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Increased Incidence of Carotid Artery Wall Changes and Associated Variables in Hemodialysis Patients without Symptomatic Cardiovascular Disease

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Cardiovascular disease (CVD) is still the major cause of the morbidity and mortality in hemodialysis (HD) patients. The characteristics of major arterial changes, atherosclerosis and related risk factors in HD patients remain unclear. We aimed to evaluate the atherosclerotic process in asymptomatic HD patients and healthy volunteers, and to determine the association between the risk factor(s) and the atherosclerotic process in these groups. 92 HD patients (female: 43, male: 49) and 62 age and sex matched healthy volunteers (female: 27, male: 35) were enrolled in this study. Diabetics, smokers, and patients with symptomatic CVD were excluded. The right and left carotid intima-media thicknesses (CIMTs) were measured and plaque structures were studied by B-mode ultrasound. The mean CIMT in patients and control group were 0.79 ± 0.16 mm and 0.54 ± 0.09 mm, respectively. Mean CIMT in HD patients was thicker ($p<0.001$) and the presence ratio of plaque was higher in patients group (n=38, %61.2 vs n=9, %17.3) ($p<0.001$). Calcified type of plaque was more frequent in HD patients than control group. Age (r=0.48, $p<0.001$), left ventricular mass (r=0.42, $p<0.05$), and homocysteine (r=0.46, $p<0.01$), mean hematocrit (r=-0.36, $p<0.05$), plasma CRP (r=0.50, $p<0.001$), ESR (r=0.43, $p<0.01$) and albumin (r=-0.34, $p<0.05$) levels were correlated with the CIMT measurements and plaque presence, significantly. -CIMT as an atherosclerotic process indicator is thicker in asymptomatic HD patients than healthy subjects. We concluded that in addition to various classical risk factors, uremic environment may also contribute to acceleration of the atherosclerotic process.

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INTRODUCTION

Cardiovascular disease (CVD) is still the major cause of the morbidity and mortality in hemodialysis (HD) patients.[1-3] The mortality risk from CVD is also elevated in young adults compared with general population.[4] The increased incidence of CVD in HD patients is probably the result of a high prevalence of both traditional and uremic risk factors. Although some authors argue against the concept of accelerated classical atherosclerosis in end stage kidney failure (ESKF), it has been still believed that only a fraction of cardiac deaths may actually result from non-atherosclerotic CVD.[5]

Recently, it has become possible to detect subclinical atherosclerotic lesions with the echographic assessment of the intimae-media thickness of the carotid artery (CIMT). Cross sectional studies in different populations have shown that CIMT is associated with cardiovascular event prevalence and risk factors.[6,7] Also, some studies showed that CIMT as an indicator of atherosclerosis was significantly thicker in HD patients than age matched healthy subjects.[8,9]

Vascular calcification and increased arterial wall stiffness in HD patients are well-known pathologies,[10] but the evaluation of asymptomatic athero-

sclerosis, and the relationship between CIMT and related risk factors in HD patients have been little studied. We have therefore investigated the CIMT and plaque characteristics, and related risk factors in HD patients without symptomatic CVD.

MATERIALS AND METHODS

Ninety two HD patients (female: 43, age: 42.8 ± 13.3, range: 20-70) and 62 age and sex matched healthy volunteers (female: 27, age: 39.6 ± 9.6, range: 21-68) who were recruited from hospital staff members and their relatives were included to the study (Table 1). The mean HD duration was 129.3 ± 43.5 months (range: 35-219 months). The causes of ESKF in HD patients were chronic glomerulonephritis in 27, hypertension in 24, chronic pyelonephritis in 5, bilateral renal stone disease in 3, polycystic kidney disease in 6 patients, atheromatous renal vascular disease in 2 patients, and amyloid nephropathy in 4 patients. The causes of ESKF in 21 patients were unknown. Diabetics, smoker patients and patients with symptomatic CVD were not included. Sixty eight patients (73.9%) were on recombinant human erythropoietin therapy and the mean dosage was 125 ± 41 IU/kg-BW/week. Hypertensive group of the patients were treated by different antihypertensive agents. The bicarbonate hemodialysis treatment schedule was 4 hours for 3 days/week, and 1.2- to 1.5 m^2 polysulphone dialyzers were used, in all patients. Dry weight was targeted in each case to achieve a normotensive edema-free state.

Blood pressure measurements

Pre and postdialysis systolic and diastolic blood pressure were calculated as the average value of all recordings (6 measurements per week) obtained during two weeks before starting the study in HD patients. In control subjects, blood pressure was measured after 15 minutes resting.

Blood tests

Peripheral venous blood samples under fasting conditions were obtained from all patients in predialysis session, and controls. Complete blood count, CRP (Normal: 0 - 0.8 mg/dl), serum biochemical parameters, and lipid parameters (total cholesterol, triglyceride, LDL, HDL and VLDL) were measured. *Chlamydia pneumoniae* (CP)-IgG was assessed and quantified as 1/50, 1/100 and 1/200 titers. Antiphospholipid antibodies (ACA) were measured. Cytomegalovirus (CMV)-IgG antibody titers were assessed and quantified as < 50, 100 and > 250 IU/ml. Serum PTH and homocysteine levels were assessed. An I/D polymorphism in intron 16 of the gene coding for angiotensin converting enzyme (ACE) was analysed by polymerase chain reaction in all patients.

The mean levels of hematocrit, albumin, BUN, creatinine, liver function tests, classical lipid parameters, albumin, phosphate, calcium, glucose, serum PTH, CRP, ESR, and homocysteine levels which were measured in last six months were assessed.

Echocardiography

Left ventricular masses were calculated with using echocardiography (Acuson 128 Computer Sonographic System, Mountain View, California, USA). The accepted cut-off values for left ventricular hypertrophy were >125 gr/m^2 and 110 gr/m^2 for male and female subjects, respectively.

CIMT Measurements

CIMT measurements and plaque evaluations were done in common, internal, and external carotid arteries by duplex ultrasound (Toshiba Sonolayer SSA 270 A equipped with a 7.5 Mhz linear array transducer, Toshiba Medical Systems, Japan) by the same author (A.O.) who was unaware of clinical and laboratory data, in semi-dark room. The measurements were done from anterolateral, posterolateral and mediolateral positions and from both carotid arteries as explained by Pignoli et al.[11] CIMT measurements were always performed in plaque-free arterial segments. Carotid plaques were defined (and counted) either as faint grey echoes (soft plaques) or bright white echoes (calcified plaques) protruding into the arterial lumen, and evaluated on both sides. Plaques' kinds and number were recorded.

Statistical analysis

Statistical analysis was performed using "*SPSS (Statistical Package for Social Sciences) for Windows Release 11.0 licensed to University of California, Davis USA*". Student's t test was used to compare the means in patient and control groups. Non-parametric data were compared with using Mann-Whitney U test. Pearson correlation test was used for all correlations. Positive correlation results were evaluated for linear model by using regression analysis. To estimate the effect of risk factors on IMT, age-adjusted regression coefficients were calculated, and multiple regression analysis was used to assess independent relationships for several explanatory variables determined to be significant by univariate analysis. Results are given as mean ± standard deviation. A p value of <0.05 was considered significant.

RESULTS

Demographic data

There was no statistically significant difference between age, gender and body mass index (BMI) characteristics of HD patients and controls. The weight gains between HD sessions and BMIs were not different significantly among HD patients. The mean weekly Kt/V was 3.4 ± 2.3. Significant difference was not found between right and left CIMT measurements in both groups.

The demographic data and mean CIMT values in groups are summarized in Table 1, and Fig. 1. Mean levels of biochemical and serological parameters in HD and control groups are summarized in Table 2. Relationship between CIMT values and mean values of risk factors in HD patients are shown in Table 3. Calcified plaque frequency was higher than controls (Fig. 2).

Ultrasound findings and clinical risk factors: The mean CIMT measurements were positively correlated with age in HD patients (r=0.48, $p<$

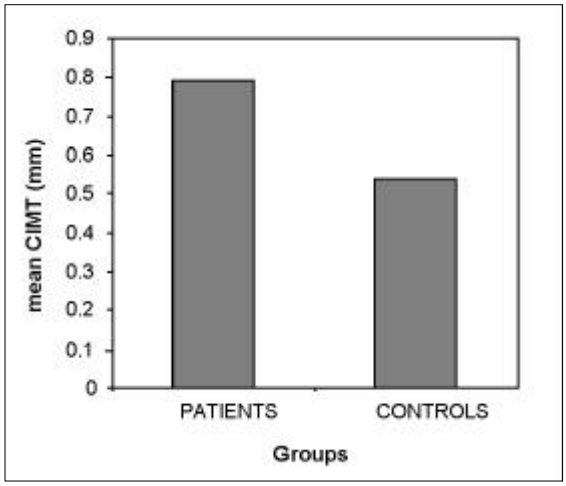

Fig. 1. Comparison of mean carotid intimae-media thickness values in hemodialysis patients and controls ($p<0.001$).

Table 1. Demographic Data and Mean Carotis Intimae-Media Thickness (CIMT) Values, Plaque Presence Ratio and Types of Hemodialysis Patients and Control Group

Parameters	HD Group (n=92)	Control group (n=62)	p
Age (year) (range)	42.8 ± 13.3 (20-70)	39.6 ± 9.6 (21-68)	NS*
Gender (F/M)	43/49	27/35	NS
Body Mass Index (kg/m^2)	24.3 ± 1.8	27.1 ± 2.1	NS
mSBP[1] (mmHg)	143 ± 5	113 ± 7	<0.005
mDBP[2] (mmHg)	86 ± 4	72 ± 3	<0.05
mLVM[3] (gr/m^2)	121.1 ± 10.3	90.2 ± 4.5	<0.01
Mean Left CIMT (mm)	0.79 ± 0.16	0.54 ± 0.09	<0.001
Mean Right CIMT (mm)	0.78 ± 0.12	0.56 ± 0.07	<0.001
Plaque presence (n/%)	58/63.0	9/17.3	<0.001
Plaque type (calcified/soft) (%)	78/22	47/53	<0.01

NS, Not significant; [1]mSBP, Mean systolic blood pressure; [2]mDBP, Mean diastolic blood pressure; [3]mLVM, Left ventricular mass.

Table 2. Comparison of Mean Levels of Biochemical and Serological Parameters in Hemodialysis and Control Groups

Parameters	HD group	Control group	*p*
ESR† (mm/h)	39.7 ± 17.3	14.1 ± 6.2	<0.001
CRP (mg/dl)	0.66 ± 0.39	0.19 ± 0.11	<0.001
Albumin (gr/dl)	3.68 ± 0.27	4.14 ± 0.27	<0.05
Triglyceride (mg/dl)	158.8 ± 38.4	172.2 ± 54.2	NS*
Total cholesterol (mg/dl)	139.3 ± 51.2	181.4 ± 24.7	<0.05
LDL- cholesterol (mg/dl)	91.6 ± 26.4	117.3 ± 29.3	<0.05
HDL- cholesterol (mg/dl)	30.2 ± 10.2	37.7 ± 9.8	<0.05
Calcium (mg/dl)	8.4 ± 0.3	9.1 ± 0.2	NS
Phosphate (mg/dl)	5.2 ± 1.4	4.2 ± 0.8	<0.01
Homocysteine (μmol/L)	18.8 ± 2.8	8.1 ± 1.9	<0.001
Intact-PTH (pg/ml)	344.2 ± 260.6	42.8 ± 10.6	<0.001
Ferritin (ng/ml)	364.7 ± 117.7	88.5 ± 32.6	<0.001
ACA1 positivity	3/92	1/62	NS
CP2-IgG seropositivity (>1/100 titers)	21/92	7/62	<0.05
CMV3-IgG seropositivity (>250 IU/ml)	31/92	9/62	<0.05

†ESR, erythrocyte sedimentation rate; *NS, Not significant.
[1]Anticardiolipin antibodies; [2]Chlamydia pneumoniae; [3]Cytomegalovirus.

Table 3. Relationship between Increment Amount of Carotid Intimae-Media Thickness Values and Mean Values of Risk Factors in Asymptomatic Hemodialysis Patients

Risk Factors	r-values*	*p*-values
Age	0.48	<0.001
Systolic blood pressure	0.11	0.59
Hemodialysis duration	0.09	0.96
Hematocrit	-0.36	<0.05
Phosphate	0.14	0.45
[Ca×P] product	0.12	0.39
ESR†	0.43	<0.01
CRP	0.5	<0.001
Total cholesterol	0.15	0.5
Plasma albumin	-0.27	<0.05

†ESR, erythrocyte sedimentation rate; *Data are expressed as partial correlation coefficients (r) and *p*.

0.001). Moreover, when the patients group was divided into two groups according to age (<45 and >45), those who were older than 45-years had significantly higher CIMT (p=0.004).

In patient group, negative correlation was found significantly between mean hematocrit level and CIMT (r=-0.36, $p<0.05$). Patients were divided into two groups according to hematocrit levels (<30% and >30%). Patients who had a hematocrit level <30% had a thicker CIMT than the patients with normal hemoglobin levels ($p<0.005$).

Ultrasound findings and inflammatory risk factors: The mean serum levels of acute phase reactants in patient and control groups are shown in Table 2. In HD patients, a significant positive correlation between mean CIMT values and ESR

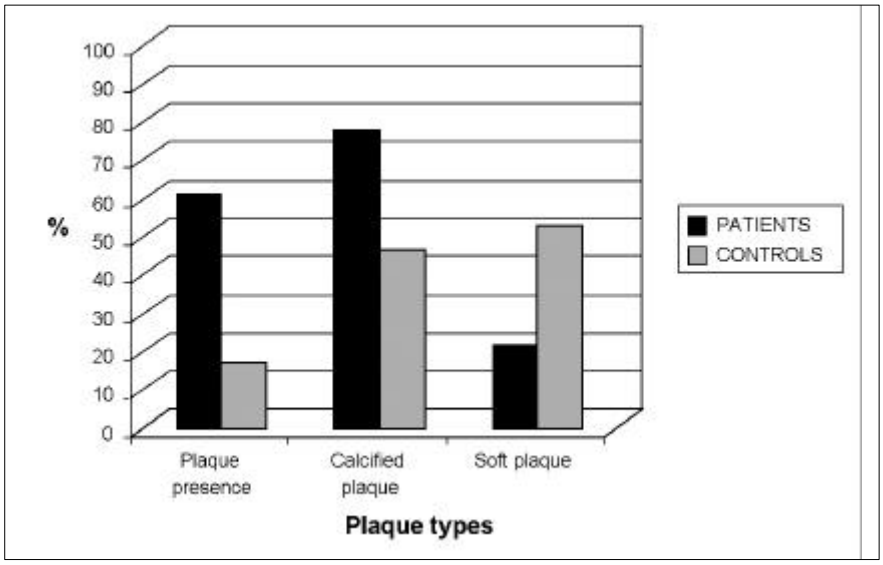

Fig. 2. Comparison of types of plaques and plaque presence ratio in both groups ($p<0.001$ for difference between plaque presence ratios, $p<0.01$ for difference between calcified plaque ratios, and $p<0.01$ for difference between soft plaque ratios).

(r=0.43, $p<0.01$) and CRP (r=0.50, $p<0.001$); and a negative correlation between mean CIMT values and albumin were found in HD patients (r=-0.27, $p<0.05$) (Table 3). Patients were classified into two groups by having a normal (n=35) or elevated (n=57) CRP levels. The patients with elevated CRP had significantly higher CIMT ($p<0.001$).

CP- and Anti-CMV-IgG antibody positivity ratio was higher in HD patients than controls (Table 3). There was also a significant positive correlation between CIMT and (1/100 values of CP-antibody titers and (250 IU values of anti-CMV IgG antibody titers ($p<0.05$), but not with lower titers in HD patients. These correlations were not observed in control group. Interestingly, CRP ($p<0.01$), ESR ($p<0.01$), plasma albumin ($p<0.05$) and homocysteine ($p<0.05$) levels in patients with CMV antibody titers (250 IU were higher than those of lower titers.

Ultrasound findings and lipid parameters: The classical lipid parameters are summarized in Table 2. There was no correlation between lipid parameters and CIMT or plaque structure in both groups.

Ultrasound findings and other risk factors: Calcium, phosphate and intact-PTH levels in both groups are shown in Table 2. Interestingly, no association was found between CIMT or plaque structure and serum calcium, phosphate, [calcium × phosphate] product and intact PTH levels in both groups. In HD patients, mean CIMT values were positively correlated with homocysteine levels (r=0.46, $p<0.01$) and left ventricular mass (r=0.42, $p<0.05$).

CIMT was not correlated with duration of HD, PTH, gender, body mass index, interdialysis weight gain, and serum ferritin levels. CIMT measurements did not differ between hypertensive (mean BP higher than 140/90 mmHg) (n=32) and normotensive (mean BP lower than 140/90 mm Hg) (n=60) patients. Interestingly, CIMT values were not significantly different between the types of polymorphisms of ACE gene.

Electrocardiographic evaluations were made by standard 12 leads ECG, did not reveal ischemic findings in all HD patients.

DISCUSSION

The pathway from cardiovascular risk factor exposure to overt cardiovascular disease partly depends on the development or progression of atherosclerosis.[12] Identification of this preclinical disease may thus enable a more precise approach to risk prediction.[13] Measurement of CIMT can be used as a marker of the total burden of atherosclerosis present in an individual. According to Iseki and Fukiyama, the incidence of acute myocardial infarction and stroke was several times higher in hemodialysis patients than in the general population.[14] In this study, we found a significant dif-

ference in CIMT and plaques, as surrogate markers of atherosclerosis, among HD patients and controls, which is in agreement with the study of London et al.[15] but in disagreement with some investigators.[16]

Age is a risk factor for atherosclerosis in general population. We showed a significant correlation between age and CIMT values and plaque presence. This result showed that the age is also an independent risk factor for atherosclerosis in uremic patients.

It is well known that hypertension is an important risk factor for atherosclerosis. It has been considered that elevated mean arterial blood pressure is known as a risk factor for CVD.[17] However, in patients without symptoms and findings of CVD, no relationship was found between duration of hypertension and CIMT in some studies.[18,19] Our study could not demonstrate that systolic or diastolic blood pressure has association with CIMT values and plaques. But, the evaluation of the effects of blood pressure on CIMT is difficult in HD patients because of instable blood pressure caused by autonomic neuropathy and instable haemodynamics.[20]

Some of the studies that investigated the classical lipid parameters and CIMT in healthy people could show a relation[18] but some could not.[21] Although lower than normal plasma cholesterol levels were associated with a higher risk of cardiovascular mortality in dialysis patients, dyslipidemia itself has adverse effects on the arterial wall and the cardiovascular event rate in ESRD patients.[22] However, we could not find a significant correlation between any classical lipid parameters and CIMT measurements. But, these results do not eliminate the importance of lipid parameters, especially unmeasured constitutional abnormalities in lipid molecules.

It has been suggested that low levels of vit-D3 and high levels of PTH were associated increased progression of atherosclerosis.[23] On the other hand, Fallo et al.[24] demonstrated that elevated PTH is not a determinant of carotid atherosclerosis in patients with primary hyperparathyroidism. We found no correlation between CIMT values and calcium, [calcium × phosphate] product and PTH levels. This result may be due to changes in diet compliance and/or intermittent active vitamin-D3 treatment. The insufficient number of participants may be another factor for insignificant result.

Anemia is associated with progression of LVH, LV dilation, higher cardiac morbidity and a higher mortality rate in HD patients.[25] Mortality progressively increases with hemoglobin values under the 10 gr/dl.[26] Locatelli et al. showed a significant increase in hospitalization and cardiac events of 5302 dialysis patients whom had a hematocrit level of 27% or less in their retrospective study.[27] The best results about cardiovascular risk were with a stable level of hematocrit between 33-36%. We found a strong negative correlation between hematocrit levels and CIMT. Patients who had a hematocrit level $<30\%$ had a higher CIMT values.

Chronic inflammation, as evidenced by increased levels of C-reactive protein (CRP), predicts all-cause and cardiovascular mortality in hemodialysis (HD) patients.[28,29] Patients with elevated serum CRP exhibit erythropoietin treatment resistance and show more pronounced anemia than patients without inflammation. Thus, inflammation-induced anemia may be one explanation for a correlation between CRP and CVD.[30] Our study revealed that, CIMT and plaque presence were positively correlated with CRP and ESR, and negatively correlated with albumin levels. Patients were divided into two groups by having normal or elevated CRP levels and CIMT was significantly higher in patients with elevated CRP levels. CP- and CMV-antibodies associated with CRP and other inflammatory markers in HD patients. So, it is reasonable to think that high titers of these antibodies would be a risk factor for accelerated atherosclerosis in dialysis patients. It is accepted that decreased albumin level is an important predictor for CVD in HD patients.[31] Low plasma albumin levels may indicate subclinic or clinical systemic inflammation. In the present study, CIMT, CIMT progression rate, ESR, CRP and ferritin levels were significantly and negatively correlated with albumin. This would mean that systemic inflammation and malnutrition may play an additive role on atherosclerotic vascular disease progression.

Elevated plasma homocysteine level is an independent risk factor for atherosclerosis in ESKF patients as well as in the general population.[32] In

contrast, a recent study by Suliman et al.[33] showed that a lower homocysteine level was an independent predictor of higher mortality in a cohort of 117 HD patients. We showed that there is a positive correlation between elevated homocysteine levels and CIMT.

Genetic polymorphisms have received great interest because they can modify the susceptibility for ischemic heart disease. Several studies demonstrated the relationships between the ACE gene polymorphism and various cardiovascular phenotypes. We observed no association between the types of polymorphism and CIMT values which is in agreement with some authors[34] and disagreement with others.[35]

In conclusion, this study has confirmed that HD patients are at increased risk for carotid artery lesions of probable atherosclerotic nature, when compared to age and sex matched controls. Elderly HD patients and the patients with anemia, hypoalbuminemia, hyperhomocysteinemia, increased left ventricular mass and chronic inflammation appear to be at increased risk for carotid artery lesions. Uremia itself may have contributed to the carotid lesions of our patients. The original aspect of our study is the wide spectrum of associated factors that were evaluated for possible associations with carotid artery lesions in HD patients.

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