Arch Nephrol Urol 2019; 2 (2): 052-061 DOI: 10.26502/anu.2644-2833009

Research Article

Carotid Artery Intima-Media Thickness and Heart Valve Calcifications in Hemodialysis Patients with Hyperparathyroidism (A Pilot Study)

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Received: 31 May 2019; **Accepted:** 11 June 2019; **Published:** 17 June 2019

Abstract

Objective: Cardiovascular disease (CVD) is currently the leading cause of morbidity and mortality in patients with end-stage renal disease (ESRD). The aim of this study was to examine carotid artery intima-media thickness (CIMT) and valvular calcification in asymptomatic hemodialysis (HD) patients, to compare them with healthy subjects, and to identify risk factors associated with atherosclerosis.

Materials and Methods: Forty-nine HD patients and age and sex-matched 48 healthy volunteers were enrolled in this study. Right and left carotid intima-media thicknesses (CIMTs) were measured, and echocardiographic evaluation of valve calcification was performed. CaxP product and parathormone (PTH) values were measured from venous blood samples.

Result: The mean CIMT thicknesses were 0.86 ± 0.16 mm in the patient group and 0.61 ± 0.11 mm in the control group. Mean CIMT was significantly higher in the patient group ($p < 0.001$) and valve calcification was measured as

53% in the patient group. Aortic valve calcification in 22.5%, mitral valve calcification in 18.3%, and calcification in both valves in 12.2%. The rate of valve calcification in the control group was 10.4%. In the HD group, the mean PTH level was 578.2 pg/ml and in the healthy control group was 36.2 pg/ml. The CaxP product was significantly higher in the dialysis group than in the control group ($p < 0.001$) (53.9 ± 11.5-33.6 ± 4.1, respectively). PTH value and CaxP product height correlated significantly with valve calcification and CIMT.

Conclusion: CIMT was more prominent as a sign of atherosclerotic development in HD patients and valve calcification was more frequent. In addition to classical risk factors, we have concluded that the uremic environment may contribute to an acceleration in the atherosclerotic process.

Keywords: Hemodialysis; Carotid intima-media thickness; Valvular calcification; Parathormone; CaxP product

1. Introduction

Chronic kidney disease (CKD) is diagnosed when there is evidence of kidney damage and /or reduced kidney function for more than 3 months [1]. Renal replacement therapies (RRT) such as dialysis or renal transplantation are necessary to maintain the survival of patients with chronic renal failure (CRF) when the creatinine clearance falls below 10 ml /min. CKD is a global health burden estimated to affect about 10% of the adult population [2-5]. Despite the advances in dialysis technology, the risk of mortality in dialysis patients is about 10 times higher than in the general population [6-7]. Cardiovascular diseases (CVD) are the most important cause of mortality and morbidity in hemodialysis patients and account for about half of all deaths [6-7]. In patients with end-stage renal disease (ESRD), the risk of developing cardiovascular events is 3.5- to 50-fold greater than in the normal population [8-9]. The development of CVD in chronic renal failure is a complex mechanism, but one of the most important causes is atherosclerosis and valvular dysfunctions. ESRD is associated with hyperphosphatemia, hypocalcemia, and secondary hyperparathyroidism, which can lead to osteopenia and progressive vascular calcifications [10-12]. Patients with end ESRD have long been observed to have early vascular and valvular calcification [13-16] and to be an important predictor of calcium-phosphorus metabolism at the rate of aortic valve disease progression in hemodialysis patients [17-19]. In cohort studies, valve calcifications have been shown to be associated with increased cardiovascular mortality and morbidity and poor prognosis in dialysis patients. The aim of our study was to evaluate echocardiography of valve calcifications causing CIMT and valve dysfunction in patients undergoing HD therapy. And to investigate their association with mineral balance impairments such as Ca, P, PTH except for classical risk factors.

2. Methods

In this prospective study, patients who underwent hemodialysis for at least three months, who were followed-up with CRF in our hospital between February 2018 and June 2018 were included in the study. We excluded the following patients from the study: known coronary artery disease, atrial fibrillation, congestive heart failure, a left ventricular ejection fraction (LVEF) of <%50, pericardial disease, chronic pulmonary disease, or pulmonary

hypertension (pulmonary arterial systolic pressure of >50 mmHg; patients with prosthetic valve, patients followed for malignancy. After the exclusion criteria, 49 patients who regularly received HD therapy for three days a week were included in the study. The control group consisted of 48 age and sex-matched healthy subjects. The medical history and physical examination findings of all patients were obtained and recorded. Age, gender, duration of illness, treatment received (acetylsalicylic acid, insulin, renin-angiotensin-aldosterone inhibitors, calcium channel blockers and beta blockers) were questioned. The body size of the patients, pre and post-dialysis body weight, HD duration and fluid withdrawal were calculated. Routine haematological and biochemical parameters of the patients and the control group were measured. Local ethics committee approval for the study was obtained. After the patients read and signed the informed consent form, they were included to study.

2.1 Echocardiographic examination

Echocardiographic data sets were obtained by using an EPIQ 7 echocardiography device (Philips, Amsterdam, Netherlands). As suggested by the American Society of Echocardiography, the measurements were made in the left lateral position. Ejection fraction (EF) was calculated by the Simpson method. Left and right ventricular end-diastolic diameters, left and right atrial diameters were measured by M-mode and 2D echocardiography techniques [20]. The aortic valve calcification grade was assessed visually according to the standard visual scoring method (including over-thickening of all valves with mild calcification and calcification) [21]. 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. 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.

2.2 Laboratory measurements

After 12 hours of fasting, blood samples were obtained from the antecubital vein. Complete blood counts were analyzed in our hospital laboratory. The venous blood sample obtained for biochemical examinations was centrifuged at 3000 rpm. They were held at -80°C until the time of analysis. Biochemical analyses were performed on the Abbott Ci-8200 (Illinois, USA) device and full blood counts were performed on the Sysmex XN-1000 (Tokyo, Japan). All analyses were performed by a laboratory technician who did not have patient data. The following parameters were measured in biochemical analysis: C-reactive protein (CRP), thyroid-stimulating hormone (TSH), parathormone (PTH), fasting blood sugar, creatinine, albumin, total protein, sodium, potassium, calcium, phosphorus, blood urea nitrogen (BUN), total cholesterol, low-density lipoprotein (LDL), very low-density lipoprotein (VLDL), high-density lipoprotein (HDL) and triglycerides. Calcium value corrected according to the following formula. Corrected Ca = Measured total Ca + [0.8 × (4.0-patient's albumin level)]. Then the value of the CaxP product was measured. Haemoglobin, hematocrit, red cell distribution width (RDW), thrombocyte count, platelet distribution width (PDW), white blood cell count (WBC), neutrophil count, lymphocyte count were measured in the full blood count.

2.3 Statistical analysis

For the analysis of the data, the package program SPSS 18.0 (Statistical Package for Social Sciences-SPSS, Inc. Chicago, Illinois, USA) was used. Categorical variables were expressed as a percentage, while numerical variables were expressed as arithmetic mean ± standard deviation (SD). One-Sample Kolmogorov-Smirnov test was used to evaluate the normal distribution of numerical variables. The linear relationship between the parameters with normal distribution was assessed using the Pearson correlation test. Spearman correlation test was used among those who did not have a normal distribution. Student's t-test was used for the parameters with normal distribution to assess differences between the groups. Mann Whitney U test was used for those with no normal distribution. In the case of $p < 0.05$, the results were considered statistically significant.

3. Results

Forty-eight consecutive healthy subjects (control group) who applied to the outpatient clinics of Cardiology and Internal Medicine and 49 dialysis patients (dialysis group) who were receiving treatment in the hemodialysis unit and who met the study criteria were compared and analyzed in this study. Both groups were statistically similar in age, height, body weight and waist circumference. Patients' HD start-up times ranged from 6 to 29 months and the mean duration of dialysis was 56 ± 33 months. Diabetes mellitus was present in twenty-two patients (45%) and hypertension was present in 17 patients (35%). The demographic and clinical characteristics of the evaluated groups are shown in Table 1.

Age	**HD group (n=49)**	**Control group (n=48)**	**P value**
	60 ± 14.0	59 ± 13	0.356
Male/female n (%)	32 /17 (65/ 35)	32/16 (67/33)	0.901
DM n (%)	22 (45)		
HT n (%)	17 (35)		
Weight, kg)	65 ± 17.3	66 ± 15	0.264
Body mass index, kg/m^2	27 ± 6.3	28 ± 5.9	0.806
Dialysis duration, months	56.2 ± 30.2		
Amount of fluid withdrawn during HD, ml	2452 ± 1125		

Data are presented as mean ± standard deviation or n (%); HD-Hemodialysis

Table 1: Demographic and clinical data.

Patients with chronic renal failure aetiology; (28%) had hypertensive nephropathy, five (9.2%) had glomerulonephritis, two (3.6%) had obstructive nephropathy and 15 (28%) patients had no known aetiology. Subsequently, the valve calcifications in the dialysis group were distinguished only as aortic, mitral and both aortic and mitral calcifications according to the valve that was held. Eleven patients with only aortic calcification, 9 with mitral calcification, and 6 with aortic and mitral calcification were seen after this distinction. We compared the

patients with each other and the control group in this way. In the control group, 6 calcific valves were detected. The result was statically significant. The presence of valvular calcification between hemodialysis patients and control groups is shown in Table 2.

	HD Group (n=49) (F/M)	**Control Group (n=48) (F/M)**	**p-value**
No calcification	23 (10/13)	43 (15/28)	<0.001
Calcification exists	26 (7/19)	5 (1/4)	<0.001
%	53%	10.4%	

n-number of persons; F-female; M-male

Table 2: Presence of valve calcification in hemodialysis and control groups.

In the CIMT evaluation, the dialysis group had a mean of 0.86 ± 0.16 cm, and the control group had a mean of 0.61 ± 0.11 cm. This difference was statistically significant (p <0.001). There was also a significant difference between the LVEDD, LVESD, LVEF and wall thicknesses of the groups. The comparison of CIMT values and echocardiographic measurements between hemodialysis patients and control groups is shown in Table 3.

	HD group	**Control group**	p value
LVEF (%)	56.07±7.46	62.54 ± 2.02	<0,001
LVEDD	5.00 ± 0.46	4.63 ± 0.34	<0,001
LVESD	3.41 ± 0.47	3.13 ± 0.47	0,013
IVS	1.41 ± 0.38	0.97 ± 0.19	<0,001
PW	1.32 ± 0.29	0.93 ± 0.16	<0,001
CIMT	0.86 ± 0.16	0.60 ± 0.11	<0,001

Data are presented as mean ± standard deviation or n (%); LVEF-Left ventricular ejection fraction; IVS-Interventricular septum; PW-Posterior wall; LVEDD-Left ventricular end-diastolic diameter; LVEsD-Left ventricular end-systolic diameter; CIMT-Carotid intima-media thickness

Table 3: Echocardiographic measurements and CIMT.

Serum PTH levels were 578. 21 ± 453. 45 pg/ml in dialysis patients and 36 ± 5.72 pg/ml in the control group. The patient group was statistically significantly higher (p <0.001). Corrected Ca and phosphorus product was found to be significantly higher in the dialysis group (53.92 ± 11.59 mg2 / dl2, 33.62 ± 4.17 m2 / dl2, respectively). As expected, urea and creatinine values were higher in the HD group than in the control group. The laboratory findings are shown in Table 4.

	HD group	Control group	p value
Htc	34.84 ± 3.73	42.00 ± 7.25	<0.001
Hb	11.45 ± 1.26	13.89 ± 1.57	<0.001
PLT	174.82 ± 61.50	289.04 ± 91.44	<0.001
WBC	7.16 ± 2.47	7.84 ± 2.58	0.131
Glukoz	127.43 ± 47.11	110.22 ± 8.50	0.375
Üre	123.51 ± 30.39	34.99 ± 41.78	<0.001
Kreatinin	6.56 ± 2.30	0.97 ± 1.12	<0.001
CaXP	53.92 ± 11.59	33.62 ± 4.17	<0.001
CRP	12.15 ± 16.76	7.78 ± 14.72	0.010
PTH	578.21 ± 453.45	36.26 ± 5.72	<0.001

Table 4: The laboratory values.

4. Discussion

Chronic renal failure is a common public health problem with significant morbidity and mortality. CRF is defined as the continuation of structural and/or functional abnormalities of the kidney for 3 months. More than two million people around the world are receiving dialysis therapy or kidney transplantation to survive. This number is thought to represent only 10% of people in need of treatment [22]. The most important morbidity and mortality of chronic renal failure are cardiovascular diseases. Dialysis patients are at increased risk for cardiovascular disease when compared to similar age and community [23]. The risk of high cardiovascular events in Chronic Kidney Disease (CKD) cannot be explained solely by traditional risk factors. In these patients, vascular damage occurs due to classical risk factors as well as disease-specific impaired mineral balance (Ca, P, PTH, D vitamin abnormalities). Arterial stiffness due to vascular and visceral calcification due to Ca-P metabolism disorders, atherosclerosis, abnormal bone turnover or direct toxicity of PTH initiates cardiovascular events [24]. Vascular calcification is a common pathology in diseases such as CKD, DM, HT and atherosclerosis with endothelial damage. Coronary artery calcification is associated with clinical manifestations of CVD; such as coronary atherosclerosis, unstable plaque and myocardial infarction [25]. Vascular calcification mechanisms are an active process. Effective mechanisms in this process include; vascular smooth muscle cells differentiate into osteoblast-like cells and initiate mineralization, abnormal bone turnover, secondary hyperparathyroidism, or increased Ca-P production through excessive calcium uptake [26]. Increased serum Ca-P product and hyperphosphatemia in patients with chronic renal failure are important contributors to the increased incidence of arterial calcification and cardiovascular events. Hyperphosphatemia increases serum PTH and bone loss by accelerating the progression of secondary hyperparathyroidism. High PTH stimulates increases in intracellular calcium and abnormal lipid metabolism that cause soft tissue calcifications. Bone losses induced by phosphate and PTH also increase Ca-P products [27]. Recently, it has become possible to detect subclinical atherosclerotic lesions by echocardiography of CIMT.

Previous cross-over studies in different populations have shown that CIMT is associated with cardiovascular event prevalence and risk factors [28-29]. In addition, some studies have shown that CIMT as a marker of atherosclerosis in hemodialysis patients is significantly thicker than age-matched healthy subjects [30-31].

Aortic valve calcification (AVC) or mitral annulus calcification (MAC) is thought to be a chronic but non-inflammatory degenerative process predominantly in elderly patients [32]. The most important factor predisposing to cardiac valve calcification, which is highly prevalent in dialysis patients, is hyperparathyroidism, which causes conditions such as hyperphosphatemia, hypercalcemia, increased Ca-P product [33]. Relationships between valve calcification, inflammation, carotid atherosclerosis and arterial calcification indicate that valve calcification is indicative of atherosclerosis and arterial calcification in ESRF patients. In some studies, foam cell groups representing early atherosclerotic lesions were seen on aortic and mitral valves of patients with coronary atherosclerosis. In large population studies, common risk factors such as age, hypertension, hyperlipidemia and diabetes have been observed for valve calcification and atherosclerosis. Lipoprotein accumulation, macrophage and T cell infiltration, tissue remodelling and angiogenesis are common pathogenesis in atherosclerosis and valve calcification. Valvular calcifications suggest that it may show the presence of atherosclerosis [34-35]. In cohort studies, aortic valve and mitral annulus calcification are associated with increased cardiovascular mortality and morbidity, while vascular or valve calcification is a poor prognostic indicator in dialysis patients [36]. In this study, CIMT and valve calcifications correlating with the risk of cardiovascular disease in dialysis patients were compared with healthy subjects. We also compared the relation with PTH and Ca × P levels. Elevated CIMT values and valvular calcifications associated with atherosclerosis in HD patients showed a positive correlation with serum calcium-phosphorus products and PTH value.

In conclusion, in this study, it was shown that CIMT of patients with chronic HD was thicker than the normal population. In addition, it is seen that valve calcification, which is another cardiovascular risk indicator, is more than a healthy group. This may be due to PTH elevated by uremic conditions in addition to classical risk factors in HD patients. This contributes to increasing the frequency of CIMT increase and valve calcificationLarge-scale randomized prospective studies are required to determine the clinical importance of these findings.

Limitations

The main limitation of our study is the relatively low number of patients. Patients with coronary artery disease (CAD) confirmed by coronary angiography without study were excluded. However, the study population had CAD equivalents such as CKD and diabetes mellitus. In these patients, the absence of CAD was not confirmed by coronary angiography. In addition, neurohormonal profile, inflammation and oxidative stress levels that may affect the development of atherosclerosis have not been evaluated. Another limitation is that it is an observational and cross-sectional study so the results may not be adaptable to the general population.

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Citation: Isa Ardahanli, Mehmet Serdar Cengizhan, Mehmet Celik, Saadet Kader, Mustafa Akarslan, Mumtaz Takir. Carotid Artery Intima-Media Thickness and Heart Valve Calcifications in Hemodialysis Patients with Hyperparathyroidism (A Pilot Study). Archives of Nephrology and Urology 2 (2019): 052-061.