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CORONARY ARTERY CALCIFICATION IN PATIENTS UNDERGOING RENAL REPLACEMENT THERAPIES

RENAL REPLASMAN TEDAVİSİ GÖREN HASTALARDA KORONER ARTER KALSİFİKASYONU

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ABSTRACT

Objective: Cardiovascular disease (CVD) is a common cause of morbidity and mortality both in patients undergoing dialysis and in transplant recipients. The presence of calcified coronary lesions, as can be determined and quantified by electron-beam computed tomography (EBCT), is closely correlated with the extent and severity of angiographically documented atherosclerotic lesions. In the present study, coronary artery calcifications (CAC) were measured and compared in hemodialysis (HD) patients and in transplant recipients and their correlation with other patient characteristics was assesed.

Materials and methods: Twenty-three (13 males, 10 females; mean age: 47.1±12.3 years) patients on chronic HD therapy and 15 (9 males, 6 females; mean age: 36.3±10.0 years) transplant recipients were included in the study. Traditional risk factors of CVD, serum calcium, phosphorus, and calcium-phosphorus ion product, duration of renal replacement therapy, and quantification of CAC were measured.

Results: Chronic HD patients had significantly higher levels of age, serum phosphorus, serum calcium-phosphorus ion products, total cholesterol, CAC scores and had higher frequency of smoking compared to the transplant recipients. However, hypertension and serum HDL-cholesterol levels were significantly low in this group. Moreover, CAC scores correlated with serum phosphorus and calcium-phosphorus ion products (r=0.511, P=0.013) in HD patients.

Conclusions: High CAC and elevated serum calcium-phosphorus product in the patients on chronic HD seems to be associated with the development of coronary artery calcification in these patients.

Key words: Coronary artery calcification, electron beam computed tomography, hemodialysis, renal transplantation

ÖZET

Amaç: Diyalize giren ve renal transplantasyon geçiren hasta gruplarında kardiyovasküler hastalıklar mortalite ve morbiditenin en sık nedenidir. Elektron-beam bilgisayarlı tomografi (EBBT) ile ölçülen kalsifiye koroner lezyonları anjiografik olarak belgelenmiş aterosklerotik lezyonların şiddeti ve tutulumu ile koreledir. Bu çalışmada hemodiyalize giren ve renal replasman geçiren hastalarda EBBT ile koroner arter kalsifikasyon skorunun (KAKS) saptanması ve KAKS değerlerinin hemodiyaliz ve transplantasyon grupları arasında karşılaştırılması ve diğer hasta özellikleri ile korelasyonunun araştırılması amaçlandı.

Gereç ve yöntem: Kronik hemodiyaliz tedavisinde olan 23 hasta (13 erkek, 10 kadın; ortalama yaş: 47,1±12,3 yıl) ve renal replasman tedavisi uygulanmış 15 hasta (9 erkek, 6 kadın; ortalama yaş: 36,3±10,0 yıl) çalışmaya alındı. Kardiyovasküler hastalıklar için geleneksel risk faktörleri, serum kalsiyum, fosfor ve kalsiyum-fosfor çarpımı, renal replasman tedavi süresi ve KAKS ölçüldü.

Bulgular: Kronik hemodiyaliz hastalarında yaş, serum fosfor, kalsiyum-fosfor çarpımı, total kolesterol, KAKS ve sigara kullananların oranı renal replasman tedavisinde olanlardan anlamlı olarak daha yüksekti. Bununla birlikte, bu grupta hipertansif olanların oranı ve serum HDL kolesterol düzeyi anlamlı olarak daha düşük saptandı. Yine hemodiyaliz hastalarındaki KAKS, serum fosfor ve kalsiyum-fosfor çarpımı ile korele idi (r=0,511, P=0,013).

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Sonuç: Bu çalışmanın sonuçlarına göre kronik hemodiyaliz hastalarında koroner arter kalsifikasyon gelişiminden kalsiyum-fosfor çarpımı yüksekliği sorumlu görünmektedir.
Anahtar kelimeler: Koroner arter kalsifikasyonu, elektron-beam bilgisayarlı tomografi, hemodiyaliz, renal transplantasyon

INTRODUCTION

Cardiovascular complications are still the leading cause of death in patients with end-stage renal disease (ESRD) (8). The cardiac mortality of dialysis patients is 10-15 times greater than the general population and according to the US Renal Data System, cardiovascular disease (CVD) is the most common cause of death in renal transplant recipients (5,8,14).

Traditional CVD risk factors for the general population are advanced age, gender, obesity, presence of hypertension, diabetes mellitus, dyslipidemia, smoking, family history of ischemic heart disease, and physical inactivity (6). Besides these factors, ESRD patients have further atherogenic factors leading to accelerated atherosclerosis and coronary artery disease. Among these factors are dyslipidemia of renal disease which is mainly due to dysfunction of key lipid metabolic enzymes; elevation of fibrinogen, lipoprotein (a) and homocysteine as well as malnutrition, inflammation, and secondary hypertension (4, 6, 7).

According to the latest studies, high serum phosphorus concentration and high values for the calcium-phosphorus ion product in the serum are independent risk factors for death in ESRD patients (6). These factors are thought to influence process of calcium deposition in arterial walls leading to coronary artery calcification (6, 7,10).

Electron-beam computed tomography (EBCT) is a new, highly sensitive, noninvasive method of obtaining cross-sectional images of the heart in subsecond scanning times (1, 12, 19). This technique can accurately detect and quantify even small areas of coronary artery calcification (CAC), an established marker for atherosclerosis and coronary artery disease (1, 11). In the present study, CAC scores were measured in the hemodialysis (HD) and renal transplant recipients using EBCT. Traditional risk factors of CVD, duration of renal replacement therapy, serum calcium, phosphorus, and CAC were compared among these renal replacement modalities.

MATERIALS and METHODS

The study design is cross-sectional. All of the patients were treated at our centre.

Patients

Twenty three (13 males, 10 females; mean age: 47.1±12.3, range: 27-64 years) HD patients and 15 (9 males, 6 females; mean age: 36.3±10.0, range: 16-51 years) renal transplant recipients, who were asymptomatic for coronary artery disease were included in the study. All the patients signed informed consent before enrollment.

The causes of ESRD were as follows: chronic glomurelonephritis (7 pts), chronic pyelonephritis (8 pts), autosomal dominant polycystic kidney disease (4 pts), hypertensive nephrosclerosis (2 pts), diabetic nephropathy (3 pts), reflux nephropathy (4 pts), and unknown (10 pts).

Hemodialysis

Bicarbonate HD was performed three times weekly for four hours using hollow fiber dialyzers in a single center. Six (40%) of the renal transplant recipients had received their grafts from cadavers and the others (9.60%) had received theirs from living (7, -related; 2, -unrelated) donors and had been using triple immunosuppression consisting of cyclosporine A, azathioprine, and prednisolone combination or cyclosporine A, mycophenolate mofetil, and prednisolone. Only one recipient was administered FK506, mycophenolate mofetil and prednisolone combination. All of the patients were transplanted for the first time.

Risk factors

Traditional CVD risk factors including age, gender, body mass index (BMI), smoking, diabetes mellitus, and hypertension were recorded for every patient. Smoking referred to current smoking and history of smoking together. Duration of renal replacement therapy in the two groups were estimated based on a review of medical files. It was estimated as the time period (months) from the start of HD till the EBCT was performed in the HD group. In the transplantation group, the time period from the day of transplantation till the performance of EBCT was calculated as the duration of renal replacement therapy. Furthermore, the duration of prior dialysis was recorded in the transplantation group.

Biochemical parameters

Biochemical parameters such as serum calcium, phosphate, total cholesterol, triglyceride, very low-density lipoprotein (VLDL) cholesterol, high-density lipoprotein (HDL) cholesterol were measured monthly with automated methods while low-density lipoprotein (LDL) cholesterol levels were calculated according to Friedewald formula (LDL- cholesterol = total cholesterol – ([triglyceride/5] + HDL-cholesterol) when triglyceride levels were less than 4.5 mmol/L and were represented as the mean of last six measurements.

Electron beam computed tomography

All imaging procedures were performed simultaneously with a GE-Imatron C-150XP Scanner without contrast medium. Forty axial slices with a distance of three milimeters between each slice were obtained during a single breath hold. The imaging began at the level of aortic root and proceeded to the level of the cardiac apex. The scan time was 100 ms per slice and was senchronized with electrocardiography. Images were reconstructed with the use of 260-mm field of view, a matrix of 512 by 512 and a sharp reconstruction filter. A significant CAC was defined as a minimum of two adjacent pixels with a density over 130 Hounsfield units. As originally described by Agatston et al (1), the degree of CAC was then calculated

by multiplying the area of each calcified lesion by a weighting factor corresponding to the peak pixel intensity for each lesion to yield a lesion specific calculation score. The sum of the scores for all arterial lesions provided an overall CAC score for each subject (1). Image quality and scoring were assessed by one experienced radiologist who was blinded to the clinical and laboratory results of the patients.

Statistical analysis

The categorical variables are presented as frequency and percentage, and the continuous data are reported as means ± SD. The comparisons between the two groups were made with Mann-Witney Test and Chi-Square Test. P values < 0.05 were accepted as significant. In each group, CAC score and its correlation with the other parameters was assessed by Pearson Correlation. P < 0.05 was considered significant for correlation.

RESULTS

When comparing the traditional CVD risk factors among the two groups, no significant difference was found for BMI and gender. Smoking and advanced age were significantly different among the groups (P<0.001, P=0.014). Hypertension and HDL-cholesterol were significantly high in the transplant recipients (P=0.037, P<0.001) (Table 1). There were only three (13%) diabetic patients in the HD group. There were not any diabetic patients among the transplant recipients.

The results of the biochemical parameters of the groups are presented in Table 1. Serum phosphorus and calcium-phosphorus ion product were significantly higher in the HD patients than those in the transplant patients (P<0.001, P<0.001). The mean durations of renal replacement therapy in the HD patients and transplant recipients were 65.7±52.1 (range: 3 to 174), and 52.4±41.5 (range: 3 to 111) months, respectively. The difference among the two groups was not statistically significant.

The mean coronary artery calcification scores of the HD and transplantation groups were 1020.9±1682.5 and 188.6±389.0, respectively. The CAC score of the HD group was significantly higher than that of the transplantation group (P = 0.041) (Figure 1).

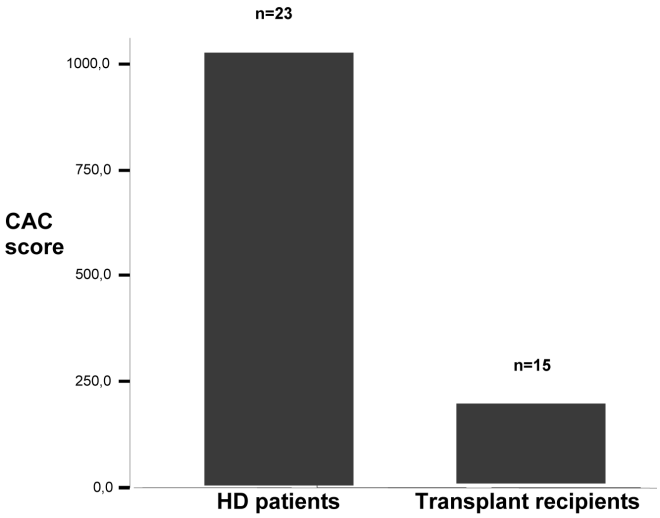

Figure 1. The CAC score of HD and transplantation groups. HD: hemodialysis, CAC: coronary artery calcification.

Table 1. The CVD risk factors and biochemical parameters

Variables	HD Patients (n=23)	Transplant recipients (n=15)	P
Gender (n; Female / Male)	10/13	6/9	0.832
Age (year)	47.1±12.3	36.3±10.0	0.014
Smoking (n,%)	17 (73.9)	2 (13.3)	<0.001
Hypertension (n, %)	6 (26.1)	9 (60.0)	0.037
Sistolic pressure (mmHg)	121.7±20.7	125.3±21.6	0.637
Diastolic pressure (mmHg)	78.1±12.7	80.6±10.8	0.703
Body mass index (kg/m^2)	22.1±3.8	22.9±4.3	0.497
Serum calcium (mmol/L)	2.25±0.23	2.42±0.07	0.064
Serum phosphorus (mmol/L)	2±0.68	1±0.19	<0.001
Serum Ca-P ion product (mmol^2/L^2)	4.48±11.44	3.07±2.5	<0.001
Serum cholesterol (mmol/L)	4.03±1.3	5.02±0.8	0.006
Serum triglyceride (mmol/L)	2.07±1.2	2.02±1.0	0,791
Serum LDL-cholesterol (mmmol/L)	2.19±1.0	2.66±0.6	0,089
Serum HDL-cholesterol (mmol/L)	0.85±0.2	1.39±0.5	<0.001
Serum VLDL-cholesterol (mmol/L)	0.98±0.6	0.91±0.5	0.768
Duration of therapy (months)	65.7±52.1	52.4±41.5	0.616
Calcification score	1020.9±1682.5	188.6±389.0	0.041

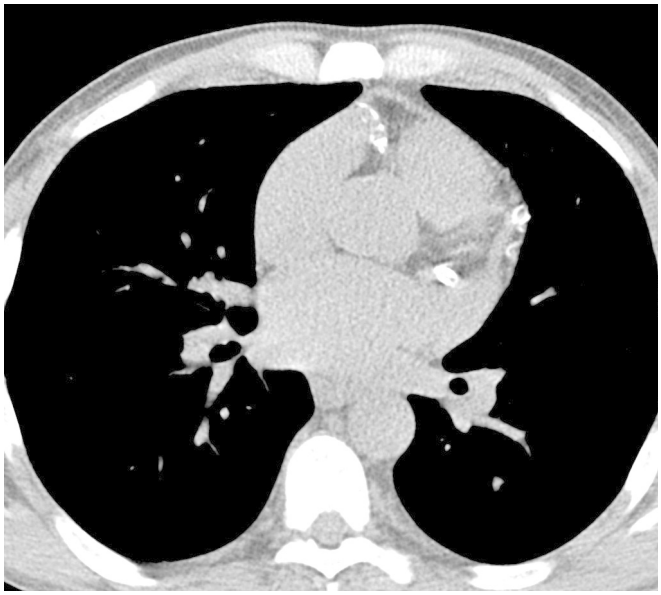

Figure 2. Calcified left anterior descending coronary artery, left circumflex artery, and right coronary artery.

There were six (26%) patients in the HD and nine (60%) patients in the transplantation groups without any CAC. The highest CAC score was recorded in a HD patient as 5644.1. There were calcified lesions in the left anterior descending artery, in the circumflex artery, and in the right coronary artery. The EBCT image of this patient (35 year old male with chronic glomerulonephritis and a calcium-phosphorus ion product of 5.29) is presented in Figure 2.

The correlation between CAC scores and biochemical parameters were analyzed in each group. Only serum phosphorus and calcium-phosphorus ion product was correlated with CAC score in the HD group (r=0.519, P=0.011 and r=0.511, P=0.013). In the transplantation group, age had a significant correlation with the CAC scores (r=0.636, P=0.011). Duration of renal replacement therapy had no correlation with the CAC scores in either group.

DISCUSSION

Cardiovascular risk is more pronounced in patients with ESRD. CVD accounts for premature deaths in more than 50% of patients undergoing dialysis (10). Even after transplantation, the risk of death is >5-fold than of age-matched general population (9). Traditional risk factors for CVD can not explain this increased mortality. Significant calcification of the heart and vascular system in ESRD patients is highly prevalent and is especially important for cardiovascular morbidity and mortality (3). Moreover CAC is used as an independent risk factor for coronary artery disease when assessing a patient's risk of disease (15). Coronary artery calcification is seen in the general population only when there is significant atherosclerosis. However, recent reports demonstrated extensive CAC in dialysis patients (2, 7,16).

Renal patients' data comparing CAC in renal transplant recipients and HD patients with each other are scarce (10). Our study population consisted of these treatment groups.

EBCT, a well established method for detecting CAC, has been proposed as a non-invasive method to predict coronary artery disease (3, 20). The use of EBCT allows precise quantification of vascular calcification than plain X-ray films (11).

In a series of 205 HD patients, Raggi et al (16) demonstrated CAC in 83% of the patients (average age 56.8) by EBCT. We also demonstrated that 73.9% of our HD group (mean age 47) had CAC. Smoking and serum lipid concentrations did not correlate with CAC, whereas serum phosphorus, calcium and calcium x phosphorus product did in Raggi's study (16). Similarly, we could not demonstrate any other correlation between CAC and biochemical and demographic parameters other than serum calcium-phosphorus ion product in the HD group. Braun et al (2) could not demonstrate any correlation between CAC and duration of HD similar to our findings. Goodman et al (7) could show that the degree of calcification correlated with the duration of dialysis. In that study, the mean duration of dialysis was 13 years in the patients with CAC and two years in those without calcification. On the other hand, Tamashiro et al (18) had found a correlation between high serum triglyceride and low HDL-cholesterol levels and progression of CAC among 24 adult HD patients.

Oh et al (13) demonstrated that the severity of CAC was more prominent in the dialysis group than that in the transplanted patients in a young population. In our study, HD patients had the highest CAC score. Goodman et al (7) demonstrated in a group of 39 dialysis (21 continuous cycling PD and 18 HD) patients that there was no significant difference between the proportion of PD patients among those with or without CAC; but they found that 13 of 27 patients who had undergone renal transplantation had coronary artery calcification, whereas only one of 12 patients who had not undergone transplantation had calcification, indicating longer duration of renal replacement therapy is an important factor for CAC.

Traditional CVD risk factors correlated with CAC in renal transplant recipients. Raggi et al (17) showed that age was the only significant predictor of aortic and coronary artery calcium among non-uremic patients. All transplantation candidates were evaluated for coronary artery disease and those without any symptoms are questioned for CVD risk factors. It could be suggested that patients with risk factors may be scanned with EBCT since the degree of coronary artery disease in those patients with occlusive atherosclerosis is linked to CAC score (9). Moreover CAC score correlates with total plaque amount and maximal stenosis in epicardial arteries (18).

Limitation of our study: It was small, cross-sectional and non-randomised study. There were differences of age between the groups and lack of screening for CAC at the time of initiation of renal replacement therapy.

In conclusion, these cross-sectional small scale studies only point out to the importance of calcium and phosphorus metabolism in CAC; so large scale prospective studies are required to analyse the effect of different modalities of renal replacement therapies on CAC.

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