Prevalence of severe carotid artery stenosis and its association with echocardiographic parameters in maintenance hemodialysis patients

Kronik hemodiyaliz uygulanan hastalarda karotis arter darlığı sıklığının belirlenmesi ve ekokardiyografik değişkenlerle ilişkisinin araştırılması

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ABSTRACT

Objectives: We aimed to determine the prevalence of significant carotid stenosis in maintenance hemodialysis patients and to identify biochemical and echocardiographic predictors of significant carotid stenosis in those patients.

Study design: One hundred and seventeen maintenance hemodialysis patients were included in this study. Echocardiography biochemical tests and carotid artery Doppler ultrasonography were performed in all patients. Data obtained from patients without severe carotid stenosis were compared with those obtained from patients with severe carotid stenosis.

Results: The mean age of the patients was 56.9±12.2 years. Eleven patients had carotid artery stenosis (9.4%). While there was a trend of higher left ventricle end diastolic diameter in severe carotid artery stenosis (p=0.06), no statistically significant biochemical or echocardiographic differences were noted between the patients.

Conclusion: This study demonstrated that the prevalence of carotid artery stenosis is 5-10- fold higher than in the general population. All patients in a chronic hemodialysis program should be screened for carotid artery stenosis for prevention of cerebrovascular diseases.

ÖZET

Amaç: Kronik hemodiyaliz programında olan hastalarda karotis arter darlığı sıklığının saptanması ve karotis arter darlığı varlığını öngörebilecek biyokimyasal, ekokardiyografik değişkenlerin araştırılması.

Çalışma planı: Kronik hemodiyaliz programında olan 117 hasta çalışmaya alındı. Hastaların biyokimyasal testleri, ekokardiyografik ve karotis arter renkli Doppler ultrasonografi ölçümleri yapıldı. Karotis arter darlığı saptanan 11 hasta ile darlık saptanmayan 106 hastadan elde edilen veriler karşılaştırıldı.

Bulgular: Kronik hemodiyaliz uygulanan (56.9±12.2 yaş) hastalarda karotis arter darlığı sıklığı %9.4 olarak saptandı. Ciddi karotis arter darlığı varlığı ile biyokimyasal, ekokardiyografik değişkenler arasında ilişki saptanmadı. Ciddi karotis arter darlığı varlığı olanlarda sol ventrikül end diyastolik çapının artma eğiliminde olduğu saptandı (p=0.06).

Sonuç: Kronik hemodiyaliz uygulanan hastalarda karotis arter darlığı sıklığı normal toplum sıklığının 5-10 katı yüksek bulunmuştur. Serebrovasküler olaylardan korunma amacıyla kronik hemodiyaliz programında olan hastalara karotis dopler ultrasonografi ile tarama yapılmalıdır.

Cardiovascular disease (CVD) is an important cause of morbidity and mortality in patients with end stage renal disease (ESRD).[1] The pathogenesis of CVD in these patients has not been well characterized, but a combination of accelerated atherosclerosis and cardiac abnormalities was suggested to play an important role.[2,3]

Diabetes mellitus (DM) and hypertension are the most common diseases leading to chronic kidney disease (CKD), and both diseases have been shown to be associated with increased frequency of carotid artery stenosis. Furthermore, the CKD itself might be complicated by accelerated atherosclerosis.[4] Increased carotid intima-media thickness (CIMT) and carotid

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plaque formation have been demonstrated in patients with CKD,[5-7] suggesting an increased risk of development of severe carotid disease. However, studies reporting the prevalence of severe carotid artery stenosis in patients with ESRD are limited.

Echocardiography is a useful tool in predicting cardiovascular risk in patients with ESRD.[8] Among the echocardiographic parameters, left ventricle mass index (LVMI) and left ventricular ejection fraction (LVEF) are the important ones used to determine systolic and diastolic function in patients.[9]

Carotid artery disease has been shown to be associated with systolic and diastolic dysfunction in the non-ESRD population.[10,11] However, to the best of our knowledge, the association among echocardiographic parameters and carotid artery disease has not been evaluated in detail in patients with ESRD. Therefore, we conducted this cross-sectional study to estimate the prevalence of carotid artery stenosis and to determine its relationship with echocardiographic parameters in prevalent hemodialysis (HD) patients.

PATIENTS AND METHODS

Subjects

One hundred and seventeen prevalent HD patients were enrolled in the present study. The exclusion criteria were age <18 years and presence of active infection, malignancy or autoimmune diseases.

The study was approved by the local Ethics Committee. All the patients had given written informed consent before enrollment.

Biochemical assays

Venous blood samples were drawn after an overnight fasting. The blood sample was obtained directly through an arteriovenous fistula or central catheter on a midweek non-dialysis day. Serum total cholesterol (CHO) and triglycerides (TG) were quantified by commercial colorimetrical assay methods (GPO-PAP and CHOD-PAP; Boehringer-Mannheim, Mannheim, Germany). High-density lipoprotein cholesterol (HDL-C) was quantified by the phosphotungstic acid precipitation method. Low-density lipoprotein cholesterol (LDL-C) was calculated by the Friedewald formula (LDL-C=CHO–TG/5–HDL-C) where CHO is serum total cholesterol and TG are triglycerides. C-reactive protein (CRP) was detected by rate nephelometry (IMAGE). Serum biochemical parameters (creatinine, blood urea nitrogen, glucose, electrolytes, albumin, and complete blood count) and intact parathormone levels were studied by a computerized autoanalyzer (Hitachi 717; Boehringer-Mannheim).

Abbreviations:

CHO	*Cholesterol*
CIMT	*Carotid intima-media thickness*
CKD	*Chronic kidney disease*
CRP	*C-reactive protein*
CVD	*Cardiovascular disease*
ESRD	*End stage renal disease*
HD	*Hemodialysis*
HDL-C	*High-density lipoprotein cholesterol*
ICA	*Internal carotid artery*
LDL-C	*Low-density lipoprotein cholesterol*
LVEDD	*Left ventricle end-diastolic diameter*
LVMI	*Left ventricle mass index*
MAC	*Mitral annular calcification*
PAP	*Pulmonary arterial pressure*
SD	*Standard deviations*
TG	*Triglycerides*

B-mode Doppler ultrasonography of the common carotid artery

A high-resolution B-mode ultrasonography of the common carotid arteries (CCA) with scanning on the longitudinal axis until the bifurcation and on the transverse axis was performed using an instrument generating a wide-band ultrasonic pulse with a middle frequency of 7.5 MHz (Siemens Elegra Ultrasonography Systems, Tokyo, Japan).

For each carotid artery, two longitudinal measurements were obtained by rotating (180° increments) the vessels along the axis. All patients were blindly examined by one experienced operator. CIMT was measured 1 cm proximal to the bifurcation on each side as described previously. The degree of stenosis was expressed as the percentage of lumen diameter reduction (i.e., the ratio of the minimal diameter within the stenosis to the lumen diameter of the nearest normal segment of the internal carotid artery (ICA) downstream from the stenosis.[12] Over 70% ICA stenosis was considered to be serious in asymptomatic patients (NASCET),[13] and over 50% was considered in symptomatic patients. Patients who had transient ischemic attack or stroke in the past six months were considered symptomatic.

Echocardiography

Conventional and Doppler echocardiography with tissue Doppler imaging (TDI) (Vingmed, WI, USA) were performed on a mid-week non-dialysis day. The EF, left ventricle end-diastolic diameter (LVEDD), and the thickness of the LV posterior wall and in-

terventricular septum were measured from the long-axis parasternal plane according to the American Society of Echocardiography (ASE) guidelines.[14] The LVMI was calculated with the Devereux formula.[15] Body surface area was calculated from the formula of DuBois and DuBois. In the Framingham Heart Study, the mean values±2 standard deviations (SD) for the LVMI by body surface area were 131 and 100 g/m^2 for men and women, respectively.[16] LV hypertrophy was diagnosed when the LVMI was greater than these values. Left atrial volume (LAV) was calculated using the biplane area length formula. The LV diastolic filling pattern was recorded from the apical transducer position of the sample volume situated between the mitral leaflet tips. The peak velocity of early rapid filling (E velocity) and peak ve-

Table 1. Characteristics of the study population according to severe carotid stenosis

Parameter	Without Stenosis			Stenosis			*p*
	n	%	Mean±SD	n	%	Mean±SD	
Number	106	90.6		11	9.4		
Male/female	48/58			4/7			
Age (y)			53.7±14.0			60.1±10.5	0.222*
Body mass index (kg/m^2)			23.8±1.7			24±1.8	0.135*
HD duration (mo)	80.5 (6-252)			102 (36-144)			0.38†
Coronary artery disease	53	50		7	63		0.46‡
Diabetes	34	32.7		1	12.5		0.41‡
Smoking	24	23.6		0	0		0.19‡
Treated for hypertension	50	47.2		4	36		0.67‡
Systolic blood pressure (mmHg)			140±15			145±20	0.52*
Diastolic blood pressure (mmHg)			75±20			80±20	0.49*
Medications							
ACEI/ARB	52	49		5	45		0.43‡
Beta blockers	32	30		3	25		0.66‡
CCB	38	38		4	36		0.86‡
$CaCO_3$	25	24		3	25		0.74‡
Ca-acetate	40	38		4	36		0.54‡
Sevelamer-HCl	9	9		1	12		0.80‡
Alfacalcidol	68	64		5	45		0.88‡
Hemoglobin (g/dL)			10.7±1.0			11.2±1.0	0.96†
Calcium (mg/dL)			9.1±0.6			9.0±0.4	0.64†
Phosphorus (mg/dL)			5.5±1.33			5.8±1.06	0.58†
Intact parathormone level (pg/mL)	387 (61-2491)			397.5 (142-2307)			0.55*
Serum creatinine (mg/dL)			10.7±2.1			10.6±2.7	0.88†
Serum albumin (g/dL)			4.1±0.4			4.0±0.3	0.47†
Total cholesterol (mg/dL)	139 (82-264)			141 (105-219)			0.97*
Triglycerides (mg/dL)	126 (51-370)			113.5 (75-168)			0.36*
LDL-C (mg/dL)	76 (29-180)			84.5 (40-150)			0.80*
HDL-C (mg/dL)	35 (23-84)			38.5 (26-70)			0.46*
C-reactive protein (mg/dL)	5.6 (3-79)			6.5 (3.1-29)			0.61*

*Student's t test, †Mann- Whitney U test, ‡Fisher's exact chi-square test. ACEI/ARB: Angiotensin converting enzyme inhibitor/angiotensin receptor blocker; CCB: Calcium channel blockers; HD: Hemodialysis.

locity of atrial filling (A velocity) were recorded, and the ratio of E to A (E/A ratio) was calculated. The deceleration time of E velocity (DcT) was measured as the time interval from the E-wave peak to the decline in velocity to baseline values. On Doppler echocardiography, we calculated the myocardial performance index (MPI; Tei index), a reliable method for the evaluation of LV systolic and diastolic functions, as the sum of the isovolumetric relaxation and contraction time divided by ejection time.[17] Mitral annular calcification (MAC) was identified by echocardiography as an echodense shelf-like structure involving the mitral valve annulus with associated acoustic shadowing.[18]

Table 2. Characteristics of the study population according to presence of increase in carotid artery intima-media thickness (CIMT)

Parameter	No Increase in CIMT			Increase in CIMT			*p*
	n	%	Mean±SD	n	%	Mean±SD	
Number (n, %)	97	83		20	17		
Male/female	49/38			12/8			
Age (y)			53±13			64±8	0.02*
Body mass index (kg/m2)			23.7±1.5			25.4±1.6	0.01*
HD duration (mo)	98 (29-252)			102 (6-166)			0.92†
Coronary artery disease (n, %)	48	49		12	60		0.15‡
Diabetes (n, %)	28	29		7	35		0.59‡
Smoking (n, %)	24	23.6		0	0		0.19‡
Treated for hypertension (n, %)	44	45		10	50		0.77‡
Systolic blood pressure (mmHg)			128±23			138±17	0.29*
Diastolic blood pressure (mmHg)			75±14			79±9	0.77*
Medications							
ACEI/ARB	49	50.5		8	40		0.17‡
Beta blockers	30	31		5	25		0.59‡
CCB	34	35		8	40		0.66‡
CaCO3	22	23		6	30		0.48‡
Ca-acetate	37	38		7	35		0.50‡
Sevelamer-HCl	9	9		1	5		0.67‡
Alfacalcidol	60	62		13	65		0.80‡
Hemoglobin (g/dL)			10.9±0.9			11.3±1.0	0.89†
Calcium (mg/dL)			9.0±0.5			9.2±0.6	0.42†
Phosphorus (mg/dL)			5.2±1.4			5.5±1.1	0.65†
Intact parathormone level (pg/mL)	411 (61-2491)			498 (142-2307)			0.89*
Serum creatinine (mg/dL)			10.6±1.8			10.9±2.2	0.64†
Serum albumin (g/dL)			4.0±0.3			3.9±0.3	0.54†
Total cholesterol (mg/dL)	155 (82-254)			146 (111-219)			0.72*
Triglycerides (mg/dL)	121 (51-342)			112 (72-329)			0.52*
LDL-C (mg/dL)	79 (29-144)			80 (48-150)			0.66*
HDL-C (mg/dL)	37 (23-88)			39 (26-79)			0.83*
C-reactive protein (mg/dL)	8 (3-55)			23 (2-45)			0.006*

*Student's t test, †Mann-Whitney U test, ‡Fisher's exact chi-square test. ACEI/ARB: Angiotensin converting enzyme inhibitor/angiotensin receptor blocker; CCB: Calcium channel blockers; HD: Hemodialysis.

Statistical analysis

Data analysis was performed using the Statistical Package for the Social Sciences (SPSS) for Windows 11.5 package program. Shapiro-Wilk test was used to determine whether or not the continuous variables were distributed normally. Continuous variables were presented as mean±SD or median (minimum-maximum) and categorical variables as the percentage of cases (%). Student's t-test and the Mann-Whitney U test were used to determine significance of differences among groups for continuous variables as appropriate. Categorical variables were analyzed via Mann-Whitney U by chi-square test or Fisher's exact yield. A p-value of <0.05 was considered statistically significant.

RESULTS

The mean age of the patients was 56.9±12.2 years. All patients were receiving four hours of conventional HD with synthetic polysulphone dialyzers F6HPS and F7HPS (Fresenius AG, Bad Homburg, Germany) three times per week, with bicarbonate dialysate and low-molecular weight heparin for standard anticoagulation. Overall, severe carotid artery stenosis was detected in 11 patients (9.4%).

There were no significant differences between demographic characteristics, comorbidities including coronary artery disease, medications, lipid parameters, levels of inflammatory markers, and other laboratory parameters among patients with or without severe carotid stenosis (Table 1). Among echocardiographic parameters, there was only a trend of having increased LVEDD in patients with severe carotid stenosis compared to patients without (Table 2).

Patients with increased CIMT (>1 mm) were older, and had higher body mass indexes and serum CRP levels (Table 3). Echocardiographic parameters of LV structure and function did not exhibit significant differences between patients with normal and increased CIMT (Table 4), or between patients stratified by the degree of carotid artery stenosis (Table 5).

CIMT values were not statistically different among patients with or without MAC (0.81±0.22 vs 0.76±0.11 mm, p=0.32).

DISCUSSION

In the present work, prevalence of severe carotid artery stenosis in a chronic HD patient cohort was found to be 9.4%. This figure is well over the proposed value of a prevalence of 4.5% considered to be cost-effective to screen a specific population.[19-21] However, the atherosclerotic process is much more

Table 3. Echocardiographic parameters of LV structure and function stratified by the presence of increase in carotid intima-media thickness (CIMT)

Parameter	No Increase in CIMT (n=97)	Increase in CIMT (n=20)	*p*
LVMI (g)	100±15	108±10	0.14*
LAVI (ml/m^2)	16.3±5.2	16.7±5.3	0.56†
Septal thickness (cm)	1.44 (1.0-2.1)	1.56 (1.3-2,2)	0.25*
Posterior wall thickness (cm)	1.30 (1.0-1.7)	1.33 (1.2-1.7)	0.66*
LVEDD (cm)	4.5 (3.0-6.0)	4.7 (3.3-6.8)	0.37*
LVESD (cm)	3.36±0.9	3.46±0.64	0.69†
Myocardial performance index	0.44±0.15	0.45±0.09	0.85*
LVEF (%)	57±11	52±8	0.14†
Sa velocity (cm/sec)	8.6±1.6	8.9±1.6	0.82†
Ea velocity (cm/sec)	9.9±2.1	9.8±2.1	0.88*
E/Ea ratio	7.5±2.1	7.4±2.2	0.27†
Mitral annular calcification (%)	48 (49.4)	9 (45)	0.90‡

*Student's t test, †Mann Whitney U test, ‡Fisher's exact chi-square test. Ea: Tissue Doppler early diastolic myocardial relaxation velocity at the lateral mitral annulus; LAVI: Left atrial volume index; LVEDD: Left ventricle end diastolic diameter; LVEF: Left ventricle ejection fraction; LVESD: Left ventricle end systolic diameter; LVMI: Left ventricle mass index; Sa: Tissue Doppler systolic myocardial velocity at the lateral mitral annulus.

Table 4. Echocardiographic parameters of LV structure and function stratified by the absence or presence of severe carotid artery stenosis

Parameter	Without Stenosis (n=106)	Stenosis (n=11)	*p*
Left ventricle mass index (g)	103±14	108±11	0.23 *
Left atrial volume index (ml/m^2)	16.2±5.4	16.7±5.2	0.49†
Septal thickness (cm)	1.5 (1-2)	1.4 (1.3-2.2)	0.91*
Posterior wall thickness (cm)	1.3 (1.0-1.7)	1.3 (1.2-1.7)	0.18*
Left ventricle end diastolic diameter (cm)	4.5 (3.0-6.8)	5.2 (3.3-6.7)	0.06*
Left ventricle end systolic diameter (cm)	3.3±0.81	4.1±1.23	0.11†
Myocardial performance index	0.45±0.10	0.47±0.09	0.23*
Left ventricle ejection fraction (%)	58.2±10.60	50.4±16.30	0.26†
Sa velocity (cm/sec)	8.9±1.7	9.0±1.6	0.85†
Ea velocity (cm/sec)	9.9±2.3	9.7±2.1	0.81*
E/Ea ratio	7.6±2.1	7.4±2.4	0.17†
Mitral annular calcification (%)	52 (49)	5 (46)	0.92‡

*Student's t test, †Mann Whitney U test, ‡Fisher's exact chi-square test. Ea: Tissue Doppler early diastolic myocardial relaxation velocity at the lateral mitral annulus; Sa: Tissue Doppler systolic myocardial velocity at the lateral mitral annulus.

Table 5. Echocardiographic parameters of LV structure and function stratified by the degree of carotid artery stenosis

Parameter	No Stenosis (n=82)	Mild Stenosis (n=24)	Severe Stenosis (n=11)	*p* for the trend
Left ventricle mass index (g)	95±12	104±11	108±11	0.10
Left atrial volume index (ml/m^2)	16.2±5.4	16.0±5.4	16.7±5.2	0.46
Septal thickness (cm)	1.42 (1.0-2.0)	1.47 (1.3-2.2)	1.50 (1.1-2.3)	0.85
Posterior wall thickness (cm)	1.30 (1.0-1.7)	1.34 (1.0-1.6)	1.40 (1.2-1.7)	0.67
LVEDD (cm)	4.72 (3.0-6.5)	4.67 (3.0-6.0)	4.85 (3.3-6.7)	0.96
LVESD (cm)	3.37±0.85	3.38±1.32	3.45±0.91	0.94
Myocardial performance index	0.43±0.14	0.47±0.16	0.53±0.04	0.55
Left ventricle ejection fraction (%)	57±11	57±14	54±4	0.94
Sa velocity (cm/sec)	8.8±1.6	9.0±1.3	9.0±1.6	0.88
Ea velocity (cm/sec)	9.9±1.3	9.6±1.8	9.7±2.1	0.63
E/Ea ratio	7.6±2.0	7.4±2.0	7.4±2.4	0.29
Mitral annular calcification (%)	41 (50)	11 (46)	5 (46)	0.89

Ea: Tissue Doppler early diastolic myocardial relaxation velocity at the lateral mitral annulus; LVEDD: Left ventricle end diastolic diameter; LVESD: Left ventricle end systolic diameter; Sa: Tissue Doppler systolic myocardial velocity at the lateral mitral annulus.

dynamic and rapid in HD patients due to not only the higher prevalence of traditional cardiovascular risk factors in these patients but the higher exposure to non-traditional risk factors[22] as well. Supporting this, a recent work on screening for carotid artery stenosis reported a prevalence of 9.8% in patients with ≥60% stenosis and 6.5% in patients with 70-99% stenosis.[23] This number belonged to patients undergoing tunneled cuffed HD catheter placement, whereas our cohort was a prevalent HD population with a mean HD vintage of 81 months. Furthermore, prevalence of stroke and carotid endarterectomy - representing clinically significant severe stenosis - was found to be 17% in a dialysis cohort (the CHOICE cohort).[24] As a result, our number seems to be somewhere between the above-mentioned numbers.

The American College of Cardiology/American Heart Association has recommended CKD to be considered as a coronary heart-disease risk equivalent, since CKD has been shown to be associated with increased stiffness of arteries.[25] Moreover, studies have mentioned that CIMT increases rapidly in a CKD population, and causes an increase in cardiovascular risk.[26]

An association was found among biochemical markers and carotid artery plaque in some studies.[27-33] However, the transition process of formation of plaque to carotid stenosis symptomatology is still a matter of debate. Musialek et al.[34] investigated several circulating biomarkers to determine the role of those biomarkers in symptomatic transformation of the atherosclerotic carotid plaque. Low HDL-C was found to be an independent predictor of symptomatic carotid stenosis, and interestingly, several previously implicated novel biomarkers were not associated with symptomatic carotid stenosis.[34] Serum HDL levels were not associated with carotid artery stenosis in the present study. Moreover, only serum CRP levels were found to be associated with increased CIMT in this work. Other studies also suggest that CRP levels have an important role in carotid atherosclerosis in patients with ESRD.[35,36] In another study, Liu et al.[37] showed that an increase in serum CRP levels correlated with carotid artery stenosis but not its severity. Moreover, patients with 1444 CC genotypic polymorphism in their CRP gene had >70% risk of stenosis.

Increased diameters of the LV and deterioration of LV systolic and diastolic function are noted in 70-80% of HD patients.[38-40] A recent study also showed that increased LV diastolic diameter has the highest predictive value for mortality and adverse events in HD patients.[41] These changes begin in the early periods of renal disease and prevalence increases with disease progression. In the present work, no significant association was demonstrated between systolic and diastolic echocardiographic parameters and the presence of carotid artery stenosis. However, patients with carotis artery stenosis had a trend toward higher LVEDDs.

Carotid artery disease has been shown to be associated with LV systolic and diastolic function.[42] Studies have depicted associations of carotid disease with coronary artery disease,[43] decreased coronary flow reserve[44,45] and the direct relation of atherosclerosis with further comorbidity, such as hypertension, known to reduce LV systolic function. Additionally, increased CIMT might lead to diastolic dysfunction[46] by increasing afterload due to increased arterial stiffness and collagen deposition,[47] which causes an enhanced augmentation index.[48] Absence of such a relationship in this study might originate from the cross-sectional design and small sample size, which are also the main limitations of this work. However, a 9.4% prevalence of carotid artery stenosis in the prevalent HD patients not only represents a significant number, which is approximately 5-10 times higher than in the normal population, but also indicates a risk of cerebrovascular disease for this patient population that should be further avoided. Furthermore, although statistically not significant, there was a trend of higher LVEDD in patients with severe carotid artery stenosis compared to the whole group free of severe stenosis.

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