Differences in Cardiovascular Disease Risk Factors Associated With Maximum and Mean Carotid Intima-Media Thickness Among Hemodialysis Patients

Amir Ahmad Nassiri,[1] Monir Sadat Hakemi,[2] Reza Asadzadeh,[1] Ali Mohammad Faizei,[1] Sudabeh Alatab,[2] Reza Miri,[1] Mehdi Yaseri[2]

[1]Shahid Beheshti University of Medical Sciences, Tehran, Iran
[2]Tehran University of Medical Sciences, Tehran, Iran

Keywords. cardiovascular disease, carotid intima-media thickness, atherosclerosis, hemodialysis

Introduction. Carotid intima-media thickness (CIMT) could be used as a surrogate marker of atherosclerosis in hemodialysis patients. Since different mechanisms are involved in the atheroma formation and arterial wall thickness, we assessed the relationship between the maximum and the mean CIMT with different cardiovascular risk factors in dialysis patients.

Materials and Methods. The mean and the maximum CIMT were measured using a B-mode ultrasonography in 75 hemodialysis patients, and the correlation between CIMT and cardiovascular risk factors were assessed.

Results. The mean and maximum CIMT measurements were 0.5 mm (range, 0.2 mm to 1 mm) and 3.4 mm (1.4 mm to 5.6 mm), respectively. Among all the studied variables, age (P = .04, r = 0.238), HS-CRP (P = .01, r = 0.284), mean arterial blood pressure (P = .003, r = 0.343), and DM (P = .02) had significant correlations with the mean CIMT, while only age (P = .02, r = 0.473) and serum creatinine levels (P = .02, r = -0.493) were significantly associated with the maximum CIMT. A positive nonsignificant correlation was observed between the mean and maximum CIMT values (P = .08, R^2 linear = 0.214).

Conclusions. These findings suggest that in dialysis patients, effects of cardiovascular risk factors on the mean and maximum CIMT might be different. Further studies are recommended to evaluate the prediction impact of each risk factor in end-stage renal disease patients compared with otherwise healthy individuals.

IJKD 2012;6:203-8
www.ijkd.org

Original Paper

INTRODUCTION

Cardiovascular disease is the principal cause of morbidity and mortality in hemodialysis patients. At any age, patients receiving dialysis, experience an excess of cardiovascular deaths, with 50% of all deaths resulting from cardiovascular events.[1] In these patients, the pathogenesis of cardiovascular damage is complex and could be attributed to traditional risk factors such as hypertension, hyperlipidemia, smoking, aging, and left ventricular hypertrophy,[1] as well as nontraditional risk factors, including uremia, anemia, hyperparathyroidism, hyperhomocyteinemia, increased oxidative stress, and a high state of inflammation.[1-3]

It is assumed that in patients with end-stage renal disease (ESRD), 2 subtypes of arterial vascular disease, atherosclerosis and arteriosclerosis, are involved. Atherosclerosis is a chronic disease that

involves the intima-media layer of the arterial wall and characterized by the presence of plaques and occlusive lesions. In hemodialysis patients, the atherosclerotic lesions are frequently calcified and have increased media thickness compared with lesions in the general population.[4,5] An accelerated atherosclerosis has been documented in hemodialysis patients. In fact, compared with age- and gender-matched nondialysis individuals, hemodialysis patients present with accelerated atherosclerosis with clinical manifestations such as coronary artery disease, stroke, and peripheral vascular disease.[2,3] On the other hand, the arteriosclerosis process has also a high prevalence in ESRD patients and could be due to either flow or pressure overload.

It is assumed that the atherosclerotic changes in the carotid artery are the mirror reflection of pathologic events of generalized atherosclerosis.[4,5] Ultrasonographic measurements of the carotid intima-media thickness (CIMT) and plaque occurrence in the carotid arteries were widely used as surrogate indicators for determining the early atherosclerotic changes, the anatomic extent of atherosclerosis, and its progression in the general population, as well as in patients with ESRD.[4,5] There are 2 major methods for carotid artery ultrasonography; one that includes the plaque and the other that excludes the plaque.[6-8] The including plaque method measures the maximum CIMT of the carotid artery and is considered as an index of arterial wall thickness and atheroma formation,[7,8] while in the excluding plaque method, the mean CIMT without plaque is considered as an index of arterial wall thickness.

Atherosclerosis is a complex process which has correlation with established coronary risk factors in the general population. However, it is thought that different mechanisms involved in the atheroma formation and arterial wall thickness in hemodialysis patients.[7-9] We aimed to investigate the relationship between the maximum and the mean CIMT values with different cardiovascular risk factors in dialysis patients.

MATERIALS AND METHODS

Patients

Patients who had been on maintenance hemodialysis for at least 3 months in the hemodialysis center of Imam Hossein Hospital were enrolled in this study, if they were aged between 22 and 85 years. By excluding the patients with parathyroidectomy, recent infection, and hospital admission, a total of 75 hemodialysis patients were enrolled in this study. All of the patients were on hemodialysis (Fresenius 4008-B, Fresenius Medical Care, Homburg, Germany), 3 times per week, with polysulfone membranes and bicarbonate-based dialysis solution, each session lasting about 4 hours. The protocol of this research study was approved by the ethics committee of Shahid Beheshti University of Medical Sciences, and the participants signed informed consent at the time of recruitment.

Data Collection

Patient's data including age, gender, cause of ESRD, history of diabetes mellitus (DM), hypertension, and smoking; duration of chronic kidney disease; and duration of hemodialysis period were collected. All the participants underwent physical examination and anthropometric evaluations at the time of recruitment. The CIMT was measured in all of the participants and the values were expressed as mean CIMT. In patients in whom an atheroma plaque was detected, the maximum CIMT was reported, and they were placed in the maximum CIMT group (n = 22).

Laboratory measurement

Blood pressure was measured using a standard calibrated mercury sphygmomanometer on the right hand after the participants had been sitting for at least 5 minutes. Venous blood samples were collected in the morning after an overnight fasting before starting the dialysis. The blood samples were centrifuged and then serum was collected for measuring the biomedical parameters of calcium, phosphorus, intact parathyroid hormone, hemoglobin, albumin, uric acid, homocysteine, high-sensitivity C-reactive protein (HS-CRP), total cholesterol, low-density lipoprotein cholesterol (LDLC), high-density lipoprotein cholesterol (HDLC), triglyceride, and 25-hydroxyvitamin D levels.

Definitions

Patients were classified as hypertensive when the average blood pressure in 3 readings before dialysis sessions was 140/90 mm Hg and greater or when the patient was taking antihypertensive drugs. The participants were considered to have

dyslipidemia when the serum total cholesterol level was 200 mg/dL and greater; HDLC was less than 40 mg/dL, or triglyceride was 150 mg/dL and greater. Patients who were taking lipid-lowering medications were categorized in this group. Patients were classified as hyperuricemic when serum uric acid level was greater than 6 mg/dL in women and greater than 7.5 mg/dL in men or when they were receiving allopurinol. Smoking status was ascertained on the basis of the self-reported history of cigarette smoking.

Carotid Ultrasonography

Ultrasonographic analysis of the carotid artery was performed with a high-resolution ultrasound scanner, equipped with a linear array 7.5-MHz transducer (ACUSON 128p/10 machine, Siemens, Erlangen, Germany). The scan was started from the proximal part of the common carotid artery toward the bifurcation, followed by scanning the internal and then the external carotid artery. Dynamic sequence images were stored for the following measurement of CIMT, defined as the distance between the leading edge of the lumen-intima interface and the leading edge of the media-adventitia interface. The scanning procedure was made first on the right common carotid artery and then on the left common carotid artery. The regions of interest were defined as 0.5-cm, 1-cm, and 2-cm distances from bifurcation. On each region of interest, the near and far wall thicknesses were measured. The CIMT was reported for each subject as the average of measurements. Maximum carotids IMT were measured if there was atheroma plaque. All the CIMT measurements were performed by one trained radiologist and a single ultrasound system.

Statistical Analyses

Continuous variables values were shown as the mean ± standard deviation. The Spearman correlation, linear regression, and logistic regression analyses were used for assessment of correlations. The analyses were performed using the SPSS software (Statistical Package for the Social Sciences, version 17.0, SPSS Inc, Chicago, Ill, USA). *P* values less than .05 were considered significant

RESULTS

Seventy-five hemodialysis patients (47 men and 28 women) were evaluated in this study. Demographic, clinical, and biochemical characteristics of the patients are shown in Table 1.

Twenty-two patients had carotid atheroma plaques. The mean and maximum CIMT measurements were 0.5 mm (range, 0.2 mm to 1 mm) and 3.4 mm (1.4 mm to 5.6 mm), respectively. Among all the studied variables, age (P = .04, r = 0.238), HS-CRP (P = .01, r = 0.284), mean arterial blood pressure (P = .003, r = 0.343), and DM (P = .02) had significant correlations with the mean CIMT, while only age (P = .02, r = 0.473) and serum creatinine levels (P = .02, r = -0.493) were significantly associated with the maximum CIMT (Table 2). A positive nonsignificant correlation was observed between the mean and maximum CIMT values (P = .08, R^2 linear = 0.214).

Table 1. Demographics, Clinical, and Biochemical Characteristics of Hemodialysis Patients*

Characteristic	Value	Reference Value
Age, y	57 ± 16	…
Male gender, %	62.7	…
Median dialysis time, mo	24	…
Median CKD duration, mo	48	…
KT/V	1.2 ± 0.4	≥ 1.3
Medical history		
Ischemic heart disease	30 (40.0)	…
Cardiovasculardisease	7 (9.4)	…
Diabetes mellitus	36 (48.0)	…
Hypertension	59 (78.7)	…
Dyslipidemia	69 (92.0)	…
Hyperurecimia	33 (44.0)	…
Blood tests		
Hemoglobin, g/dL	11.1 ± 1.6	Female, 12.0 to 15.8 Male, 13.3 to 16.2
Triglyceride, mg/dL	162 ± 85	< 150
Cholesterol, mg/dL	143 ± 32	< 200
HDL cholesterol, mg/dL	84 ± 26	> 40
LDL cholesterol, mg/dL	29 ± 9	< 13
Creatinine, mg/dL	7.0 ± 2.2	0.8 to 1.2
Calcium, mg/dL	9 ± 1	8.5 to 10.0
Phosphorus, mg/dL	5.5 ± 1.6	3.5 to 5.5
IPTH, pmol/L	26.4 ± 36.7	0.8 to 3.9
Albumin, g/dL	4.1 ± 0.7	3.5 to 5.5
Uric acid, mg/dL	6.0 ± 1.1	Female, 2.5 to 6.0 Male, 3.1 to 7.5
Homocysteine, µmol/L	41.9 ± 29.9	0 to 50
HS-CRP, mg/L	9.4 ± 15.8	< 5
Fibrinogen, mg/dL	286 ± 76	50 to 400
25-hydroxyvitamin D, nmol/L	78 ± 43	47.7 to 144.0

*CKD indicates chronic kidney disease; HDLC, high-density lipoprotein cholesterol; LDLC, low-density lipoprotein cholesterol; IPTH, intact parathyroid hormone; and HS-CRP, high-sensitivity C-reactive protein.

Table 2. Correlations Between Mean and Maximum Carotid Intima-Media Thickness Values and Clinical and Demographic Parameters*

Parameter	Mean CIMT		Maximum CIMT	
	r	*P*	r	*P*
Age	0.238	.04	0.473	.03
Duration of CKD	0.047	.69	0.045	.84
Duration of dialysis	0.089	.46	0.301	.17
Hemoglobin	0.039	.74	0.017	.94
Triglyceride	0.054	.65	0.231	.30
Cholesterol	0.143	.23	0.298	.18
LDLC	0.104	.38	0.337	.13
HDLC	0.009	.94	0.085	.71
Calcium	0.052	.67	0.112	.62
Phosphorus	0.029	.81	0.070	.76
Calcium-phosphorus product	0.018	.88	0.170	.45
IPTH	0.074	.54	0.048	.83
Albumin	-0.128	.28	0.090	.69
Uric acid	0.116	.33	0.085	.71
Homocysteine	0.159	.18	0.138	.54
Fibrinogen	0.142	.24	0.263	.25
HS-CRP	0.284	.02	0.242	.28
KT/V	0.048	.70	0.099	.66
Creatinine	0.204	.08	0.493	.02
25-hydroxyvitamin D	0.023	.85	0.296	.18
Mean arterial blood pressure	0.343	.003	0.172	.45
Uric acid	0.056	.64	0.037	.87

*The correlation coefficients are calculated using the Spearman correlation test. CIMT indicates carotid intima-media thickness; CKD, chronic kidney disease; LDLC, low-density lipoprotein cholesterol; HDLC, high-density lipoprotein cholesterol; IPTH, intact parathyroid hormone; and HS-CRP, high-sensitivity C-reactive protein.

DISCUSSION

Cardiovascular disease is the most common cause of death in ESRD patients. These patients are 5 to 30 times more likely to die due to atherosclertic cardiovascular disease than the general population.[1-3,7] In these patients, CIMT measured by ultrasonography, could be used as a noninvasive marker of carotid artery atherosclerosis that reflects the atherosclerotic changes through the whole vascular system.[10-13] However, in the literature, there is controversy regarding the correlation between different atherosclerotic cardiovascular risk factors and CIMT in patients who are undergoing hemodialysis.[8,10-12]

In this study, we found that age is a variable that could affect both mean and maximum CIMT in hemodialysis patients. Although patients with chronic kidney disease are suffering from a premature atherosclerotic process, increasing age is a risk factor that would accelerate the arteriosclerosis and atherosclerosis process. Our finding in this study is in line with several other studies that reported aging as a recognized risk factor for development and progression of atherosclerosis.[5,8] Ossareh and coworkers measured the mean of CIMT in 72 hemodialysis patients and consistent to our results, found a significant positive correlation between CIMT values and age.[14]

Hypertension is a major risk factor for cardiovascular mortality in the general population; however, it is not clear that whether this risk factor has the same impact on the cardiovascular disease in dialysis patients.[8] We found a significant correlation between mean arterial blood pressure and mean CIMT; however, such a relation did not exist between mean arterial blood pressure and maximum CIMT. One plausible explanation could be that in this study, blood pressure readings were recorded before dialysis session. Considering the great variability of blood pressure and extreme changes in volemic state of dialysis patients that could affect the blood pressure values, it may not be accurate to just consider blood pressure measurements in the dialysis center as a representative of blood pressure value in these patients.[13,15] Ambulatory blood pressure monitor has been considered as a gold standard for evaluating the blood pressure status of patients. Unfortunately, in this study we did not performed the ambulatory blood pressure monitor which might explain the lack of correlation between blood pressure and maximum CIMT. There are indeed some studies which are in line with our findings,[6,8] including a study by Nakashima and colleagues, in which no significant relationship between hypertension and maximum CIMT was observed.[8] According to these findings, we could suggest that in hemodialysis patients, hypertension plays a major role in arteriosclerosis process rather than in atherosclerosis.

In this study, DM showed a positive association with the mean CIMT but not with the maximum CIMT. Although previous studies have reported such an association between CIMT and DM, there are also some contrary findings. For example, Nakashima colleagues and Brozosko and coworkers reported no significant relationship between DM and the mean CIMT.[8,12]

Lipid abnormalities have been shown to be very prevalent in hemodialysis patients. We also found that more than 90% of our study subjects were suffering from dyslipidemia manifested by

high levels of cholesterol, triglyceride, or both, and low levels of HDLC. We could not detect any significant correlation between dyslipidemia and the maximum and mean CIMT values. The role of high serum concentrations of total cholesterol, LDLC, and triglycerides in the pathogenesis of atherosclerotic process has been confirmed by several studies in general population[16]; however, in dialysis patients, the results are controversial. More recently, it has been proposed that in ESRD patients, abnormalities in lipoprotein composition or in LDLC oxidation rather than the elevation of lipoprotein levels might be a more important athrogenic factor,[17] and an association between oxidized LDLC and atherosclerosis in ESRD patients has been reported.[18,19] An enhanced oxidation of LDLC has been observed in ESRD patients.[8,17,18] Moreover, Maggi and associates showed the significant relationship between oxidized LDLC and accelerated atherosclerosis process in ESRD patients.[18] Accordingly, it would not be surprising that serum lipid levels, in our dialysis patients, had no significant correlation with CIMT, since we did not evaluate the role of oxidized LDLC in the atherosclerosis process. Similar to our study, Nakashima and colleagues could not find a relationship between abnormal lipid profile and atherosclerosis in dialysis patients.[8]

The present study showed that the HS-CRP was associated with the mean CIMT but not with the maximum CIMT. Some other studies have also shown this relationship.[19-21] It seems that the HS-CRP could be considered as a marker of arteriosclerosis in hemodialysis patients. Considering the other risk factors, we could not detect an association between serum levels of calcium, phosphorus, parathyroid hormone, and 25-hydroxyvitamin D and the mean or maximum CIMT.

An association between atherosclerosis, arterial calcification, and hyperphosphatemia and hyperparathyroidism has been reported.[7,22] However, in hemodialysis patients, serum phosphorus level is varied overtime. In this study, serum phosphorus was measured once, which might explain why we could not detect a relationship between this factor and CIMT. Unfortunately, we did not assess the arterial calcification, and as a result, we could not evaluate the association between this complication and calcium-phosphorus metabolism, which is considered as one of the limitations in this study.

Lack of a healthy age- and sex-matched control group in order to compare the values of the mean and maximum CIMT between controls and hemodialysis patients is another limitation of this study. Further studies with well-matched control groups could better verify the risk factors in ESRD patients.

CONCLUSIONS

Atherosclerosis process has a complex pathophysiology and its progression is variable among hemodialysis patients with different cardiovascular risk factors.[4,5] The available cardiovascular disease risk scoring systems could be applied to the general population.[23,24] However, these scoring systems are not able to predict cardiovascular events in the dialysis patients. Early detection of atherosclerosis using noninvasive methods such as ultrasonography is valuable for primary prevention of cardiovascular events in dialysis patients. Our results confirmed that different risk factors are involved when the mean CIMT or the maximum CIMT is measured as a marker of atherosclerosis. A prospective multicenter study to address the early diagnosis of vascular disease, evaluation of cardiovascular disease risk factors and prediction of subclinical atherosclerotic lesions in ESRD patients in comparison with a control group is suggested.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Longenecker JC, Coresh J, Powe NR, et al. Traditional Cardiovascular disease risk factors in dialysis patients compared with the general population: The CHOICE study. J Am Soc Nephrol. 2002;13:1918-27.
2. Levey AS, Eknoyan G. Cardiovascular disease in chronic renal disease. Nephrol Dial Transplant. 1999;14:828-33.
3. Ma KW, Greene EL, Raij L. Cardiovascular risk factors in chronic renal failure and hemodialysis populations. Am J Kidney Dis. 1992;19:505-13.
4. Ross R. Atherosclerosis-an inflammatory disease. N Engl J Med. 1999;340:115-26.
5. Von Baeyer H, Hopfenmüller W, Riedel E, Affeld K. Atherosclerosis: current concepts of pathophysiology and pharmacological intervention based on trial outcomes. Clin Nephrol. 2003;60[Suppl 1]:S31-48.
6. Kawagishi T, Nishizawa Y, Konishi T, et al. High resolution B- mode ultrasonography in evaluation of atherosclerosis

in Uremia. Kidney Int. 1995;48:820-6.

7. Krasniak A, Drozdz M, Pasowicz M, et al. Factors involved in vascular calcification and atherosclerosis in maintenance hemodialysis patients. Nephrol Dial Trasplant. 2007;22:515-21.
8. Nakashima A, Yorioka N, Asakimori Y, et al. Different risk factors for the maximum and the mean Carotid Intima-media Thickness in hemodialysis patients. Int Med. 2003;42:1095-9.
9. Yilmaz FM, Akay H, Duranay M, et al. Carotid atherosclerosis and Cardiovascular risk factors in hemodialysis and peritoneal dialysis patients. Clin Biochem. 2007;40:1361-6.
10. Benedetto FA, Mallamaci. F, Tripepi G, Zoccali. C. Prognostic value of ultrasonographic measurement of Carotid Intima Media Thickness in dialysis patients. J Am Soc Nephrol. 2001;12:2458-64.
11. Goodman WG and Salusky IB. Non-invasive assessments of cardiovascular disease in patients with renal failure. Curr Opin Nephrol Hypertens. 2001;10:365-9.
12. Brzosko S, Lebkowska U, Malyszko J, Hryszko T, Krauze-Brzosko K, Mysliwiec M. Intima media thickness of common carotid arteries is associated with traditional risk factors and presence of ischaemic heart disease in hemodialysis patients. Physiol Res. 2005;54:497-504
13. Hojs R. Carotid intima-media thickness and plaques in hemodialysis patients. Artif Organs. 2002;24:691-5.
14. Ossareh S, Alaei A, Saedi D. Carotid intima-media thickness in maintenance hemodialysis patients role of cardiovascular risk factor. Iran J Kidney Dis. 2011;5: 169-74.
15. Ekart R, Hojs R, Pecovnik- Balon B, Bevc S, Dvorsak B. Blood Pressure measurements and Carotid Intima Media Thickness in hemodialysis patients. Ther Apher Dialy. 2009;13:288-93.
16. De Boer IH, Kestenbaum B, Schoben AB, Michos ED, Sarnak MJ, Siscovick DS. 25(hydroxy) vitamin D levels inversely associate with risk for developing coronary artery calcification. J Am Soc Nephrol. 2009;20:1805-12.
17. Kitiyakara C, Gonin J, Massy Z, Wilcox CS. Nontraditional Cardiovascular disease risk factors in end stage renal disease:Oxidative stress and hyperhomocysteinemia. Curr Opin Nephrol Hypertens. 2000;9:477-87.
18. Maggi E, Bellazzi R, Falaschi F, et al. Enhanced LDL oxidation in uremic patients: an additional mechanism for accelerated atherosclerosis? Kidney Int. 1994;45:876-83.
19. Cottone S, Lorito MC, Riccobene R, et al. Oxidative stress, inflammation and cardiovascular disease in chronic renal failure. J Nephrol. 2008;21:175-9.
20. Fjisawa M, Haramaki R, Miyazaki H, Imaizumi T, Okuda S. Role of lipoprotein(a) and TGF-beta 1 in atherosclerosis of hemodialysis patients. J Am Soc Nephrol. 2000;11: 1889-95.
21. Papagianni A, Kalovoulos M, Kirmizis D, et al. Carotid atherosclerosis is associated with inflammation and endothelial cell adhesion molecules in chronic haemodialysis patients. Nephrol Dial Trasplant. 2003;18:113-9.
22. Polak JF, Pencina MJ, Pencina KM, O'Donnel CJ, Wolf PA, D'Agostino RB. Carotid wall Intima Media Thickness and Cardiovascular Events. N Engl J Med. 2011;365: 213-21.
23. Riccioni G, D'Orazio N, Palumbo N, et al. Relationship between plasma antioxidant concentrations and carotid intima- media thickness: the asymptomatic carotid atherosclerotic disease in Manfredonia study. Eur J Cardiovasc Prev Rehabil. 2009;16:351-7.
24. Coll B, Betriu A, Martinez Alonso M, et al. Cardiovascular risk factors underestimate atherosclerotic burden in chronic kidney disease: usefulness of non-invasive tests in cardiovascular assessment. Nephol Dial Transplant. 2010;25:3017-25.

Correspondence to:
Monir Sadat Hakemi, MD
Department of Nephrology, Dr Shariati Hospital, North Kargar Ave, Tehran 1411413137, Iran
Tel: +98 21 8822 0033
Fax: +98 21 8490 2469
E-mail: mhakemi@sina.tums.ac.ir

Received October 2011
Revised January 2012
Accepted January 2012