Increased Carotid Artery Wall Lesions and Associated Variables in Hemodialysis Patients

HEMODİYALİZ HASTALARINDA ARTMIŞ KAROTİD ARTER DUVAR LEZYONLARI VE İLİŞKİLİ RİSK FAKTÖRLERİ

Ahmet A. KIYKIM, MD,[a] Ahmet ÇAMSARI, MD,[b] Serkan KAHRAMAN, MD,[c] Mustafa ARICI, MD,[c] Bülent ALTUN, MD,[c] Dilek ÇİÇEK, MD,[b] Yunus ERDEM, MD,[c] Ünal YASAVUL, MD,[c] Çetin TURGAN, MD,[c] Şali ÇAĞLAR, MD,[c] Aytekin OTO, MD[d]

Department of Internal Medicine, [a]Division of Nephrology, [b]Division of Cardiology, Mersin University School of Medicine, MERSİN
Department of Internal Medicine, [c]Division of Nephrology, [d]Department of Radiology, Hacettepe University School of Medicine, ANKARA

Abstract

Objective: Atherosclerotic cardiovascular disease (CVD) is still the major cause of the morbidity and mortality in end-stage renal disease (ESRD) patients. However, the characteristics of major arterial changes, atherosclerosis and related risk factors in hemodialysis (HD) patients without symptomatic CVD remains unclear. The aim of the present study was to evaluate the atherosclerotic process in HD patients and to determine the association between the risk factors and the atherosclerotic process.

Material and Methods: Sixty-two HD patients [(female:27, male:35), (age: 42±13)] and age and sex matched 52 healthy volunteers [(female:23, male:29), (age: 39±9)] 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 evaluated.

Results: 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 the patient group (%61.2 vs %17.3, $p<0.001$). Calcified plaque type was more frequent in HD patients than control group ($p<0.001$). Age ($r=0.48$, $p<0.001$), left ventricular mass ($r=0.42$, $p<0.05$), homocysteine ($r=0.46$, $p<0.01$), haematocrit ($r=-0.36$, $p<0.05$), 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 significantly correlated with CIMT measurements and plaque presence.

Conclusion: CIMT, as a putative atherosclerotic process indicator, appears to be thicker in HD patients than in healthy subjects. We concluded that, in addition to classical risk factors, an uremic environment may also contribute to acceleration in the atherosclerotic process.

Key Words: Atherosclerosis, hemodialysis, carotis intimae-media thickness

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Özet

Amaç: Son dönem böbrek yetmezliği hastalarında mortalite ve morbiditenin en önemli nedeni aterosklerotik kardiyovasküler hastalıktır. Semptomatik kardiyovasküler hastalığı olmayan hemodiyaliz (HD) hastalarında arteriyel değişiklikler, ateroskleroz ve ilişkili risk faktörleri iyi bilinmemektedir. Bu çalışmanın amacı, asemptomatik HD hastalarında aterosklerotik yapıyı incelemek, sağlıklı kişilerle karşılaştırmak ve aterosklerozla ilişkili risk faktörlerini ortaya koymaktır.

Gereç ve Yöntemler: Çalışmaya 62 HD hastası [(kadın:27, erkek:35), (yaş: 42±13)] ve 52 yaş ve cins uyumu sağlanmış sağlıklı gönüllü [(kadın:23, erkek:29), (yaş: 39±9)] dahil edildi. Diyabetikler, sigara içenler ya da bırakmış olanlar ile semptomatik kardiyovasküler hastalığı olanlar çalışma dışı bırakıldı. Sağ ve sol karotid intima media kalınlıkları (KIMK) ölçüldü, plak yapıları değerlendirildi.

Bulgular: Ortalama KIMK kalınlıkları hasta grubunda 0.79±0.16 mm, kontrol grubunda ise 0.54±0.09 mm idi. Ortalama KIMK hasta grubunda anlamlı olarak daha kalındı ($p<0.001$) ve plak bulunan hasta yüzdesi hasta grubunda daha fazla idi ($p<0.001$). Kalsifiye plak tipi hasta grubunda daha yüksek idi ($p<0.001$). Yaş ($r=0.48$ $p<0.001$), sol ventrikül kitlesi ($r=0.42$, $p<0.05$), homosistein ($r=0.46$, $p<0.01$), ortalama hematokrit ($r=-0.36$, $p<0.05$), plazma CRP ($r=0.50$, $p<0.001$), ESR ($r=0.43$, $p<0.01$) ve albumin ($r=-0.34$, $p<0.05$) düzeyleri ortalama KIMK ve plak sayısı ile anlamlı derecede korelasyon gösteriyordu.

Sonuç: Aterosklerotik yapının bir göstergesi olarak KIMK, HD hastalarında daha kalındı. Klasik risk faktörleri yanısıra üremik ortam ve risk faktörleri de HD hastalarındaki artmış KIMK kalınlığı ve plak yüzdesine katkıda bulunmaktadır.

Anahtar Kelimeler: Ateroskleroz, hemodiyaliz, karotis intima media kalınlığı

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Yazışma Adresi/*Correspondence:* Dr.Ahmet A. KIYKIM
Mersin Üniversitesi Tıp Fakültesi
İç Hastalıkları AD, 33079, MERSİN
ahmetkiykim@mersin.edu.tr

Cardiovascular disease (CVD) is still the major cause of the morbidity and mortality in end-stage renal disease (ESRD) patients.[1-4] The mortality risk from CVD is also

elevated in young adults compared with general population.[5] The increased incidence of CVD in ESRD patients is probably the result of a high prevalence of both traditional (such as hypertension, diabetes mellitus, dyslipidemia, and smoking) and nontraditional (such as infection, inflammation, and increased oxidative stress) risk factors. Although some authors argue against the concept of accelerated classical atherosclerosis in ESRD, 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 use of echographic assessment of the intima-media thickness of the carotid artery (CIMT). Previous crossectional 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 hemodialysis (HD) patients than age matched healthy subjects.[8,9]

Although increased arterial wall stiffness in HD patients are well-known pathologies,[10] the evaluation of asymptomatic atherosclerosis and the related traditional and uremic atherosclerotic risk factors in HD patients have been little studied. So, we investigated the relationship between CIMT and plaque characteristics, and related risk factors in HD patients without symptomatic CVD.

Material and Methods

This study was performed in accordance with the Helsinki Decleration Principles, approved by ethical committee, and all subjects provided informed consent.

Sixty two HD patients [(female:27, male:35; age: 42.81±13.36, range: 20-70)] and age and sex matched 52 healthy volunteers who were recruited from hospital staff members and their relatives [(female:23, male:29), (age: 39.68±9.68, range: 21-68)] were included to the study (Table 1). The mean HD duration was 129.32 ± 43.54 months (range: 35-219). The causes of ESRD were chronic glomerulonephritis in 21, chronic pyelonephritis in 5, bilateral renal stone disease in 3 patients, polycystic kidney disease in 5 patient, atheromatous renal vascular disease in 2 patients, amyloid nephropathy in 3 patients. The causes of ESRD in 23 patients were unknown. Diabetics, smoker patients and patients with symptomatic CVD were not included. Fifty two patients (83.8%) were on recombinant human erythropoietin therapy and the mean dosage was 125±41 IU/kg-BW/week. Hypertensive group of the patients (n=20) were treated by different antihypertensive agents (angiotensin converting enzyme inhibitors in five patients, chalcium channel blockers in eight patients, beta blockers in three patients, alpha blockers or in combination in four patients). None of the patients were used the HMG-CoA Reductase inhibitors.

Table 1. Demographic data and mean CIMT values of HD patients and control group

Parameters	HD Group (n:62)	Control group (n:52)	p
Age (range)	42.81±13.36 (20-70)	39.68±9.68 (21-68)	NS*
Sex (F/M)	27/35	23/29	NS
Body Mass Index (kg/m^2)	24.31±1.87	27.19±2.14	NS
mSBP[1] (mmHg)	143±5	113±7	<0.005
mDBP[2] (mmHg)	86±4	72±3	<0.05
mLVM[3] (gr/m^2)	119.11±10.31	90.22±4.56	<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	
Plaque presence (n/%)	38/61.2	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 pressureı, 3: mLVM: Left ventricular mass

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: Predialysis 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 hemodialysis patients. In control subjects, blood pressure was measured after 15 minutes recumbency and five measurements 2 minutes apart were averaged.

Blood Tests: Peripheric venous blood samples under fasting conditions were obtained from all patients in predialysis session, and controls. Complete blood count (CBC), serum biochemical parameters, classical lipid parameters (total cholesterol, triglyceride, LDL, HDL and VLDL) were measured. CRP was determined by nephelometry. Chlamydia pneumoniae (CP)-IgG was assessed with "immunefluorescence" technique; quantified as 1/50, 1/100 ve 1/200 titers. Antiphospholipid antibodies (ACA) were measured by ELISA. CMV-IgG antibody titers were assessed with ELISA and quantified as <50, 100 and >250 IU/ml. Serum PTH levels were assessed with "solid phase chemiluminescent immunometric assay" (Immulite, Diagnostic Products Corporation, USA) method (Normal: 12-72 pg/ml). Serum homocysteine levels were assessed with "reverse phase high pressure liquid chromatography"method (Normal: 7.0-14.2 μmol/L). An I/D polymorphism in intron 16 of the gene coding for angiotensin converting enzyme (ACE) was analysed by polymerase chain reaction.

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

Echocardiography: Left ventricular masses were calculated at the beginning and at the end of the study with using echocardiography (Acuson 128 Computer Sonographic System, Mountain View, California, USA). The accepted cut-off value was >125 gr/m^2 and 110 gr/m^2 for male and female subjects, respectively, for left ventricular hypertrophy.

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) at baseline and at the end of the follow up period by the same author (A.O.) who was unaware of clinical and laboratory data, in semi-dark room. The CIMT measurements were obtained from anterolateral, posterolateral and mediolateral directions as explained by Pignoli et al[11] The mean CIMT value was derived from the measurements made in the aforementioned locations of both carotid arteries. 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 kind 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. Spearman correlation test was used for all correlations. Positive correlation results were evaluated for linear model by using regression 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

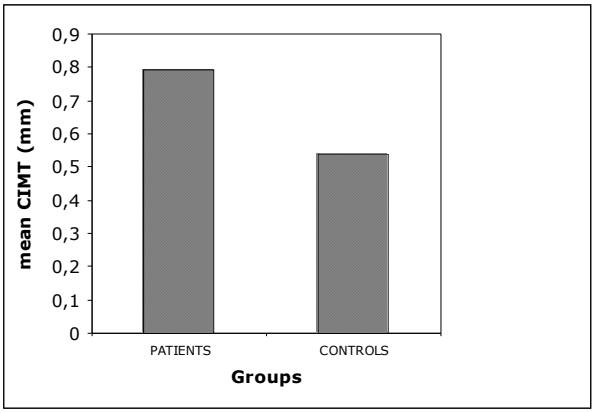

Figure 1. Comparison of mean CIMT levels in HD patients and controls (p<0.001).

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 (p>0.05).

The demographic data and mean CIMT values in groups are summarized in Table 1, and Figure 1. Mean levels of biochemical and serological parameters in HD and control groups are summarized in Table 2. Relationship between increment amount of CIMT values and mean values through follow up period of risk factors in asymptomatic hemodialysis patients are shown in Table 3. Plaque types and differentiation are demonstrated in Figure 2.

Ultrasound findings and clinical risk factors: The mean CIMT measurements were positively correlated with age in HD patients (r=0.48, p<0.001) (Figure 3a). Moreover, when the patients group was divided into two groups according to age (<45 and >45), 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 (r=0.43, p<0.01) (Figure 3b) and CRP (r=0.50, p<0.001) (Figure 3c); and a negative correlation between mean CIMT values and albumin were found in HD patients (r=–0.27, p<0.05) (Table 3).

Table 2. Mean levels of biochemical and serological parameters in HD and control groups

Parameters	HD Group	Control Group	P
ESR (mm/h)	39.76 ± 17.32	14.11 ± 6.21	<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)	158.82 ± 38.43	172.22 ± 54.28	NS*
Total cholesterol (mg/dl)	139.37 ± 51.21	181.45 ± 24.76	<0.05
LDL- cholesterol (mg/dl)	91.65 ± 26.43	117.32 ± 29.37	<0.05
HDL- cholesterol (mg/dl)	30.23 ± 10.28	37.76 ± 9.89	<0.05
Calcium (mg/dl)	8.46 ± 0.31	9.19 ± 0.22	NS
Phosphorus (mg/dl)	5.14 ± 1.43	4.16 ± 0.86	<0.01
Homocysteine (µmol/L)	18.81 ± 2.89	8.11± 1.91	<0.001
Intact-PTH (pg/ml)	344.21 ± 260.64	42.80 ± 10.61	<0.001
Ferritin (ng/ml)	364.76 ± 117.70	88.58 ± 32.61	<0.001
ACA[1] positivity	1/34	0/30	NS
CP[2]-IgG seropositivity*	7/34	4/30	NS
CMV[3]-IgG seropositivity**	14/34	7/30	NS
mLVM (gr/m^2)	121.11±10.31	90.22±4.56	<0.01

*NS: Not significant, 1: Anticardiolipin antibodies, 2: Chlamydia pneumoniae, 3: Cytomegalovirus, * >1/100 titers, ** >250 IU/ml, NS: No significant, mLVM: mean left ventricular mass

Table 3. Relationship between increment amount of CIMT values and mean values through follow up period of risk factors in asymptomatic hemodialysis patients

Risk Factors	r-values*	p-values
Age	0.48	<0.001
Gender	0.19	0.12
Blood pressure	-0.11	0.59
Hemodialysis duration	-0.09	0.96
Hematocrit	-0.36	<0.05
Phosphorus	0.14	0.45
[Ca×P] product	0.12	0.39
ESR	0.43	<0.01
CRP	0.50	<0.001
Total cholesterol	0.15	0.50
Plasma albumin	-0.27	<0.05
Ferritin	0.25	0.15
Homocysteine	0.46	<0.01
Left ventricular mass	0.42	<0.05
Intact-PTH	0.14	0.13

*Data are expressed as partial correlation coefficients and P.

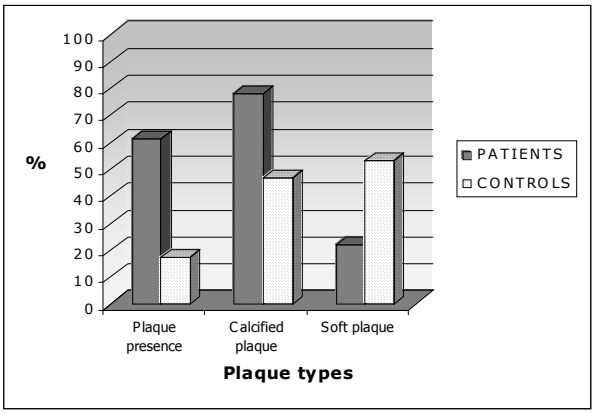

Figure 2. Comparison of types of plaques and plaque presence ratio in both groups (p<0.001 and p<0.01, p<0.01, respectively).

Patients were classified into two groups by having a normal (n=24) or elevated (n=38) CRP levels. The patients with elevated CRP had significantly higher CIMT (p<0.001). There was no difference in CP and Anti-CMV-IgG antibody titers frequencies between groups (Table 2). However, there was 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 titres of ≥250 IU were higher than those of lower titers.

Ultrasound findings and lipid parameters: The classical lipid parameters are summarized in Table 2. Correlation was not found between lipid parameters and CIMT or plaque structure in both groups.

Ultrasound findings and other risk factors: Calcium, phosphorus 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, phosphorus, [calcium x phosphorus] 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) (Figure 3d), and left ventricular mass (r=0.42, p<0.05).

CIMT was not correlated with HD duration, PTH, gender, body mass index, interdialytic weight gain and serum ferritin levels. CIMT measurements was not different between hypertensive (mean BP higher than 140/90 mmHg) (n=20) and normotensive (mean BP lower than 140/90 mmHg) (n=42) patients, and when was compared with control group.

Discussion

It is evident that there are unique uremia-related risk factors for cardiac disease that are present in HD patients. These risk factors include anemia, hyperparathyroidism, volume overload, and acidosis. They influence vascular remodeling, cardiac structure and function. 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.[12] In this study, we found a significant difference in CIMT and plaques, as surrogate markers of atherosclerosis among HD patients and controls, which is in agree-

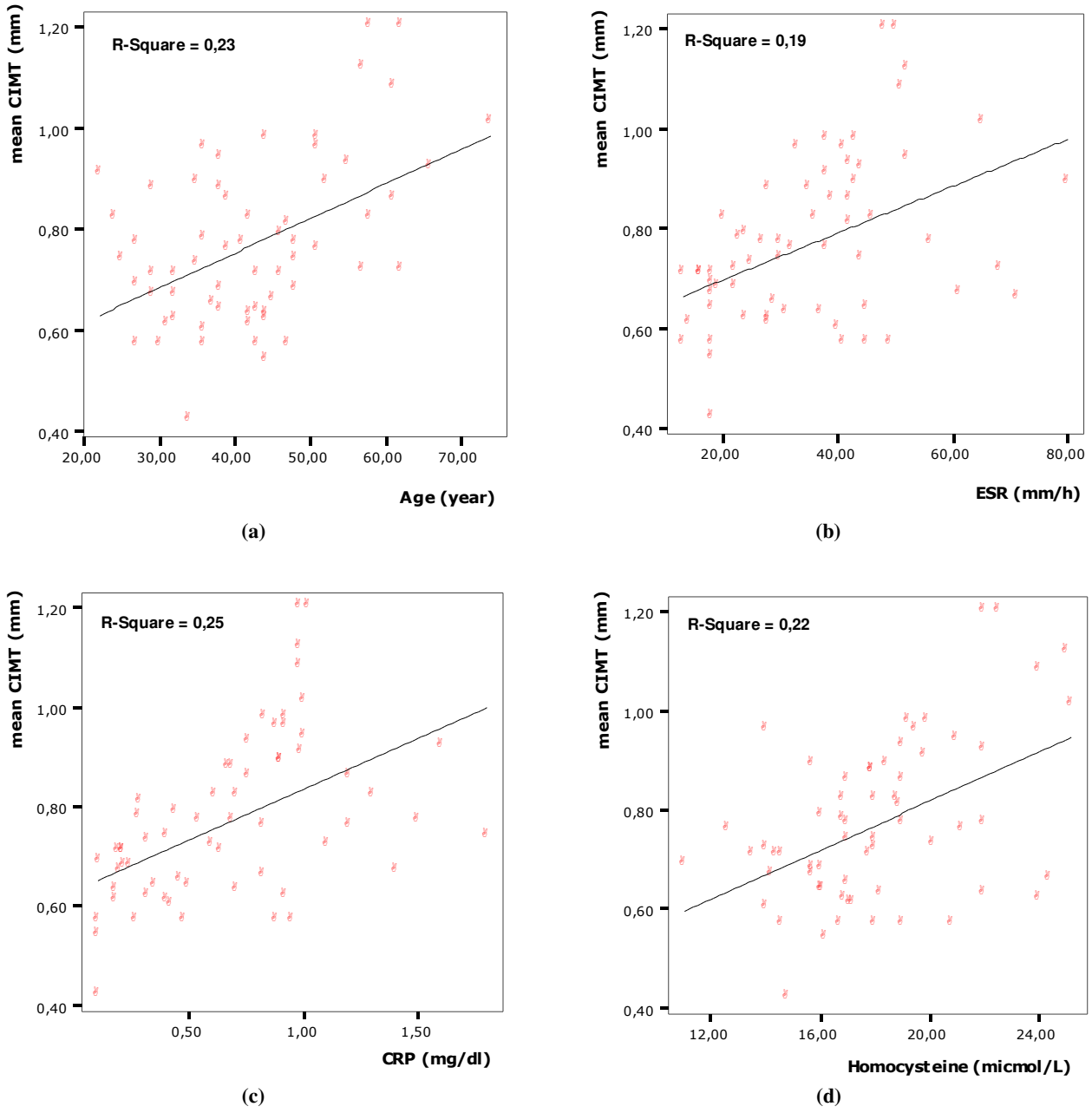

Figure 3. Correlations between the mean CIMT and age (r=0.48, p<0.001) (a), ESR (r=0.43, p<0.01) (b), CRP (r=0.50, p<0.001) (c), homocysteine (r=0.46, p<0.01) (d) levels in HD patients.

ment with the study of London et al[13] but in disagreement with other investigators.[14]

Aging is a risk factor for atherosclerosis in general population. We showed a positive correlation between age and CIMT values. Statistical analysis showed that the age is an independent risk factor for atherosclerosis in uremic patients.

It has been considered that elevated mean arterial blood pressure is known as a risk factor for CVD,[15] but in patients without symptoms and findings of CVD, no relationship was found between duration of hypertension and CIMT in some studies.[16,17] In our study, the arterial blood pressure, systolic or diastolic was not associated with CIMT

values. But the evaluation of the effects of hypertension on CIMT is difficult in HD patients because of instable blood pressure caused by autonomic neuropathy and instable hemodynamics.[18]

Some of the studies that investigated the classical lipid parameters and CIMT in healthy people could show a relation[16] but some could not.[19] Although a lower plasma cholesterol level was 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.[20] 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-D_3 and high levels of PTH were associated increased progression atherosclerosis.[21] On the other hand, in a recent study demonstrated that hyperphosphatemia (>6.5 mg/dl) and [Ca×phosphate] predicts incident cardiovascular complications.[22] Furthermore, it has been shown that controlling hyperphosphatemia reduces the progression rate of vascular calcifications in aorta and in coronary arteries.[23] Surprisingly, we showed no correlation between CIMT values and calcium, [Ca×phosphate] product. PTH levels did not correlate with CIMT values in our study agree with Zoccali et al.[24] This result may be due to changes in diet compliance and/or intermittent active vitamin-D_3 treatment. The insufficent number of participitants 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 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 were divided into two groups according to hematocrit levels (<30 and >30). Patients who had a hematocrit level <30% had a higher CIMT values. In these patients, hematocrit levels were also significantly correlated with acute phase reactants, homocystein and arterial blood pressure.

Among potential candidates for the high rate of hospitalization and mortality in maintenance dialysis patients, both malnutrition and inflammation continue to be at the top of the list. Longstanding inflammation, malnutrition, and oxidative stress are known to be associated with accelerated atherosclerosis in patients with end-stage renal failure.[24] Epidemiological studies repeatedly and consistently have shown a strong association between clinical outcome and measures of both malnutrition[28,29] and inflammation[30] in dialysis patients. CRP predicts all-cause and cardiovascular mortality in HD patients.[31,32] 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 as a "negative acute phase protein" levels. Patients were devided into two groups by having a normal or elevated CRP levels and CIMT was significantly higher in patients with elevated CRP levels. CP- and CMV-antibodies were associated with CRP and other inflammatory markers in HD patients. So, it is reasonable to think that high titers of these antibodies as 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.[34] 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 ESRD patients as well as in the general population.[35] In contrast, a recent study by Suliman et al showed that a lower homocysteine level was an independent predictor of higher mortality in a cohort of 117 hemodialysis patients.[36] We showed that there is a positive correlation between elevated homocysteine levels and CIMT.

Several studies demonstrated the relationships between the ACE gene polymorphism and various cardiovascular phenotypes. We observed an association between DD type polymorphism and CIMT values which is in agreement with some authors[37] and disagreement with others.[38]

In conclusion, this study has confirmed that HD patients are at increased risk for carotid artery lesions of probable atherosclerotic nature, as compared to age and sex matched controls and it has helped to further characterize possibly associated variables. Elderly HD patients and those with hypertension, anemia, hypoalbuminemia, hyperhomocysteinemia, hyperphosphatemia, and increased evidence of 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. We were able to confirm the strong association between left ventricular mass and increased CIMT in HD patients.

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