Arterial Hypertension Is Associated with Increased Serum Lipoprotein(a) Levels in End-Stage Renal Disease Patients

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In addition to disorders in lipoprotein metabolism, several other factors are involved in the development of atherosclerotic changes in end-stage renal disease (ESRD) patients. One of these is arterial hypertension.

We evaluated serum lipids—total cholesterol (TC), triglycerides (TG), apolipoproteins (A_I, A_{II}, B, E), lipoprotein(a) [Lp(a)]—in 109 ESRD patients on dialysis [46 on hemodialysis (HD); 63 on continuous ambulatory peritoneal dialysis (CAPD)] and in 45 hyperlipidemic patients without renal failure (HL group). Dialysis patients were divided in two groups. Group A included 42 hypertensive patients (mean age: 62.3 ± 15.5 years) whose blood pressure (BP) was satisfactorily controlled with anti-hypertensive medications. Group B included 67 non hypertensive patients (mean age: 66.6 ± 11.9 years).

Levels of Lp(a) were significantly higher in both the HD ($p = 0.001$*) and the CAPD (*$p < 0.05$*) patients as compared with the HL group. When the HD and CAPD groups were divided into hypertensive and non hypertensive patients, Lp(a) levels were significantly higher in the hypertensive patients; this difference was not observed among non renal failure patients.*

These results indicate that arterial hypertension is associated with elevated Lp(a) serum levels in ESRD patients undergoing either HD or CAPD.

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Key words

Continuous ambulatory peritoneal dialysis, arterial hypertension, lipids, lipoprotein(a)

Introduction

Cardiovascular complications account for 50% of deaths in patients on renal replacement therapy (RRT). Half of these deaths are due to atherosclerotic arterial occlusive episodes in the form of myocardial or cerebral infarction [1,2]. The high incidence of cardiovascular complications even in the first year on RRT indicates that atherogenic lesions either start or are already present early in the course of chronic renal failure (CRF).

Indeed, end-stage renal disease (ESRD) patients undergoing hemodialysis (HD) or continuous ambulatory peritoneal dialysis (CAPD) have multiple atherogenic risk factors—age, diabetes mellitus, hypertension, smoking, and dyslipidemia—that may be present in the pre-dialysis period, as well as risk factors associated with uremia and the renal replacement modality. Among all factors that undoubtedly contribute to the development of atherosclerotic lesions, lipid disorders are considered to be the main cause [3].

Renal failure is characterized by alterations in the concentrations and components of various lipoproteins, especially those containing triglycerides (TG). Also, increased serum levels of lipoprotein(a) [Lp(a)] are found either pre-dialysis or after initiation of RRT. Furthermore, Lp(a) levels at or above 30 mg/dL have been found to be an independent risk factor for the early development of coronary and cerebrovascular atherosclerotic disease [4–6].

Recently, an association between Lp(a) and coronary artery disease and target-organ damage in hypertensive patients has been described [7,8]. Atherosclerosis in ESRD patients might therefore be accelerated by an interaction between hypertension and abnormal lipid metabolism, as both factors are consistently found both in end-stage renal disease and in dialyzed patients.

The present study was designed to look at the relationship of arterial hypertension to uremic dyslipoproteinemia and Lp(a) levels in ESRD patients undergoing hemodialysis or continuous ambulatory peritoneal dialysis.

Material and methods

We studied 109 ESRD patients undergoing chronic RRT by either HD (thrice weekly 4-hour sessions) or CAPD (four 2-L exchanges daily). The 46 HD patients had a mean age of 60 ± 12 years, and a mean duration on HD of 50 ± 40 months. The 63 CAPD patients had a mean age of 65 ± 13 years, and a mean duration on dialysis of 25 ± 19 months. A third group—45 hyperlipidemic (HL) patients without evidence of renal disease, but with serum levels of total cholesterol (TC) ≥200 mg/dL and triglycerides (TG) ≥170 mg/dL—acted as a control.

Hypertension was defined as systolic blood pressure ≥160 mmHg or diastolic blood pressure ≥95 mmHg, or both. The presence of long-standing systolic and diastolic hyper-

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tension was confirmed by the patients' monthly records. In the HL controls, BP determinations were obtained during the 2 months before the initiation of the study. Pre-dialysis measurements were used in the hemodialysis patients.

Hypertension was present in 21 of 46 HD patients (45.6%), in 21 of 63 CAPD patients (33.3%), and in 20 of 45 non renal failure HL controls (44.4%).

The dialyzed patients were divided in two groups according to the presence of arterial hypertension. Group A consisted of 42 hypertensive patients: mean age 62.3 ± 15.5 years (range: 24 – 85 years); 25 men, 17 women; body weight, 69.9 ± 12.6 kg (range: 41 – 102 kg); systolic and diastolic arterial pressures, 156 ± 17 mmHg and 87 ± 10 mmHg respectively. Antihypertensive medications included either single-agent or combined therapy with calcium channel blockers and angiotensin converting enzyme (ACE) inhibitors. Group B consisted of 67 non hypertensive patients: age 66.6 ± 12.0 years (range: 29 – 87 years); 39 males, 28 females; body weight, 67.7 ± 11.6 kg (range: 48 – 92 kg); mean systolic and diastolic arterial pressures, 124 ± 20 mmHg and 73 ± 10 mmHg respectively. Table I summarizes the demographic characteristics of the dialyzed patients.

The following lipids were measured: total cholesterol [TC (mg/dL)]; high-density lipoprotein cholesterol [HDLc (mg/dL)]; low-density lipoprotein cholesterol [LDLc (mg/dL)]; triglycerides [TG (mg/dL)]; apolipoproteins A_I [apoA_I (g/L)], A_{II} [apoA_{II} (mg/dL)], B [apoB (g/L)], E [apoE (mg/dL)]; and lipoprotein(a) [Lp(a) (mg/dL)]. Serum cholesterol and triglyceride levels were determined by automated enzymatic methods using an AU 560 analyzer (Olympus, Hamburg, Germany). Levels of HDLc were enzymatically determined in the supernatant after precipitation of other lipoproteins with phosphotungstic acid. Levels of LDLc were calculated using the Friedewald formula [9]. Apolipoproteins A_I, A_{II}, B, and E, and Lp(a) were measured using a nephelometer [Analyzer II (BNII): Behring, Marburg, Germany]. For the nephelometric measurement of Lp(a), polystyrene microbodies coated with antibodies to human Lp(a) were agglutinated when mixed with serum containing Lp(a). The intra-assay and inter-assay coefficients of variation were less than 3.5%.

TABLE I Characteristics of chronic dialysis patients.

	Group A (hypertensive)	*Group B (non hypertensive)*	*p Value*
Patients *(n)*	42	67	
Age (years)	62.3±15.5	66.6±12.0	NS
Sex (M/F)	25/17	39/28	
Body weight (kg)	69.9±12.6	67.7±11.6	NS
Arterial hypertension			
Systolic BP (mmHg)	156±17	124±20	0.0001
Diastolic BP (mmHg)	87±10	73±10	0.0001

NS = nonsignificant; BP = blood pressure.

Statistical analysis

The Student t-test was used to compare normally distributed variables between the various groups. Comparisons of Lp(a) were performed using the Mann–Whitney U-test (nonparametric statistics) because of the abnormal distribution. Results were considered statistically significant at $p < 0.05$.

Results

The incidence of arterial hypertension among HD patients tended to be higher than among CAPD patients; it was present in 45.6% of the HD patients as compared with 33.3% of CAPD patients. The mean patient age and body weight were not significantly different between the groups of hypertensive and normotensive dialyzed patients (Table I).

Regarding lipid profile, several differences were observed between HD and CAPD patients, with the latter group showing a more lipidemic profile (Table II). Serum TC and TG concentrations were significantly higher in the CAPD patients than in the HD patients (270 ± 71 mg/dL and 294 ± 188 mg/dL vs 198 ± 39 mg/dL and 161 ± 73 mg/dL respectively; $p < 0.001$ in both cases). The HD patients showed statistically significantly higher levels of HDLc than did CAPD patients (36 ± 7.8 mg/dL vs 32.3 ± 6.4 mg/dL, $p < 0.01$); but, the opposite results were observed in LDLc levels, which were lower in HD patients than in CAPD patients (131 ± 36 mg/dL vs 190 ± 69 mg/dL, $p < 0.001$). Statistically significantly higher serum levels of Lp(a) were found in HD patients as compared to CAPD patients (43.3 ± 46.9 mg/dL vs 28.1 ± 30.5 mg/dL, $p < 0.05$).

Lipid disturbances in dialyzed CAPD patients resembled the lipid profiles of HL controls; however, CAPD patients showed statistically significantly higher values for TG, LDLc, apoE, and Lp(a) values, and lower values for TC, HDLc, and apoA_I (Table II). Comparing apolipoproteins between dialyzed patients and the HL control group, HD and CAPD patients both showed statistically significantly lower apoA_I levels, but their apoE and Lp(a) levels were significantly higher (Table II).

Levels of Lp(a) were also higher in hypertensive HD patients as compared with non hypertensive HD patients (55.6 ± 47.1 mg/dL vs 32.0 ± 45.6 mg/dL, $p = 0.018$), and a nonsignificant difference was observed for the CAPD patients (Table III). Increased Lp(a) levels, at or above 30 mg/dL, were found in half of the hypertensive patients on HD and in 24% of the normotensive patients on hemodialysis. Comparing Lp(a) levels between hypertensive HD and CAPD patients, no significant difference was observed ($p = 0.118$). On the other hand, the lowest values of Lp(a) (<10 mg/dL) were found in 4% of hypertensive patients and 20% of normotensive patients undergoing HD; the corresponding percentages in CAPD patients were 19% and 31%, respectively.

Regardless of the renal replacement modality, the lipid profile of hypertensive patients was similar to that of normotensive patients. Only Lp(a) levels were statistically significantly higher in hypertensive HD patients (55.6 ± 47.1 mg/dL

TABLE II Lipid profiles of hemodialysis (HD) and continuous ambulatory peritoneal dialysis (CAPD) patients, and hyperlipidemic (HL) controls.

Parameter	*HD (n=46)*	*CAPD (n=63)*	*HL (n=45)*	*p Values HD vs HL*	*CAPD vs HL*	*HD vs CAPD*
TC (mg/dL)	198±39	270±71	282±39	<0.001	<0.001	<0.001
TG (mg/dL)	161±73	294±188	204±54	<0.001	<0.001	<0.001
HDLc (mg/dL)	36.0±7.8	32.3±6.4	34.2±6.4	<0.001	<0.001	<0.01
LDLc (mg/dL)	131±36	190±69	163±34	<0.001	<0.001	<0.001
$apoA_I$ (g/L)	1.40±0.25	1.47±0.32	1.67±0.40	<0.001	<0.001	NS
$apoA_{II}$ (mg/dL)	33.9±7.4	33.9±7.3	34.8±8.0	NS	NS	NS
apoB (g/L)	1.30±0.35	1.57±0.53	1.60±0.40	<0.001	NS	<0.01
apoE (mg/dL)	4.53±1.7	7.83±4.0	3.60±1.1	<0.05	<0.001	<0.001
Lp(a) (mg/dL)	43.3±46.9	28.1±30.5	19.4±19.6	<0.001	<0.05	<0.05

NS = nonsignificant; TC = total cholesterol; TG = triglycerides; HDLc = high-density lipoprotein cholesterol; LDLc = low-density lipoprotein cholesterol; $apoA_I$ = apolipoprotein A_I; $apoA_{II}$ = apolipoprotein A_{II}; apoB = apolipoprotein B; apoE = apolipoprotein E; Lp(a) = lipoprotein(a).

TABLE III Lipid profiles in hypertensive and non hypertensive dialysis patients by renal replacement therapy.

	Hemodialysis		*Continuous ambulatory peritoneal dialysis*		*p Values*	
Parameter	*Hypertensive (n=21)*	*Non hypertensive (n=25)*	*Hypertensive (n=21)*	*Non hypertensive (n=42)*	*HD*	*CAPD*
TC (mg/dL)	197±41	198±39	271±69	270±73	NS	NS
TG (mg/dL)	173±84	153±67	266±185	311±199	NS	NS
$ApoA_I$ (g/L)	1.34±0.21	1.45±0.29	1.54±0.32	1.44±0.32	NS	NS
ApoB (g/L)	1.29±0.36	1.31±0.37	1.56±0.41	1.59±0.58	NS	0.04
ApoE (mg/dL)	4.13±1.3	4.85±2.0	7.25±3.5	8.1±4.3	NS	NS
Lp(a) (mg/dL)	55.6±47.1	32.0±45.6	30.4±33.3	26.6±28.9	0.018	NS

HD = hemodialysis; CAPD =continuous ambulatory peritoneal dialysis; NS = nonsignificant; TC = total cholesterol; TG = triglycerides; $apoA_I$ = apolipoprotein A_I; apoB = apolipoprotein B; apoE = apolipoprotein E; Lp(a) = lipoprotein(a).

vs 32.0 ± 45.6 mg/dL, $p = 0.018$) and in the combined hypertensive HD and CAPD patients (44.2 ± 42.4 mg/dL vs 28.4 ± 35.6 mg/dL, $p < 0.035$; Table IV). This difference was not found among hypertensive and non hypertensive non renal failure patients (HL group; Table V).

Discussion

The present study was designed to evaluate the relationship between arterial hypertension and lipid profiles in HD and CAPD patients.

In both HD and CAPD patients, important differences in lipoprotein concentrations and profiles of apolipoproteins were observed. The CAPD patients had a more atherogenic profile, consisting mainly of lower HDLc concentrations and higher levels of TC, TG, LDLc, apoB, and apoE. The group of CAPD patients also showed lipid disturbances similar to those seen in hyperlipidemic non renal failure controls, although the degree of the disturbance was sometimes higher and sometimes lower (Table II).

Regarding Lp(a), HD patients showed significantly higher serum levels as compared with levels in CAPD patients; but both groups of dialyzed patients had higher levels than were seen in the HL controls. Levels of Lp(a) were significantly higher in hypertensive HD patients as compared with normo-

TABLE IV Lipid profiles in hypertensive and non hypertensive dialysis patients.

Parameter	*Hypertensive (n=42)*	*Non hypertensive (n=67)*	*p Value*
TC (mg/dL)	233±67	242±71	NS
TG (mg/dL)	219±140	249±178	NS
$ApoA_I$ (g/L)	1.44±0.28	1.43±0.30	NS
ApoB (g/L)	1.43±0.39	1.48±0.52	NS
ApoE (mg/dL)	5.73±3.1	6.70±3.8	NS
Lp(a) (mg/dL)	44.2±42.4	28.4±35.6	0.035

NS = nonsignificant; TC = total cholesterol; TG = triglycerides; $apoA_I$ = apolipoprotein A_I; apoB = apolipoprotein B; apoE = apolipoprotein E; Lp(a) = lipoprotein(a).

TABLE V Lipid profiles in hypertensive and non hypertensive non renal failure patients.

Parameter	*Hypertensive (n=20)*	*Non hypertensive (n=25)*	*p Value*
TC (mg/dL)	289±46	251±82	NS
TG (mg/dL)	228±73	269±83	NS
$ApoA_I$ (g/L)	1.28±0.36	1.43±0.43	NS
ApoB (g/L)	1.75±0.33	1.72±0.51	NS
ApoE (mg/dL)	3.64±1.0	3.62±1.1	NS
Lp(a) (mg/dL)	18.4±24.3	19.8±16.0	NS

NS = nonsignificant; TC = total cholesterol; TG = triglycerides; $apoA_I$ = apolipoprotein A_I; apoB = apolipoprotein B; apoE = apolipoprotein E; Lp(a) = lipoprotein(a).

tensive HD patients; a similar trend was observed in CAPD patients, although the difference was not statistically significant. Half of the hemodialysis hypertensive patients showed Lp(a) levels ≥30 mg/dL, but only one quarter of the normotensive patients on hemodialysis had similarly increased serum Lp(a) levels. The lowest values of Lp(a) in dialysis patients (<10 mg/dL) were seen only in the normotensive patients.

Regardless of the renal replacement modality, increased Lp(a) level was the only statistically significant finding observed when lipid profiles of hypertensive patients were compared with those of normotensive patients. Such a statistically significant difference was not found between hypertensive and non hypertensive patients in the HL group. Moreover, the observed difference in Lp(a) levels between each dialysis group and the HL controls was not present between non hypertensive dialyzed patients and the control group.

It therefore seems that, among all abnormalities of apolipoprotein profile and lipoprotein composition seen in ESRD patients, the presence of arterial hypertension is associated with increased Lp(a) concentration. Because hypertension and abnormal lipid metabolism are consistently found in dialyzed ESRD patients, such an interaction might accelerate atherosclerosis and its important consequences.

Indeed, an association between Lp(a) and target-organ damage in hypertensive patients has recently been described by Sechi *et al.* [7], who compared patients with untreated hypertension to healthy controls. Levels of Lp(a) were related to target-organ damage independent of blood pressure level.

Conclusion

Further studies are required to elicit cause and effect in the relationship between arterial hypertension and Lp(a) and other lipoprotein disorders in dialyzed ESRD patients. Lipoprotein metabolism is altered in most patients with renal insufficiency, and elevated Lp(a) concentrations have been consistently described across nearly all renal diseases and their treatments [10].

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