associated with previous CVD events, the exclusion of these patients might underestimate the predictive value of these variables.

Other studies that included type 1 and type 2 diabetic patients reported inconsistent results (20,21). The study by James et al. (20) reported an association of Lp(a) with ischemic heart disease or macroangiopathy.

Several investigations are available in type 2 diabetic patients, including four prospective studies (22–25). With the exception of one study (24), the other three showed positive associations (22,23,25). Together, these inconsistent results show a clear demand for further and larger studies. Our study is the largest prospective study in type 1 diabetic patients with a mean observation period of almost 6 years, therefore adding important information.

One of the strengths of our study is the prospective observation period of, on average, 5.8 years in a well-defined group of type 1 diabetic patients. We used stringent criteria for CVD complications of atherosclerotic origin, excluding entities such as heart failure. The main limitation of our study is that the investigated patients are not an incident cohort of newly identified type 1 diabetic patients but a prevalent cohort of patients with a wide variation of diabetes duration. Therefore, effects of survival bias could have influenced our results.

We conclude that an Lp(a) value >30 mg/dl is strongly and independently associated with CVD complications in type 1 diabetic patients. Thus, measurement of Lp(a) in type 1 diabetic patients might be a helpful tool for stratifying patients with an increased risk for CVD complications, which could carry a higher predictive potential than some of the currently used measures in CVD risk profiles of type 1 diabetic patients.

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