Carotid Intima-Media Thickness in Maintenance Hemodialysis Patients

Role of Cardiovascular Risk Factor

Shahrzad Ossareh,[1] Anoosha Alaei,[1] Daryoush Saedi[2]

[1]Division of Nephrology, Department of Medicine, Hasheminejad Kidney Center, Tehran University of Medical Sciences, Tehran, Iran
[2]Department of Radiology, Hasheminejad Kidney Center, Tehran University of Medical Sciences, Tehran, Iran

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Introduction. Carotid intima-media thickness (CIMT) has been introduced as a cardiovascular disease predictor which may increase in hamodialysis patients. As there are many risk factors in the uremic state that theoretically lead to increase in CIMT, this study was aimed to determine risk factors of CIMT increase in a group of hemodialysis patients.

Materials and Methods. Seventy-two hemodialysis patients with a mean age of 61.3 ± 15.0 years and 49 individuals with no history of chronic disease (control group) underwent ultrasonography for measurement of CIMT. Correlation of demographic, clinical, and laboratory factors with CIMT was studied. Carotid intima-media thickness was measured by one radiologist in the bilateral common carotid artery, and the mean value of the two sides was reported.

Results. The mean duration on dialysis was 82.4 ± 78.0 months. The mean CIMT was 0.96 ± 0.25 mm (range, 0.4 to 1.7 mm) in hemodialysis patients and 0.76 ± 0.06 mm (range, 0.58 to 0.91 mm) in the control group ($P < .001$). The mean CIMT was significantly higher in men compared to women on dialysis and in diabetic compared to nondiabetics patients. There was a positive correlation between CIMT and age (r = 0.266, $P = .02$) and serum cholesterol (r = 0.375, $P = .002$). No correlation was found between CIMT and other studied variables.

Conclusions. Carotid intima-media thickness was greater in hemodialysis patients compared to the control group. It was mainly affected by traditional cardiovascular risk factors and uremic risk factors did not specifically affect CIMT.

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INTRODUCTION

Cardiovascular disease is the leading cause of mortality in chronic kidney diseases (CKD) and hemodialysis patients.[1-4] According to epidemiologic studies, a high prevalence for many of the traditional risk factors of atherosclerotic cardiovascular disease, such as hypertension, diabetes mellitus, low serum high-density lipoprotein cholesterol (HDLC), left ventricular hypertrophy, and increased age, is seen in patients with CKD and end-stage renal disease (ESRD).[5,6] Other risk factors such as uremia itself, anemia, and increased serum homocysteine and fibrinogen levels, as well as increased levels of oxidative factors, have also been reported to be risk factors of cardiovascular disease in patients with CKD and ESRD.[7-10]

One of the factors currently considered as a risk factor for coronary artery disease in adults is the increase in intima-media thickness (IMT) of the carotid and femoral arteries. This factor

serves as an independent predictor of coronary artery disease and is itself connected with other risk factors.[11] Most studies have shown a modest positive relationship between carotid IMT (CIMT) and coronary atherosclerosis and also a graded positive relationship between CIMT and future cardiovascular events.[12] A meta-analysis of 8 studies showed a relative risk of 1.15 for myocardial infarction and 1.18 for stroke, for each 0.10 mm increase in CIMT.[13] In patients with CKD, IMT was linked to mean arterial pressure (MAP), CKD stage, and serum calcium-phosphorus product, but not with the Framingham risk factors.[14] Also cumulative intake of calcium-containing phosphate binders and active vitamin D preparations, together with other traditional and nontraditional risk factors, has been shown to be correlated with IMT in patients with ESRD.[15]

This study was designed to investigate the mean value of CIMT in maintenance hemodialysis patients of Hasheminejad Kidney Centre in Tehran, to compare it with patients without a history of CKD, and to investigate its possible correlation with various traditional and nontraditional risk factors of cardiovascular disease in these patients.

MATERIALS AND METHODS

Patients

In June 2007, patients who had been on maintenance hemodialysis for at least 6 months in Hasheminejad Kidney Center's hemodialysis unit were chosen for this cross-sectional study. Of 150 patients on maintenance hemodialysis, 72 consented to participate in the study. Data including age, sex, duration of dialysis, history of diabetes mellitus and hypertension, height, weight, total intake of supplemental calcium and calcitriol during dialysis years, MAP before and after hemodialysis, amount of cigarette smoking (pack-year), serum calcium, serum phosphorus, serum parathyroid hormone, calcium-phosphorus product, serum cholesterol, serum triglyceride, serum HDLC, serum low-density lipoprotein cholesterol (LDLC), and C-reactive protein (CRP) level were collected. Total intake of calcium supplement and calcitriol were calculated according to the patients' medical charts which included sheets showing the monthly prescription of drugs and interview with the patients regarding compliance to medical orders. Body mass index (BMI) was calculated as height/weight^2.

Carotid Intima-Media Thickness

Carotid IMT was measured in all of the participants by one radiologist with Esaoate Technos ultrasonography machine (Genova, Italy) in grey scale mode with a linear 7.5 mHz probe. The common carotid artery was assessed in the supine position with semi-extended neck. The distance from the leading edge of the first echogenic line to the leading edge of the second echogenic line at the level of the lower segment of common carotid artery was 0.5 cm, 1 cm, and 2 cm from bifurcation at the end of diastolic phase, bilaterally. Carotid IMT was considered as the mean of 6 measurements (3 on each side). Carotid IMT was also measured in 49 patients with no history of CKD, cardiovascular disease, diabetes mellitus, or hypertension, who underwent ultrasonography for evaluation of other disorders such as nephrolithiasis, prostatic hypertrophy, and gall stones, and was compared with the study group, as the control group.

Statistical Analyses

Data were analyzed using the SPSS software (Statistical Package for the Social Sciences, version 13.0, SPSS Inc, Chicago, Ill, USA). The *t* test and the 1-way analysis of variance test were used for comparison of continuous variables between groups and subgroups. The correlation of continuous variables was examined by the Pearson correlation coefficient test. A *P* value less than .05 was considered significant.

RESULTS

Seventy-two patients, including 39 women (54.2%) and 33 men (45.8%), were included in the study. The mean age of the patients was 61.3 ± 15.0 years (range, 21 to 86 years), and their mean BMI was 24.3 ± 5.4 kg/m^2. The mean age of the control group, 27 women (55.1%) and 22 men (44.9%), was 61.4 ± 7.1 years. The mean age and female-male ratio was not significantly different between the patient and the control groups (*P* = .96 and *P* = .91, respectively).

The mean duration of dialysis was 82.4 ± 78.0 months (range, 6 to 324 months). Forty-three patients (59.7%) were hypertensive (blood pressure ≥ 140/90 mm Hg or taking antihypertensive therapy). Seventeen patients (23.6%) were diabetic and their mean duration of the disease was 17.8 ± 9.2 years (range, 5 to 34 years). Nine patients (12.5%) were

smokers who smoked 27.1 ± 7.0 pack-years (range, 15 to 40 pack-years). The mean values for serum calcium, phosphorus, parathyroid hormone, and lipid levels are shown in Table 1.

The mean CIMT was 0.96 ± 0.25 mm (range, 0.4 to 1.7 mm) in hemodialysis patients and 0.76 ± 0.06 mm (range, 0.58 to 0.91 mm) in the control group ($P < .001$). Carotid IMT was significantly higher in the men compared to the women in the patients group (1.04 ± 0.24 mm versus 0.89 ± 0.25 mm, respectively; $P = .01$), and in diabetics compared to nondiabetic patients (1.09 ± 0.30 mm versus 0.90 ± 0.20 mm, respectively; $P = .02$). Carotid IMT had also a trend to be higher in smokers compared to nonsmokers (1.10 ± 0.25 mm versus 0.93 ± 0.25 mm, respectively; $P = .06$; Table 1). However, it was not different between hypertensive and normotensive patients (0.95 ± 0.26 mm versus 0.97 ± 0.24 mm, respectively; $P = .69$). Duration of diabetes mellitus and pack-years of smoking did not have any correlation with CIMT (Table 1). In the control group, CIMT was not different between the men and the women (0.76 ± 0.07 versus 0.77 ± 0.05, respectively; $P = .60$).

The relationship of different variables with CIMT was studied (Table 1). There was a significant relationship of age (r = 0.27, $P = .02$) and total serum cholesterol (r = 0.29, $P = .02$) with CIMT. There was a marginal correlation between CIMT and MAP before hemodialysis with a trend for significance (r = 0.22, $P = .06$), but not with MAP after hemodialysis. There was no relationship between CIMT and BMI, duration of hemodialysis, mean calcium and calcitriol prescription during dialysis years, duration of hypertension, and serum levels of calcium, phosphorus, parathyroid hormone, LDLC, HDLC, and triglyceride levels, as shown in Table 1.

Table 2. Mean Carotid Intima-Media Thickness (CIMT) in Patients With Different C-Reactive Protein (CRP) Levels*

CRP	Mean CIMT, mm
Negative	0.93 ± 0.25
1+	0.85 ± 0.24
2+	1.00 ± 0.19
3+	1.05 ± 0.30
4+	1.40 ± 0.14

*$P = .04$

C-reactive protein was measured qualitatively which was negative in 34 patients (47.2%), 1+ in 13 (18.1%), 2+ in 15 (20.8%), 3+ in 8 (11.1%), and 4+ in 2 patients (2.8%; Table 2). One-way analysis of variance showed a significantly higher mean CIMT value in patients with a positive CRP ($P = .04$).

DISCUSSION

Hemodialysis patients are highly prone to cardiovascular disease, which accounts for roughly half of the mortality in these patients. Atherosclerosis is the most common cause of cardiovascular morbidity in ESRD patients. Atherosclerotic changes in carotid arteries are assumed to be indicative of

Table 1. Relationship Between Clinical and Laboratory Factors and Carotid Intima-Media Thickness*

Factor	Mean Value	Correlation With CIMT	
		Pearson r	*P*
Age, y	61.3 ± 15.0	0.266	.02
Duration of dialysis, mo	82.4 ± 78.0	0.108	.36
Body mass index, kg/m^2	24.4 ± 5.4	0.084	.48
Duration of diabetes mellitus, y	2.2 ± 6.1	0.190	.45
Pack-years of smoking	1.4 ± 5.7	0.170	.68
Total prescribed calcium, kg	2.1 ± 1.9	0.009	.94
Total number of prescribed calcitriol during dialysis	1157.1 ± 943.8	0.023	.86
Mean arterial pressure before dialysis, mm Hg	96.2 ± 9.5	0.225	.06
Mean arterial pressure after dialysis, mm Hg	90.6 ± 8.1	-0.095	.43
Serum triglyceride, mg/dL	141.7 ± 78.5	0.140	.25
Serum cholesterol, mg/dL	159.4 ± 37.7	0.375	.001
Serum LDLC, mg/dL	94.6 ± 27.5	0.146	.22
Serum HDLC, mg/dL	35.0 ± 10.6	0.030	.80
Serum calcium, mg/dL	9.1 ± 0.7	0.046	.70
Serum phosphorus, mg/dL	4.9 ± 1.2	-0.033	.78
Serum parathyroid hormone, pg/mL	445.3 ± 571.6	-0.097	.42

*CIMT indicates carotid intima-media thickness; LDLC, low-density lipoprotein cholesterol; and HDLC, high-density lipoprotein cholesterol

atherosclerosis throughout the body and peripheral arteries.[16-19] In this study, we could show a mean CIMT of 0.96 ± 0.25 mm in a group of hamodialysis patients, which was significantly higher than in an age- and sex-matched control group. Carotid IMT was significantly higher in men, diabetic patients, and smokers. We could show a positive correlation between CIMT and age, serum cholesterol, and MAP before dialysis.

Benedetto and colleagues showed an increase in CIMT as an independent predictor of cardiovascular death, retaining an independent effect in a model that included left ventricular mass.[19] End-stage renal disease is considered as a risk factor for arterial stiffness and increased arterial IMT,[7] and increased IMT, arterial sclerosis, and stiffness and calcification of the coronary arteries have been reported in hemodialysis patients.[20] Intima-media thickness is linked with concentric left ventricular hypertrophy in dialysis patients and serves as an independent predictor of cardiovascular events and cardiovascular and all-cause mortality in these patients.[19,20] Our study showed a mean CIMT of 0.96 ± 0.25 mm, which is higher than the 0.8-mm value reported for normal populations,[21] and significantly higher than the value in our control group.

Hojas reported a significant relationship between CIMT and age.[16] Increased CIMT with age has been also reported by other authors.[22,23] Our study also showed a significant relationship between CIMT and age, which is in concordance with previous studies and indicates the natural progression of atherosclerotic progression with increasing age. We also found a significant difference in CIMT between men and women on dialysis, with a significantly higher value in the male patients. Gender difference in CIMT, with lower CIMT in female patients, has been shown in patients with coronary artery disease[24]; however, not all studies in hemodialysis patients admit this finding.[25]

Briese and colleagues showed the correlation between IMT and several risk factors such as duration of dialysis, systolic and diastolic blood pressure, LDLC and HDLC levels, serum homocysteine level, and total intake of calcium from medications.[26] In the study by Delucchi and colleagues, IMT was correlated with duration of dialysis.[27] Tseke and colleagues showed a significant relationship between carotid plaques and wall thickening and diastolic blood pressure, visceral obesity, and intact parathyroid hormone levels. They also showed the correlation between systemic and carotid stiffness with CRP, serum ferritin, lipids, and age.[28] On the other hand, Hojas did not find any relationship between serum cholesterol level or smoking and CIMT.[16] Szeto and colleagues showed a significantly higher CIMT in diabetes vs. non- diabetic patients.[25] However, IMT was not related to gender, BMI, blood pressure, cigarette smoking, kidney function, proteinuria, or calcium-phosphate product in their study.

In our study, there was a significant relationship between CIMT and serum cholesterol level, mean arterial pressure (MAP) before dialysis, and age. On the other hand, CIMT was clearly higher in diabetic patients than nondiabetic dialysis patients and there was a trend for higher CIMT value in smokers versus nonsmokers. These findings emphasized the relationship between traditional cardiovascular risk factors and CIMT, which have been shown to be a predictor of cardiovascular disease in many studies as stated previously.

We could not show any relationship between CIMT and serum calcium, serum phosphorus, calcium-phosphorus product, parathyroid hormone level, or the total amount of calcium or calcitriol prescription during hemodialysis years. These findings are similar to the findings of Szeto and colleagues,[25] although some authors have reported a positive correlation between IMT and calcium-phosphorus product or cumulative intake of calcium-containing phosphate binders and active vitamin D preparations.[14,15]

In our patients, BMI did not correlate with CIMT. Although obesity is an important cardiovascular risk factor and has been shown to be significantly correlated with BMI in many studies,[29-31] some investigators have not confirmed this finding in hemodialysis patients.[25] In our patients, the mean BMI was 24.4 ± 5.4 kg/m^2, with a median of 23.9 kg/m^2, and it seems that we have a group of rather "lean" patients, which may make it difficult to show the differences in CIMT between different subgroups with regards to BMI.

Correlation between CIMT and inflammation has been shown in hemodialysis patients as well as healthy people.[18,27-29] Zoccali and colleagues showed a strong interrelationship between asymmetric dimethylarginine and CRP in hemodialysis

patients, and the interaction between asymmetric dimethylarginine and CRP was found as the sole independent predictor of the progression of intimal lesions.[32] We could also show a greater CIMT in patients with positive CRP, and this can emphasize the relationship between inflammation and CIMT value.

Our limitations in this study were the unavailability of quantitative CRP kit at the time of our study which could have provided a more precise tool for determining the correlation between CIMT and inflammation status. Including magnesium and 25-hydroxyvitamin D level measurements might have added significant findings to the results of this study.

CONCLUSIONS

Various risk factors have been correlated to CIMT value in different studies, with some conflicting results. In the present study, we found no significant relationship between CIMT and serum calcium, phosphorus, and parathyroid hormone levels. Among the various described risk factors, we could show a significant relationship between CIMT and age, gender, predialysis MAP, serum cholesterol level, CRP, diabetes mellitus, and smoking. Therefore, it seems that the traditional risk factors of cardiovascular disease in the normal population also affect the value of IMT in dialysis patients, and that uremia and its accompanying risk factors do not specifically affect IMT in this group of patients. We suggest prospective cohort studies for evaluation of the prognostic value of CIMT for various vascular events and patient survival in hamodialysis patients.

CONFLICT OF INTEREST

None declared.

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Correspondence to:
Daryoush Saedi, MD
Department of Radiology, Hasheminejad Kidney Center, Vanak Sq, Tehran 19696, Iran
E-mail: daryoush_saedi@yahoo.com

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