Increased Lipoprotein (a) and Its Relationships with Other Parameters of Lipoprotein Metabolism in Chronic Renal Failure Treated by Hemodialysis

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SUMMARY

Background. Studies have shown that patients with chronic renal failure have a high frequency of cardiocascular atheromatous disease.

Methods. We examined serum lipoprotein (a) [Lp(a)], very-low density lipoprotein cholesterol (VLDL-C), low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C), apolipoprotein A1 (apo A1) and B (apo B), triglyceride (TG) and total cholesterol (TC) levels as possible risk factors for atherosclerosis in 45 patients with chronic renal failure (CRF) treated by hemodialysis (HD) and in 15 CRF patients who were not on HD. A control group of 20 healthy subjects was also studied.

Results. The proportion of smokers and body mass indexes were similar between the groups. In both patient groups, higher TG, TC and Lp(a) and lower apo A1 and HDL-C levels in serum were found than in those of controls. Serum apo B and LDL-C were similar in the patients treated by HD and the controls. Serum VLDL-C and LDL-C were similar in the CRF patients who were not on HD and the controls. The highest ratios of apo B/apo A1 and LDL-C/HDL-C were found in HD patients. The highest ratio of TC/HDL-C was found in the other patient group.

We found significant correlations between Lp(a) and other parameters of lipoprotein metabolism in CRF patients, both those who were and those who were not on HD.

Conclusions. Our results indicate that CRF patients who both were and were not on HD show atherogenic changes in the lipoprotein pattern, and that the increase in Lp(a) during the CRF phase is basically related to the loss of renal function and may also depend on the resultant alterations which are produced in other lipoprotein variables. (Jpn Heart J 1997; 38: 83-89)

Key words: Apolipoproteins, Lipoprotein (a), Chronic renal failure and hemodialysis

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ATHEROSCLEROSIS is a multifactorial disease that encompasses both genetic and environmental factors. Numerous epidemiological studies have shown that lipids/lipoproteins have a major role in the evolution of atherosclerosis.¹⁾ Subjects with chronic renal failure (CRF) have a greatly increased risk of coronary heart disease and dislipidemia, and cerebrovascular and cardiovascular diseases are the major causes of death in maintenance hemodialysed patients with CRF.^{2,3)} Lipid abnormalities have been identified as significant risk factors for the development of premature atherosclerosis in such patients. These abnormalities include significant elevations of serum triglycerides, triglyceride-rich lipoproteins (VLDL, IDL, LDL remnant particles) and Lp(a) and decrease in HDL, accompanied by changes in apolipoprotein content.²⁾ However, little is known about the mechanisms involved in the lipid and lipoprotein abnormalities in patients with CRF treated by HD.

Lp(a) is a known risk factor for coronary heart disease in the general population.⁴⁻⁷⁾ Relatively few studies have examined the relationship of CRF and Lp(a) concentrations and investigated the relationship between Lp(a) and other lipid and lipoprotein concentrations in patients with CRF treated by HD.^{3,8,9)} The purpose of this study was to determine Lp(a) levels and to investigate the association of Lp(a) and atherosclerotic risk factors in patients with CRF, who were and were not on HD.

METHODS

Subjects: The study was conducted in accordance with the ethical standards of the Research Hospital of Atatürk University, in Erzurum City, Turkey. We prospectively studied 45 subjects (25 men and 20 women) with CRF treated by HD, 15 patients with CRF who were not on HD (9 men, and 6 women) and 20 normal subjects as the reference group (11 men and 9 women). The proportion of smokers was similar among the groups. The patients were not receiving antilipemic drugs. Following a 12-hour fasting period, sample collection was carried out between 08 : 00–10 : 00 h both in control subjects and patients. Blood samples were withdrawn in hemodialysis patients at the start of the first dialysis session of the week. Blood was allowed to clot, and the serum was separated by centrifugation at 800 g for 15 min. Serum aliquots were stored at – 20°C until determination of serum lipids and lipoproteins.

Renal function tests and lipid profiles: Serum BUN and creatinine levels were measured with the UV-kinetic and Jaffe's methods, respectively.^{10,11)} TC and TG were determined enzymatically (Boehringer GmbH Mannheim, Mannheim, Germany) on a Mitsubishi Super Z 818 analyzer, (Mitsubishi, Tokyo, Japan). HDL-C was quantified by the same enzymatic method after

precipitation of VLDL-C and LDL-C with phosphotungstic acid. LDL-C and VLDL-C were calculated according to the Friedewald equation:¹²⁾ $\text{LDL-C} = \text{TC} - (\text{HDL-C} + \text{VLDL-C})$. This widely used formula is based on the assumption that the mass of VLDL-C present in serum is equivalent to one fifth of the mass of triglycerides in serum VLDL.¹³⁾

Serum Lp(a) concentrations were measured with a commercial ELISA (Boehringer Mannheim GmbH, Mannheim, Germany). Serum apo A-1 and apo B concentrations were measured by immunoturbidimetric analysis (Isolab Inc., Ohio, USA, Cat No 8253 and 8220, respectively).

Statistical analysis: All results are expressed as mean $\pm$ SD. Two-sample *t*-test was used to compare results for patients and controls. In order to analyse the relationships between parameters, correlation analysis was used. Day-to-day coefficients of variation (CVs) were 3% for assay of TC, 5.1% for HDL-C, 4.8% for TG, 5.6% for apo A-1, 4.2% for apo B, and 5.3% for Lp(a).

RESULTS

All patients had increased serum BUN and creatinine, as shown in Table I. Compared with controls, patients with CRF treated by HD had significantly higher amounts of TG, TC, VLDL-C, Lp (a), and lower apo A-1 and HDL-C in serum (Table II). Serum apo B and LDL-C were similar in the patients who were on HD and the controls. The ratios of apo B/apo A-1, LDL-C/HDL-C, and TC/HDL-C were higher in these patients than in the controls ($p < 0.001$). Patients who were not on HD had higher serum TG, TC, Lp (a), and lower apo A-1, apo B and HDL-C levels than the controls. Also, they had higher LDL-C/HDL-C and TC/HDL-C ratios than the controls. However, there was no difference in the apo B/apo A-1 ratio between these patients and the controls.

The relationships between serum Lp(a) and other lipid parameters involved

Table I. Baseline Clinical and Laboratory Profiles of the Study Population

	Controls	Patients		Statistical significance*
		CRF not on HD	CRF on HD	
Number of subjects	20	15	45	
Sex, M/F	11/9	9/6	25/20	
Age, years	44.9 $\pm$ 6.5	45 $\pm$ 7.1	42.2 $\pm$ 12	NS
BMI (kg/m ²)	24.7 $\pm$ 2.4	23.5 $\pm$ 2.84	25.5 $\pm$ 5	NS
MAP (mmHg)	105 $\pm$ 21	109 $\pm$ 22	108 $\pm$ 24	NS
BUN (mg/dl)	17.8 $\pm$ 5.6	64.6 $\pm$ 15.3	80.4 $\pm$ 29.4	< 0.001
Creatinine (mg/dl)	1.03 $\pm$ 0.18	7.14 $\pm$ 1.73	8.25 $\pm$ 3.9	< 0.001

*Comparison between control group and patients who were and were not on hemodialysis, NS = not significant; MAP = mean arterial pressure; HD = hemodialysis.

Table II. Serum Lipid, Apolipoprotein, Lipoprotein Cholesterol and Lipoprotein
(a) Levels in the Controls and Patients

Parameters	Controls	Patients		Statistical significance		
		CRF not on HD	CRF on HD	1	2	3
Lipids, mg/dl						
TG	115 ± 21.8	137 ± 32.6	163 ± 44	<0.05	<0.001	<0.05
TC	145 ± 31.5	186 ± 44.2	188 ± 85	<0.01	<0.05	NS
Apolipoprotein, mg/dl						
apo A1	116 ± 10.8	100 ± 21	87 ± 19	<0.01	<0.001	<0.05
apo B	98.9 ± 13.7	87.5 ± 15.7	114 ± 33	<0.05	NS	<0.01
Lipoprotein cholesterol, mg/dl						
VLDL	24.9 ± 3.7	26.4 ± 8.2	32.3 ± 9	NS	<0.01	<0.05
LDL	96.5 ± 22.3	88 ± 23.4	123 ± 87	NS	NS	NS
HDL	41.8 ± 8.2	31.9 ± 5.6	33.2 ± 11	<0.001	<0.01	NS
Lipoprotein (a), mg/dl	19.4 ± 4.9	26.8 ± 5.2	29.7 ± 19.5	<0.01	<0.01	NS
apo B/apo A1	0.86 ± 0.13	0.92 ± 0.28	1.33 ± 0.59	NS	<0.001	NS
LDL-C/HDL-C	2.31 ± 0.30	3.09 ± 0.97	3.69 ± 0.91	<0.01	<0.001	<0.05
TC/HDL-C	3.53 ± 0.78	6.03 ± 1.87	5.68 ± 1.46	<0.001	<0.001	NS

1: Comparison between control group and patient group which was not on HD; 2: Comparison between control group and patient group on HD; 3: Comparison among the two patient groups which was or was not on HD.

Table III. Correlation Coefficients (r) between Lp(a) and Other Parameters in Controls and Patients

Parameters	Control Lp (a)	Patient Lp (a)	
		CRF not on HD	CRF on HD
TG	-0.18 ^{NS}	0.73**	0.52**
TC	0.33 ^{NS}	0.76**	0.87**
HDL-C	-0.08 ^{NS}	-0.60**	-0.55**
LDL-C	-0.28 ^{NS}	0.75**	0.87**
VLDL-C	0.19 ^{NS}	0.47*	0.52**
apo A1	0.12 ^{NS}	-0.52**	-0.40*
apo B	0.09 ^{NS}	0.54*	0.59**

^{NS} = not significant; * = significant at $p < 0.05$ and ** = $p < 0.001$

in lipids of patients and controls were also studied (Table III). In patient groups, serum Lp(a) levels were negatively correlated with serum HDL-C and apo A-1 levels, and positively correlated with TG, TC, LDL-C, VLDL-C, and apo B. In the controls, there were no significant relationships between serum Lp(a) and other lipid, lipoprotein, and apolipoprotein levels.

DISCUSSION

Our study conclusively demonstrates lipoprotein and lipid abnormalities associated with CRF in patients both on and off HD. The concentrations of TG and TC in serum were higher in both patient groups than those in the controls,

and apo A-1 and HDL-C levels were lower in patients. These findings confirm previous reports in the literature. Roh¹²⁾ reported that atherogenesis accelerates in HD patients. Cuxart et al.¹⁴⁾ detected hypertriglyceridemia in 34% of HD patients. In the present study, the prevalence of hypertriglyceridemia (greater than 200 mg/dl) was 20% and 16% in patients who were not on HD and were on HD, respectively. Schumaker et al.¹⁵⁾ reported increased concentrations of serum TG and apo B in patients with CRF. Haaber et al.¹⁶⁾ found that the plasma concentrations of lipoproteins showed an atherogenic pattern in CRF patients with increased levels of VLDL-C and TG, but a decreased level of HDL-C. According to the study of Kaysen,¹⁷⁾ plasma TG is increased in the majority of patients with advanced renal failure but cholesterol is not. He also reported that the HDL-associated apolipoproteins apo A-1 and A-II are decreased, while apo B is increased in these patients. Segerra et al.⁹⁾ reported that patients with CRF had lower serum levels of HDL-C and apo A-1, and higher TG and VLDL-C than did the control group. In the present study, apo B and LDL-C were similar in the patients treated by HD and controls.

Lipoprotein catabolic rate is reduced in patients with CRF, but the cause of hyperlipidemia is multifactorial; e.g. reduced lipoprotein lipase activity (LPL), increased concentration of apo C-III (a specific inhibitor of LPL) in plasma, secondary hyperparathyroidism, and insulin resistance.¹⁷⁻¹⁹⁾ Hörkkö et al.²⁰⁾ reported that the clearance of LDL in patients with advanced uremia on conservative management is frequently decreased. These alterations in the metabolism of the most atherogenic particle in plasma or serum may contribute to the accelerated atherosclerosis in uremic patients. While atherosclerotic disease and thrombosis are the leading causes of death in dialysis patients, it is not certain that the specific lipid disorders of CRF are responsible for this morbidity, nor is it recommended at this time that qualitative abnormalities be treated pharmacologically in the absence of increased lipid levels.^{17,20)} When hyperlipidemia is present, plasma newly-synthesized cholesteryl ester transfer rates are raised and may contribute to elevated levels of the proatherogenic apo B-containing lipoproteins in patients with renal failure.²¹⁾

Querfeld et al.²²⁾ found that the distribution of Lp(a) levels in normal subjects was skewed to the left with 97% having levels less than 30 mg/dl. All normal subjects in this study had serum Lp(a) levels below 30 mg/dl. Cuxart et al.¹⁴⁾ showed a higher prevalence of positive Lp(a) (greater than 30 mg/dl) in the HD group. The number of high-Lp(a) level patients on HD was 14 (31%) in this study.

Cressman et al.²³⁾ found that patients on HD have four-fold higher Lp(a) levels in serum than those of controls. They suggested that dialysis has a negative effect on lipid metabolism.

In this study, the ratios of apo B/apo A-1, LDL-C/HDL-C, and TC/HDL-C were higher in patients with CRF on HD as compared with controls. Also, patients who were not on HD had higher ratios of LDL-C/HDL-C and TC/HDL-C. However, the ratio of apo B/apo A-1 in these patients was not different than that of the controls. We could not find similar reports in terms of these parameters in the literature.

There were significant correlations between Lp(a) and other parameters of lipid and lipoprotein metabolism in patients with CRF who were or not on HD in the present study. However, conflicting results about these relationships have been reported in previous studies.^{8,9,24-26} Segerra et al.⁹ reported that there was no relationship between Lp(a) and other parameters of lipoprotein metabolism, for example, apolipoproteins A1, B, C-II, and C-III, HDL-C and LDL-C in patients with CRF before renal transplantation. Thus, they concluded that the increase in Lp(a) during the CRF phase is basically related to the loss of renal function and does not depend on the resultant alterations which are produced in other lipoprotein variables. Takegoshi et al.²⁵ found a statistically significant correlation of Lp(a) with serum lipoprotein and apolipoprotein levels in patients with CRF treated by continuous ambulatory peritoneal dialysis (CAPD). Hoffner et al.⁸ reported that Lp(a) levels were not correlated with the level of creatinine in subjects with CRF. Thus, the elevation of Lp(a) levels in renal failure must occur early in renal failure, or alternatively, elevated Lp(a) levels may promote progression to CRF. However, the cause of the controversial results may stem from the different study groups in our study and the above studies. For example, Kandoussi et al.²⁶ reported that plasma Lp(a) level was high in predialysis or HD, but not in CAPD, as compared to healthy controls, though Takegoshi et al.²⁵ found high Lp(a) levels in CAPD patients. Hörkkö et al.²⁰ showed that the Lp(a) levels were related to the plasma TC ($r = 0.69$), VLDL-C ($r = 0.86$), and LDL-C ($r = 0.66$) in patients with CRF. These results are consistent with our results.

Our results indicate that increased serum Lp(a) together with other lipoprotein abnormalities in patients with CRF who were and were not on HD imply an increased cardiovascular risk, and that there were significant relationships between Lp(a) and other parameters of lipoprotein metabolism such as TG, TC, HDL-C, LDL-C, VLDL-C, apo A-1 and apo B.

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