Increased Risk of Premature Atherosclerosis at Initiation of Chronic Hemodialysis: A Possible Link with Hypertriglyceridemia?

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Background. *Patients with end-stage renal failure have high rates of cardiovascular morbidity and mortality. It is not clear yet whether it is the hemodialysis procedure or the uremia itself that is the major determinant of this increased risk. We set out to determine whether atherosclerosis was more accelerated in patients with uremia at the initiation of chronic hemodialysis therapy compared with that in a control group of those without uremia who had a similar cardiovascular risk profile. Also, risk factors related to premature atherosclerosis were investigated.*

Patients and Methods. *High-resolution B-mode ultrasonography was used to determine the intima-media thickness (IMT) of the carotid arteries in 30 patients with uremia just before the initiation of chronic hemodialysis therapy and in 26 controls without uremia.*

Results. *The 2 groups were similar in age, sex, presence of hypertension, presence of dyslipidemia, and smoking habits. Serum levels of total cholesterol, triglycerides, total HDL, fibrinogen, inorganic phosphorus, and total calcium were evaluated. The IMT values of the patients with uremia were significantly higher than were those of the control group. The patients with uremia had higher levels of serum fibrinogen, inorganic phosphorus, and triglycerides. The IMT values significantly correlated with age, male sex, and triglyceride level in the patients with uremia. In the control group, only age showed a significant correlation with IMT values.*

Conclusion. *These results indicate that patients with uremia at the initiation of chronic hemodialysis therapy had higher carotid IMT values than did a control group of those without uremia who have a similar cardiovascular risk profile. Thus, uremic status per se may be responsible for the increased risk of premature atherosclerosis. Identification of a positive correlation between carotid IMT and triglyceride levels may indicate that therapeutic interventions are necessary to reduce this risk.*

Because patients with end-stage renal failure have high rates of cardiovascular morbidity and mortality, early detection and prevention of atherosclerosis is important.[1,2] It is not clear yet whether it is the hemodialysis (HD) procedure or uremia itself that is the major determinant of this increased risk. In early studies it was found that prolonged HD accelerated atherosclerosis.[3] However, patients with uremia are also known to have atherosclerotic cardiovascular events even in the predialytic stage.[4] Thus, determination of early atherosclerosis and the relevant risk factors before the initiation of chronic HD therapy is important for the development of treatment and/or prevention strategies.

High-resolution B-mode ultrasonography is used in the noninvasive evaluation of early atherosclerosis in superficial arteries.[6,7] With the help of this technique, even in the absence of discrete plaque or stenosis, the combined thicknesses of the arterial intima and media can be measured with considerable precision.[8] Intima-media thickness (IMT) is accepted as being associated with the early phase of atherosclerosis.[9] It was demonstrated that vascular changes in carotid arteries reflect general atherosclerosis[10] and have a strong association with coronary status.[11]

The aim of this study was to determine whether atherosclerosis was more accelerated in patients with uremia just before initiation of chronic HD therapy compared to a

control group of those without uremia but with a similar cardiovascular risk profile. Also, risk factors related to premature atherosclerosis were investigated.

Methods

Subjects

The participants in the study were divided into 2 groups. The first group was composed of 30 patients with uremia who were at the stage of initiation of chronic HD therapy (mean age ± SD: 52.33 ± 8.18 years, range 40–70 years), and the second group was composed of 26 control subjects who did not have uremia (mean age ± SD: 54.42 ± 9.15 years, range 40–68 years). In the uremic group, 21 patients were hypertensive and 9 were normotensive. In the nonuremic control group, 18 subjects were hypertensive and 8 were normotensive.

Those with diabetes mellitus, nephrotic syndrome, vasculitis, peripheric and cerebrovascular disease, or secondary hypertension—which are additional risk factors—were excluded. In addition, subjects with clinically manifest and/or a history of coronary artery disease also were not included. The nonuremic control subjects were classified as having normal kidney function on the basis of normal values of blood urea nitrogen and creatinine and a normal urine analysis.

The serum glucose, creatinine, total cholesterol, triglycerides, total HDL cholesterol, total calcium, inorganic phosphorus, fibrinogen, body surface area (BSA), and body mass index (BMI) of all subjects were evaluated. Other laboratory investigations included hemogram, urine analysis, abdominal ultrasonography, and creatinine clearance. Creatinine clearance was calculated according to the Cockcroft and Gault formula; CG-GFR (mL/min): [{(140−age [years])×lean body weight [kg]}/{serum creatinine× 72}]×(0.85 if female).

All patients in the uremic group had a creatinine clearance less than 10 mL/min (mean ± SD: 6.39 ± 1.95 mL/min); additionally, they had high serum creatinine levels (mean ± SD: 11.52 ± 2.55 mg/dL). In abdominal ultrasonography grade 3 or grade 4 renal parenchymal disease and decreased kidney size were observed. Other laboratory findings of the uremic subjects were also consistent with end-stage renal failure. Blood pressure was measured from the right arm after 10 minutes of rest in the supine position. Results were determined as the average of three measurements. Hypertension was diagnosed if a subject had received antihypertensive agents or had a systolic pressure of 160 mmHg or greater and/or a diastolic pressure of 95 mHg or greater.

For patients on antihypertensive treatment, the number and types of antihypertensive drugs were recorded. The presence of dyslipidemia was diagnosed if a subject was taking antilipidemic agents and/or if serum cholesterol was greater than 200 mg/dL, total HDL cholesterol was less than 35 mg/dL, or triglycerides were greater than 200 mg/dL. Exposure to cigarettes was evaluated in package-years, which was the product of years smoked times the number of package consumed daily.

Ultrasonography

Ultrasonographic investigations were performed with a Hitachi EUB 420 high-resolution B-mode ultrasonography system (Hitachi Medical Corp., Tokyo, Japan). A 4-cm-long, 7.5-mHz linear transducer was used. All examinations were carried out by the same operator. Measurement of IMT of the bilateral common carotid artery was performed at 10, 20, and 30 mm proximal to the bifurcation in the anterior oblique lateral and posterior oblique longitudinal views during end diastole and on the far wall of the artery between the lumen-intima and media-lumen interfaces.[6] No measurement was made on sites where a plaque existed. The mean of the 18 IMT measurements was calculated, and this was defined as the IMT of the common carotid artery.

Statistical Analysis

All analyses were carried out with the SPSS-PC statistical package. The Student's *t*-test, chi-square test, two-way ANOVA, multiple regression analysis, and correlation analysis were used. Data are expressed as means ± SD. A p value <0.05 was considered statistically significant.

Results

A comparison of the demographic and clinical characteristics of the subjects with uremia and the control subjects without uremia showed the 2 groups to be similar in age, sex, BSA, presence of hypertension, systolic and diastolic blood pressures, smoking habits, and presence of dyslipidemia. In the patients with uremia, serum triglycerides, fibrinogen, and phosphorus levels were significantly higher than in the controls. The control group had significantly higher BMI and total cholesterol level compared with those of the patients with uremia. In patients who were on antihypertensive treatment, the number and overall distribution of antihypertensive drugs did not differ significantly. However, the duration of hypertension was longer in the control group (*Tables I* and *II*).

The carotid IMT of the patients with uremia was significantly increased compared with that in the controls: 1.17 ± 0.19 mm versus 1.03 ± 0.15 mm, $p < 0.01$ (*Figure 1*).

Among all the variables, age and triglycerides were found to be positively correlated with carotid IMT in the patients with uremia. In the controls, only age was found to be positively correlated with carotid IMT (*Table III*).

In the group of patients with uremia male sex, not female sex, was

Table I. Clinical characteristics of the study patients.

	Uremic Group (n = 30)	Nonuremic Group (n = 26)
age	52.33 ± 8.18	54.42 ± 9.15
BMI (kg/m^2)*	24.29 ± 3.68	27.63 ± 5.02
BSA (m^2)	1.65 ± 0.16	1.74 ± 0.21
glucose (mg/dL)	88.00 ± 9.28	88.19 ± 9.93
total cholesterol (mg/dL)†	174.98 ± 49.21	204.00 ± 47.57
triglyceride (mg/dL)†	187.41 ± 74.64	145.23 ± 54.93
total HDL cholesterol (mg/dL)	44.20 ± 7.57	44.96 ± 7.03
total calcium (mmol/L)	1.96 ± 0.38	2.07 ± 0.44
inorganic phosphorus (mmol/L)‡	2.16 ± 0.50	1.22 ± 0.28
systolic blood pressure (mmHg)	137.97 ± 15.32	136.23 ± 16.41
diastolic blood pressure (mmHg)	85.36 ± 10.57	85.80 ± 18.90
hypertension duration (mo)*	21.61 ± 13.55	34.77 ± 10.97
fibrinogen (g/L)*	3.84 ± 1.15	3.08 ± 0.89
cigarette (package-years)	21.85 ± 17.86	17.45 ± 9.56

*$p<0.01$
†$p<0.05$
‡$p<0.001$
BMI = body mass index, BSA = body surface area

Table II. Comparison of the groups according to gender, smoking habits, presence of hypertension, and dyslipidemia.

	Uremic Group (n = 30)	Nonuremic Group (n = 26)
gender		
male	16 (53.3%)	13 (50.0%)
female	14 (46.7%)	13 (50.0%)
smoking		
−	17 (56.7%)	14 (53.8%)
+	13 (43.3%)	12 (46.2%)
hypertension		
−	9 (30%)	8 (30.8%)
+	21 (70%)	18 (69.2%)
dyslipidemia		
−	19 (63.3%)	16 (61.5%)
+	11 (36.7%)	10 (38.5%)

P is not significant for all findings.

shown to increase carotid IMT. However, both male and female patients with uremia had greater carotid IMT values than did the controls without uremia. When the subjects with dyslipidemia were considered, those with uremia had greater carotid IMT values than did the controls. The presence of dyslipidemia was shown to increase carotid IMT values in those with uremia. Cigarette smoking was found not to affect carotid IMT values. When the subjects with and without hypertension were considered, the patients with uremia had greater carotid IMT values than did the controls. Having hypertension was shown not to affect carotid IMT values, both in the patients with uremia and in the controls (*Table IV*).

Multiple regression analysis taking all the continuous cardiovascular risk parameters into account showed that age and triglycerides contributed significantly to the carotid IMT in the group of those with uremia, whereas only age was significantly contributed to the carotid IMT in the control group (*Tables V* and *VI*).

Discussion

In the present study, carotid IMT was determined in patients with uremia just before the initiation of chronic HD therapy and in control subjects, without uremia and similar both in demographic features and, most important, in cardiovascular risk profile. Such a study design is important to determine the influence on atherosclerosis of uremia itself, rather than the conventional cardiovascular risk factors, which are well known to be found abundantly in uremic patients.

We detected a significant increase in the carotid IMT of patients with uremia compared with that in the nonuremic control group, indicating that atherosclerosis was more accelerated in the presence of uremia. Our results also suggest that atherogenic factors are already operative even before the initiation of chronic HD therapy. It was previously

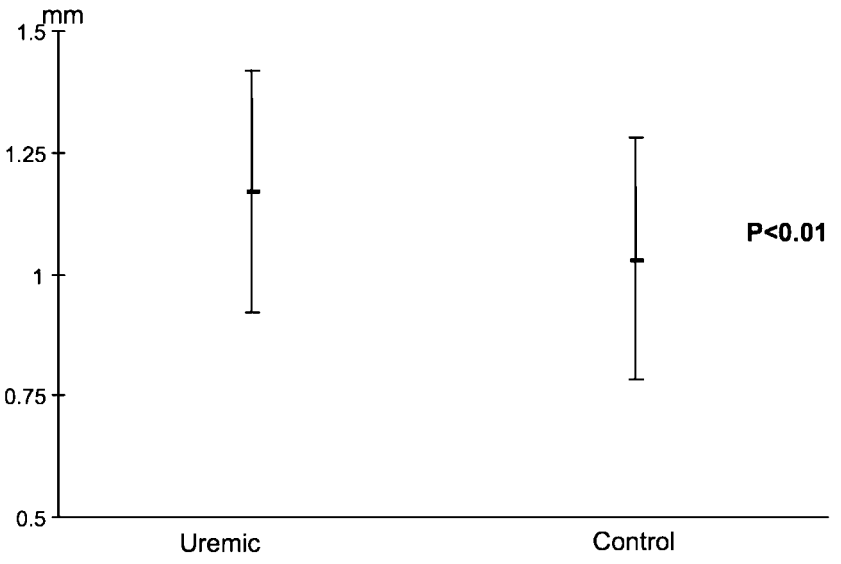

Figure 1. Carotid intima-media thickness (IMT) in patients with uremia and without uremia (controls).

demonstrated that the carotid IMT of HD patients was significantly increased compared with that in the general population.[5] Also, a higher prevalence of carotid artery lesions was detected in HD patients by Doppler echocardiography.[13] HD may accelerate atherosclerosis by inducing an imbalance between prooxidative and antioxidative mechanisms, which may result from loss of antioxidant substances via dialysis and hemoincompatibility of the dialysis system (membrane, dialysis purity).[12]

It is not clear yet whether it is the HD procedure or the uremia itself that is the major determinant of the increased risk of premature atherosclerosis. However, a high prevalence of carotid artery lesions was even found in predialytic or renal transplant patients.[4] On the basis of the results of these studies and ours,

Table III. Relationship of variables with carotid IMT by group.

	Uremic Group		Nonuremic Group	
	r	p	r	p
age (yr)	0.34*	<0.05	0.55†	<0.01
BMI	0.14	NS	−0.10	NS
BSA	0.24	NS	−0.04	NS
glucose	0.22	NS	0.15	NS
total cholesterol	0.10	NS	0.32	NS
triglyceride	0.40*	<0.05	0.13	NS
total HDL cholesterol	−1.12	NS	−0.26	NS
total calcium	0.18	NS	−0.11	NS
inorganic phosphorus	0.20	NS	−0.29	NS
Ca×P product	0.21	NS	−0.13	NS
systolic blood pressure	0.23	NS	0.33	NS
diastolic blood pressure	0.17	NS	0.32	NS
fibrinogen	0.15	NS	0.07	NS
cigarette (package-years)	−0.02	NS	0.39	NS
hypertension duration (months)	0.13	NS	0.37	NS

*$p<0.05$
†$p<0.01$
Correlation analysis of variables with carotid IMT values, r = correlation coefficient

Table IV. Effect of categorical variables on carotid IMT.

	Uremic Group (n = 30)	Nonuremic Group (n = 26)
gender		
male	1.25 ± 0.23[a]	1.04 ± 0.17
female	1.08 ± 0.11	1.02 ± 0.14
dyslipidemia		
−	1.09 ± 0.13	1.03 ± 0.17
+	1.31 ± 0.22[b,c]	1.04 ± 0.14
cigarettes		
−	1.14 ± 0.19	1.00 ± 0.12
+	1.22 ± 0.20	1.07 ± 0.18
hypertension		
−	1.12 ± 0.13[d]	0.98 ± 0.15
+	1.20 ± 0.19[e]	1.06 ± 0.15

The effect of categorically used variables on carotid IMT was analyzed with two- way ANOVA.
[a]*p<0.05; uremic males vs. uremic females.*
[b]*p<0.05; uremics with dyslipidemia vs. uremics without dyslipidemia.*
[c]*p<0.01; uremics with dyslipidemia vs. nonuremics with dyslipidemia.*
[d]*p<0.05; uremics without hypertension vs. nonuremics without hypertension.*
[e]*p<0.05; uremics with hypertension vs. nonuremics with hypertension.*

Table V. Risk factors affecting carotid IMT in the uremic group.

	B	S_B	t	p
triglycerides	0.0011	0.0004	2.26	<0.05
age	0.319	0.159	2.00	<0.05

B = regression coefficient; S = standard error; t = t-test statistics for B
Significant predictors of carotid IMT were investigated with multiple regression analysis. These are the final results.

Table VI. Risk factors affecting carotid IMT in the control group.

	B	S_B	t	p
age	0.0088	0.0026	3.41	<0.01

B: regression coefficient; S = standard error; t = t-test statistics for B
Significant predictors of carotid IMT were investigated with multiple regression analysis. These are the final results.

we have concluded that it is likely that it is uremic status per se, rather than HD, that accelerates atherosclerosis.

A positive correlation was found between age and carotid IMT both in the patients with uremia and in the controls. The aging of the uremic population in the last decades seems to have contributed to the high rate of cardiovascular morbidity and mortality. Studies in the general population also have shown a positive correlation between age and carotid IMT.[7,10,14]

In our study, an association was found between males and increased carotid IMT in those with uremia, which was consistent with the results of other studies.[7,10] In patients with end-stage renal failure, the prevalence of hypertension reaches 75% – 80% in the predialysis period.[1] In our study, 70% of the patients with uremia and 69.2% of the control subjects, who did not have uremia, were hypertensive.

The 2 groups were similar in presence of hypertension and systolic and diastolic blood pressures. Nevertheless, the patients with uremia had greater carotid IMT values than did the controls. When hypertensive and normotensive patients were considered separately, patients with uremia had higher carotid IMT values than did controls, both among those with hypertension and those with normal blood pressure. No correlation was found between systolic blood pressure, diastolic blood pressure, duration of hypertension, and carotid IMT. Therefore, the presence of hypertension was not shown to affect carotid IMT values in either group. This was consistent with the results of some previous studies[15,16] but not with others.[3]

On the basis of our findings, we suggest that the effect of uremia on early atherosclerosis may occur through a mechanism other than hypertension. Also, autonomic neuropathy, which may lead to unstable

blood pressure with uremia, might have affected the results.[17] However, the similarity in blood pressure in both groups at the time of testing does not preclude the possibility of a greater load of hypertension in the group of patients with uremia over time. A longitudinal study would resolve this issue. An alternate possibility is that hypertension has a less detrimental effect on carotid atherosclerosis in the presence of uremia.

In the present study, we did not find any relation between smoking and carotid IMT. Although several studies[8,14,18] have shown a strong association between smoking and carotid atherosclerosis, others have not.[1,16] BMI was found to be lower in the patients with uremia than in the controls. This may be a result of a reduction in muscle mass because of the impaired nutritional and physical status that occurs with uremia.

The patients with uremia in our study had higher fibrinogen levels. Although fibrinogen has been shown to be positively correlated with atherosclerosis,[19] we did not find such a relationship. The findings of other studies indicated that hyperphosphatemia and hyperparathyroidism were associated with atherosclerosis.[20] However, we did not find such a relationship of carotid IMT with serum phosphorus level and Ca $\times$ P product.

A significant association between triglycerides and carotid IMT was found in patients with uremia. Hypertriglyceridemia is the most common lipid abnormality in uremia, predominantly occurring because of reduced catabolism of triglyceride-rich lipoproteins and their remnants including intermediate-density lipoprotein (IDL). The relationship between hypertriglyceridemia and atherosclerosis is not clear. Triglyceride-rich lipoproteins and their remnants have a high affinity to macrophages; they convert them into foam cells and thereby may enhance the inflammatory reactions that eventually result in vascular endothelial cell damage and atherosclerosis.[21,22] Therefore, our findings suggest that the role of triglyceride-rich lipoproteins as an atherogenic factor may be important in uremia.

Conclusion

Our findings indicate a greater risk of premature atherosclerosis in patients with uremia at the initiation of chronic HD therapy than in those without uremia but with a similar cardiovascular risk profile. These results may suggest that uremic status has a unique influence on early atherosclerosis. The association between triglyceride level and carotid IMTin patients with uremia may bring out the importance of triglyceride-rich lipoproteins as an atherogenic culprit and of the necessity for therapeutic interventions to reduce this risk factor.

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