Renal Disease as a Determinant of Increased Lipoprotein(a) Concentrations in Diabetic Patients

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OBJECTIVE — This study examined the hypothesis that kidney function is an independent determinant of lipoprotein(a) [Lp(a)] concentrations in people with diabetes.

RESEARCH DESIGN AND METHODS — Lp(a) concentrations were measured in plasma samples from 273 type 2 and 223 type 1 diabetic patients recruited from a diabetes clinic. Kidney function was categorized as normal or pathological according to plasma creatinine levels and creatinine clearance rates.

RESULTS — Macroalbuminuria was uniformly associated with significantly raised plasma concentrations of Lp(a) regardless of the marker used to identify kidney dysfunction. In contrast, in patients with microalbuminuria, significantly raised plasma Lp(a) levels were observed only when creatinine clearance rates or plasma creatinine levels indicated pathological kidney function. These conclusions were independent of diabetes type.

CONCLUSIONS — In microalbuminuria and apparently in normoalbuminuria, altered kidney function determined by creatinine clearance rates or creatinine levels appears to be a major determinant of raised Lp(a) levels in both type 1 and type 2 diabetic patients. In contrast, Lp(a) concentrations were uniformly raised in patients with macroalbuminuria.

Diabetes Care 22:2033–2036, 1999

Lipoprotein(a) [Lp(a)] is an independent risk factor for cardiovascular disease (1–6). Several studies have reported higher concentrations of Lp(a) in diabetic patients, which has led to speculation that Lp(a) may contribute to the greatly increased incidence of vascular disease associated with diabetes (7–10). Considerable debate remains, however, regarding the precise cause of supranormal Lp(a) levels in people with diabetes (11,12). In nondiabetic patients, renal disease correlates with higher levels of Lp(a) that are normalized by kidney transplantation (13). Recent studies have also demonstrated urinary excretion of Lp(a) degradation products (14,15), but they have not established evidence for an active role of the kidney in Lp(a) catabolism. Renal disease is a frequent complication of diabetes that has prompted speculation that kidney dysfunction is the principal cause of raised Lp(a) in type 1 and type 2 diabetic patients (11,16–18). These observations emphasize the need to define fully the relationship between Lp(a) and renal disease in diabetic patients. This study addressed the hypothesis that kidney function is an independent determinant of Lp(a) in diabetic patients. We demonstrated that, particularly in microalbuminuric patients, raised plasma Lp(a) levels are only associated with renal dysfunction.

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Received for publication 8 June 1999 and accepted in revised form 5 August 1999.

Abbreviations: apo(a), apolipoprotein(a); Lp(a), lipoprotein(a).

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

RESEARCH DESIGN AND METHODS

Patients

Diabetic patients (n = 496; type 2 diabetes = 273, type 1 diabetes = 223) were recruited from patients consecutively attending the Diabetes Centre of Ancona Hospital in the course of regular follow-up visits. Exclusion criteria included urinary tract infection, inability to obtain a 24-h urine sample, presence of prerenal causes of albuminuria, hypercatabolic states, and use of lipid-lowering medications. Demographic data are shown in Table 1. A fasting blood sample was obtained, and a 24-h urine sample was collected.

Informed consent was obtained from all patients. The study was performed according to the principals of the Declaration of Helsinki.

Analyses

Creatinine was measured by using a commercial kit (Du Pont, Wilmington, DE). In our laboratory, intra- and interassay coefficients of variation were 3.4 and 5.8 for serum and 0.6 and 1.1 for urine, respectively. Plasma values >1.3 mg/dl in at least two samples indicated renal insufficiency. Creatinine clearance was also calculated. Cutoff values were <70 ml/min for renal insufficiency and >120 or >150 ml/min for hyperfiltration for men and women, respectively. Albumin was measured from the 24-h urine collection and was used to classify patients as normoalbuminuric (<30 mg/24 h), microalbuminuric (>30 < 300 mg/24 h), and macroalbuminuric (>300 mg). HbA_{1c} was quantified by high-performance liquid chromatography (Bio-Rad, Hercules, CA); the normal value in our laboratory is ≤6.1%. Plasma lipids (19,20) and Lp(a) concentrations (9) were measured with commercially available kits as described previously. HDL cholesterol was assayed after precipitation of LDL and VLDL (19,20), and LDL cholesterol was calculated according to the Friedewald formula (21).

Table 1—*Demographic data for type 1 and type 2 diabetic patients*

	Type 1 diabetic patients	Type 2 diabetic patients
n	223	273
Sex (% men)	53.8	52.4
Age (years)	43.2 ± 14.2	63.5 ± 10.7
Duration (years)	18.3 ± 11.8	17.2 ± 9.8
BMI	23.9 ± 2.7	27.8 ± 4.5
HbA_{1c}	9.4 ± 1.7	9.6 ± 2.0
Cholesterol (mmol/l)	5.27 ± 1.09	5.86 ± 1.46
LDL cholesterol (mmol/l)	3.29 ± 0.96	3.72 ± 1.18
HDL cholesterol (mmol/l)	1.48 ± 0.44	1.24 ± 0.41
Triglycerides (mmol/l)	1.08 ± 0.74	2.01 ± 1.90
Microalbuminuria (%)	41.3	42.5
Macroalbuminuria (%)	6.3	15.4
Creatinine >1.3 mg/dl (%)	5.8	17.9
Creatinine (mg/dl)	0.97 ± 0.48	1.14 ± 0.65
Creatinine clearance (ml/min)	110.6 ± 30.9	93.1 ± 32.9
Lp(a) (mg/dl)	10.0 (4.0–21.0)	11.0 (4.7–28.2)

Data are means ± SD or medians (25th–75th percentiles).

Statistical analyses

Triglyceride and albumin values were log transformed before analysis. Lp(a) was analyzed with nonparametric tests. Continuous variables were compared with one-way analysis of variance and two-factor general linear modeling. Categorized data were examined with the χ^2 test. The Kruskal-Wallis and Mann-Whitney tests were performed for variables that were not normally distributed. Correlation analysis was performed by using the Spearman partial correlation coefficient with the forward selection procedure. Scheffe and Tukey tests for multiple comparisons were applied where appropriate. All analyses were performed with the SPSS statistical package (Version 7.5 for Windows; SPSS, Chicago).

Table 2—*Clinical data on diabetic patients as a function of albuminuria and creatinine clearance*

	Normoalbuminuria	Microalbuminuria	Macroalbuminuria	Total
Subgroup A				
n	158	142	28	328
Sex (% men)	58.2	54.9	50.0	56.1
Age (years)	56.2 ± 14.9*	53.0 ± 16.6*	62.7 ± 10.7	55.4 ± 15.5
Creatinine (mg/dl)	0.93 ± 0.17*†	0.98 ± 0.17*†	1.04 ± 0.16†	0.96 ± 0.17
Clearance (ml/min)	98.5 ± 16.4*†	96.9 ± 56.9*†	91.9 ± 14.8*†	97.2 ± 15.8
Albuminuria (mg/24 h)	10.2 ± 6.6‡§	99.3 ± 60.6‡	706.1 ± 603.5	108.2 ± 258.4
Cholesterol (mmol/l)	5.52 ± 1.38	5.47 ± 1.27†	5.61 ± 1.34†	5.51 ± 1.33
Triglycerides (mmol/l)	1.41 ± 1.14	1.55 ± 1.80†	2.13 ± 1.77*†	1.53 ± 1.52
LDL cholesterol (mmol/l)	3.49 ± 1.16	3.49 ± 0.93	3.48 ± 1.24	3.46 ± 10.7
HDL cholesterol (mmol/l)	1.37 ± 0.44	1.35 ± 0.43	1.20 ± 0.32	1.35 ± 0.43
Lp(a) (mg/dl)	11 (5–60)	8 (3–73)	22 (8–91)	10 (4–23)
Subgroup B (hyperfiltration)				
n	64	38	3	105
Sex (% men)	35.9	44.7	33.3	39.0
Age (years)	42.7 ± 13.5†	47.7 ± 14.7	59.0 ± 13.0	45.0 ± 14.2
Creatinine (mg/dl)	0.71 ± 0.17†¶	0.77 ± 0.15†¶	0.76 ± 0.20†	0.73 ± 0.17
Clearance (ml/min)	146.2 ± 17.7†	145.7 ± 22.8†	139.6 ± 15.5†	145.8 ± 19.5
Albuminuria (mg/24 h)	11.1 ± 7.0‡§	108.5 ± 73.1†‡	952.3 ± 632.2†	73.2 ± 186.3
Cholesterol (mmol/l)	5.23 ± 1.07§	6.04 ± 1.29	5.01 ± 0.69†	5.60 ± 1.21
Triglycerides (mmol/l)	1.07 ± 0.62†	1.72 ± 1.60	0.75 ± 0.15†	1.30 ± 1.12
LDL cholesterol (mmol/l)	3.27 ± 1.01	3.76 ± 1.06	3.29 ± 0.72	3.45 ± 1.04
HDL cholesterol (mmol/l)	1.41 ± 0.43	1.47 ± 0.51	1.38 ± 0.10	1.47 ± 0.45
Lp(a) (mg/dl)	8 (3–59)	8.5 (5–52)	35 (8–90)	8 (4–20)
Subgroup C (renal insufficiency)				
n	10	28	25	63
Sex (% men)	80.0	46.4	68.0	60.3
Age (years)	58.5 ± 10.1	69.0 ± 11.7	61.3 ± 12.1	64.3 ± 12.3
Creatinine (mg/dl)	1.48 ± 0.22	2.16 ± 1.36	2.32 ± 0.82	2.12 ± 1.07
Clearance (ml/min)	56.5 ± 8.7	44.3 ± 14.2	41.9 ± 12.9	45.3 ± 13.7
Albuminuria (mg/24 h)	9.1 ± 8.7	132.2 ± 75.7	902.4 ± 310.0	418.3 ± 445.1
Cholesterol (mmol/l)	5.58 ± 1.21	6.03 ± 1.28	6.60 ± 1.60	6.19 ± 1.43
Triglycerides (mmol/l)	1.84 ± 0.77	2.29 ± 1.27	2.76 ± 2.95	2.40 ± 2.07
LDL cholesterol (mmol/l)	3.62 ± 1.33	3.83 ± 1.02	4.33 ± 1.29	3.99 ± 1.20
HDL cholesterol (mmol/l)	1.13 ± 0.24	1.18 ± 0.49	1.14 ± 0.37	1.16 ± 0.42
Lp(a) (mg/dl)	17 (1–38)	21 (7–67)	16 (8–90)	20 (7–40)

Data are means ± SD or medians (25th–75th percentiles). Cutoff values for clearance were as follows: normal >70 < 120 (women) and >70 < 150 ml/min (men), hyperfiltration >120 (women) and >150 ml/min (men), and renal insufficiency <70 ml/min. *$P < 0.05$ vs. subgroup B and †$P < 0.05$ vs. subgroup C for between-group comparisons for the same parameter; ‡$P < 0.05$ vs. macroalbuminuria and §$P < 0.05$ vs. microalbuminuria for within-group comparisons for the same parameter.

RESULTS — Of the total diabetic population, 232 patients had normal albuminuria [Lp(a) median (25th–75th percentiles) 10.0 mg/dl (5–26)], 208 patients had microalbuminuria [Lp(a) 10.0 mg/dl (5–26)], and 55 had macroalbuminuria [Lp(a) 22.5 mg/dl (8–50)] (P = 0.001 vs. normo- and microalbuminuria subgroups). Table 2 shows the clinical parameters of the patients as a function of creatinine clearance (three subgroups: A, normal clearance; B, hyperfiltration; and C, renal insufficiency) and albuminuria. Regarding lipid levels, macroalbuminuric patients in creatinine clearance subgroups A and C tended to have higher triglycerides than patients with normo- or microalbuminuria. Macroalbuminuric patients in subgroup C also had higher total and LDL cholesterol levels. Triglycerides tended to be higher and HDL cholesterol tended to be lower in all albuminuria subgroups of the renal insufficiency patients.

Lp(a) concentrations did not differ between normo- and microalbuminuric patients with normal clearance or hyperfiltration (Table 2, subgroup A and B). Lp(a) concentrations were significantly higher in macroalbuminuric patients from both creatinine clearance subgroups (P = 0.018) independent of sex and diabetes type. Patients with renal insufficiency (Table 2, subgroup C) had raised Lp(a) levels regardless of the presence or absence of albuminuria. Thus, microalbuminuric patients in the normal clearance subgroup had significantly lower Lp(a) concentrations than the renal insufficiency patients (P = 0.006), again independent of sex and diabetes type. The data are shown in Fig. 1, where median Lp(a) levels are given as a function of albuminuria and creatinine clearance.

Lp(a) and creatinine (r = 0.11, P = 0.02) and Lp(a) and clearance (r = 0–0.14, P = 0.002) were significantly but weakly associated independent of diabetes and albuminuria.

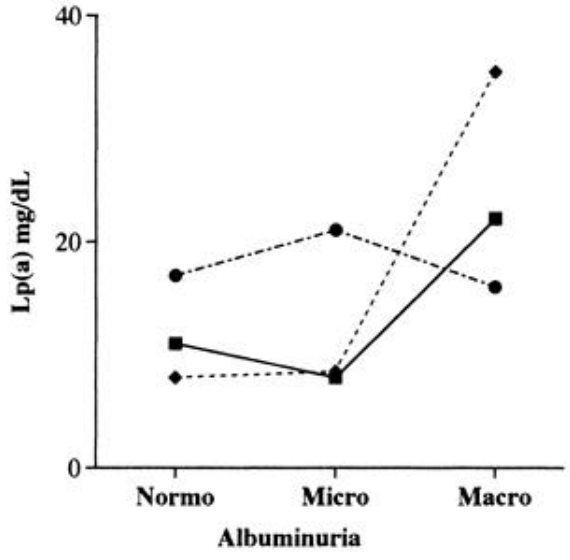

Figure 1—*Median plasma concentrations of Lp(a) as a function of albuminuria in diabetic patients categorized according to creatinine clearance.* ■, *Group A clearance >70 < 120 (women) or <150 ml/min (men);* ◆, *group B clearance >120 (women) or >150 ml/min (men);* ●, *group C clearance <70 ml/min. Normo, normoalbuminuria; Micro, microalbuminuria; Macro, macroalbuminuria.*

CONCLUSIONS — In the combined group of diabetic patients, macroalbuminuria was uniformly associated with significantly raised plasma concentrations of Lp(a) regardless of the marker used to identify kidney dysfunction. In contrast, for patients with microalbuminuria, raised Lp(a) levels were observed only when creatinine clearance rates or plasma creatinine levels indicated pathological kidney function. Note that statistical analyses by two-factor general linear modeling gave no indication that diabetes type or sex influenced the results. The conclusions thus apply to type 1 and type 2 diabetic patients. If raised Lp(a) in macroalbuminuria results from increased hepatic protein synthesis (13,22), altered kidney function revealed by creatinine clearance or creatinine levels then appears to be a major determinant of raised Lp(a) levels in microalbuminuric and normoalbuminuric patients.

Studies in nondiabetic patients have firmly established renal disease as a cause of increased plasma Lp(a) levels (13). Increased levels of Lp(a) are an independent risk factor for vascular disease in the general population (3,4,6) and in diabetic patients (7–10), although researchers do not complete agree on this point (18,23,24). In view of these considerations, defining the relationship between renal complications and Lp(a) in diabetic patients is important. Studies that have considered renal disease, usually expressed as albuminuria, and Lp(a) have resulted in conflicting conclusions. Some reports have stated that renal disease does not exert a particular effect (25–31), whereas other studies have reported increased plasma levels of Lp(a) in patients with renal disease who have either type 2 (32–34) or type 1 (16,32,35–37) diabetes. Our results suggest that a confounding factor that is evident within the microalbuminuric subgroup is kidney failure, which was speculated by Jenkins et al. (16) in an earlier study. Kidney failure may arise from a reduced capacity to excrete Lp(a) because apolipoprotein(a) [apo(a)] degradation products are present in urine (14,15). However, a recent study by Clodi et al. (38) found that urinary apo(a) excretion was increased in type 1 diabetic patients, especially those with incipient nephropathy.

Our study identifies kidney failure as a primary determinant of raised Lp(a) in type 1 and type 2 diabetic patients with microalbuminuria. Kidney failure may also modulate Lp(a) concentrations in normoalbuminuric diabetic patients. Our results agree with the hypothesis that renal dysfunction is a primary determinant of higher Lp(a) levels in diabetic patients. This has important implications for the increased susceptibility to vascular disease associated with Lp(a) in diabetic patients.

Acknowledgments — The study was supported by a grant from the Swiss National Research Foundation.

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