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Orginal Article

Comparıson of Atherosclerotıc Rısk Factors and Coronary Artery Calcıfıcatıon Scores in Contınous Ambulatory Perıtoneal Dıalysıs and Hemodıalysıs Patıents

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Abstract

Background. Patients with chronic renal failure (CRF) are significantly susceptible to atherosclerosis. Even dialysis itself may accelerate atherosclerosis. Studies comparing the atherogenicity of dialysis modalities are few and the findigs are controversial.
Methods. The aim of this study was to investigate and to compare the traditional atherosclerotic risk factors and homocysteine (Hcy) levels with coronary artery calcification (CAC) scores in patients receiving continuous ambulatory peritoneal dialysis (CAPD) or hemodialysis (HD) treatment.
Patients. Seventy-four patients (26 HD, 24 CAPD and 24 controls) were enrolled. Serum triglyceride, total cholesterol, HDL, LDL, Lp(a), CRP, Hcy, calcium, phosporus and iPTH levels were measured in each patient. CAC scores were calculated by the same radiologist in dialysis group by using Multi-Slice Computed Tomography (MSCT).
Results. Serum triglyceride, total cholesterol, LDL, Lp(a), CRP, Hcy, calcium, phosporus and iPTH levels were significantly higher in dialysis patients than those in the control group ($p<0.01$). Moreover, these parameters did not differ significantly between HD and CAPD groups ($p>0.05$).
The median CAC scores for 17 (65.4%) HD and for 15 (62.5%) patients in CAPD group were 632 and 542, respectively. Similarly, there was no statistically significant difference in CAC scores between HD and CAPD patients ($p>0.05$). No coronary artery calcification was detected in the control group. Although serum Hcy levels were at least twice higher in dialysis patients when compared to the control group ($p<0.05$), the mean Hcy levels did not significantly differ between HD and CAPD group. In patients with prolonged dialysis treatment, serum Hcy levels were found to be higher than that of the patients with short dialysis treatment but neither HD nor CAPD modality seemed to be superior to each other ($p>0.05$).
Conclusions. In conclusion, this study revealed that none of the two dialysis methods seems to be less atherogenic. So, these two methods are not competitive but are different modalities which are useful for the management and the rehabilitation of uremic patients. Further studies are warranted to confirm our results.

Keywords: dialysis; homocysteine; coronary artery calcification

Introductıon

Atherosclerotic cardiovascular disease is the most important cause of mortality and morbidity in patients undergoing hemodialysis (HD) and peritoneal dialysis (CAPD) [1]. Cardiovascular mortality rate in chronic renal failure (CRF) is 10-20 fold higher compared to age and sex-matched individuals from the general population [2]. Although the increased mortality rate in CRF is well established, studies comparing the overall survival rate between the two dialysis modalities are few and the results obtained are conflicting. In a recent guideline published by the National Kidney Foundation (NKF), CRF patients are shown in a higher risk group and physicians are strongly recommended to treat every CRF patient as a possible candidate for atherosclerotic heart disease [3].
The deposition of calcium ions in coronary arteries is a "condition sine qua non" of the development of atherosclerotic plaque. Thus, CAC is a well established and widely accepted diagnostic marker of the diagnosis of atherosclerosis. In daily practice, CAC can readily be measured by Electron-Beam Computed Tomography (EBCT) or Multi-Slice Computed Tomography (MSCT). In many clinics throughout the world asymptomatic CRF patients are screened by using these sensitive methods [4]. Data obtained from recent studies showed that more than 90% of atherosclerotic plaques in elderly patients are calcified [5]. CAC has become a reliable indicator to identify the atherosclerotic burden in general population [6]. In many studies CAC scores were found to be positively correlated with histologic, angiographic and ultrasonographic measurements [7]. Moreover, CAC is proposed as an independent predictive factor for cardiac events in both symptomatic and asymptomatic patients [8].
Although several studies have been carried out investigating atherosclerosis and atherosclerotic risk factors in HD and CAPD patients [9], studies comparing both techniques are limited with conflicting results [10-13]. Our aim was to compare the atherosclerotic risk factors and CAC scores between the two groups.

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Patients and methods

Seventy-four patients were enrolled (26 HD, 24 CAPD, 24 controls). Patients with acute or chronic infections, with a history of coronary artery disease, peripheral artery disease, cerebrovascular disease and vascular surgery, those having uncontrolled hypertension and those switched from HD to CAPD were excluded. During the selection of the HD and CAPD patients, we carefully paid attention to the similarity in the blood pressure, duration of the dialysis, body mass index (BMI), smoking and family history of vascular disease between the two groups (Table 1).

Table 1: Demographic features of patients in the study groups.*

	HD (n=26)	CAPD (n=24)	Control (n=24)
Age (Years)	42.8±17.4	42.5±15.5	40.2±18.6
Gender (Female / Male)	9/17	7/17	10/14
Dialysis duration (months)	48	42	-
Smokers (n, %)	5 (20.1 %)	4 (19.8 %)	6 (20 %)
Hypertension (n, %)	8 (30.2%)	7 (29.2 %)	10 (38 %)
Diabetes mellitus (n, %)	4 (14.7%)	5 (20.8%)	5 (18 %)
Family history of vascular disease (n, %)	7 (26 %)	9 (35 %)	11 (41.6 %)
BMI	23.8±4.5	25.1±4.8	24.4±3.8

Values are mean ± SD. p* > 0.05; BMI= Body mass index

Moreover, we selected, among patients receiving either HD or CAPD, the ones with similar atherosclerotic risk factors and biochemical parameters such as lipid profile, Hcy, CRP, Ca, P and intact PTH (iPTH) were selected with great care (Table 2). Serum triglyceride (TG), total cholesterol, HDL, LDL, Lipoprotein (a), C-reactive protein (CRP), Homocysteine (Hcy), calcium, phosphorus and intact Parathormon (iPTH) levels were obtained. CAC scores were calculated by the same radiologist by using MSCT. CAPD patients were treated with 2000 ml standard solutions four times daily (Gambro® glucose solutions 1.5%, 2.5% and 4%). HD patients were undergoing bicarbonate hemodialysis 4-6 hours three times a week. Dialysis membranes were polysulphane with surface area of 1.2 m^2. All HD patients had at least 1.2 Kt/V ratios. In order to evaluate the peritoneal membrane, PET test was used. Plasma dailysate/plasma creatinine ratio was >0.5 for all CAPD patients.

The control group was added and compared. We thought that ıt will be useful to compare CAC scores in the complately healthy people who had similar known atherosclerotic risk factors (smoking, diabetes, BMI age, sex, gender etc.)

Blood was drawn from patients and controls in the morning for biochemical parameters including Hcy. Within 30 minutes Hcy was measured by HPLC method. Values between 5-14µg/ml is accepted as normal. Total CAC scores was calculated from all patients and controls from right coronary, left main coronary, left anterior descending coronary, and circumflex coronary arteries by using MSCT (Aquilion 16 system, Toshiba Medical Systems Corporation, Japan)**. C**a score measurements were made in accordance with the Agatston's Method [14].

Statıstıcal analysıs

Result are displayed as mean ± SD for normally distributed data; those with non-normal distribution are presented as median (range) and (95% confidence interval). Comparision of unpaired data were performed using unpaired T-test for parametric data and Mann-Whitney U-test for non-normally distributed data. Comparisons of more than two sets of unmatched data were performed by one way ANOVA using the Tukey test or Kruskal-Wallis test dependent upon the distribution. Chi-squared test was used to analyse the nominal data. Correlation plots were analysed by linear regression, coefficient of determination was calculated from Pearson correlation. Stepwise linear regression analysis and binary logistic regression analysis was undertaken using SPSS release 12.0 for Windows®.

Results

Seventy-four patients were enrolled. There were no significant difference in age, gender, duration of dialysis, BMI, smoking habits, presence of hypertension and diabetes mellitus between the dialysis groups (p>0.05; Table 1). When compared to the control group, serum TG, total cholesterol, LDL, Hcy, CRP, Lp (a), Ca, P, iPTH levels were higher in dialysis patients (p<0.01), with the exception of lower serum HDL levels. When total cholesterol TG, HDL, LDL, CRF, Lp(a), Hcy, serum Ca, P, iPTH and CAC scores were compared between HD and CAPD patients, no statistically significant difference was found (p>0.05); (Table 2). Both dialysis groups were very well-matched according to the dialysis vintage, serum biochemistry and relevent prescribed medications. Number of patients who are on medications such as vitamin D, non-calcium-based phosphate binders, calcium-based phosphate binders, calcium channel blokers and ACE inhibitors were similar in both groups. Overall, this patient population was characterized with respect to mean time averaged serum phosphate, corrected calcium and calcium x phosphate product.

Table 2: Comparison of the labaratory results of HD and CAPD patients

	HD (n=26)	CAPD (n=24)	Control (n=24)
Trıglyceride (mg/dl)	194.7± 48.9[a]	196.7± 94.8[a]	175.4±27.6[b]
Total cholesterol (mg/dl)	188.4± 36.3[a]	192.5± 61.3[a]	171.5±34.6[b]
HDL (mg/dl)	36.5± 13.4[a]	39.8± 10.4[a]	45.2±8.5[b]
LDL (mg/dl)	119.3± 27.4[a]	113.1± 33.9[a]	98.6±17.2[b]
Hcy (µmol/dl	29.5± 10.4[a]	24.3± 9.7[a]	20.1±9.2[b]
CRP (mg/dl)	19.3± 7.4[a]	16.3± 8.4[a]	10.1±6.3[b]
Lp(a) (mg/dl)	17.6± 7.4[a]	19.6± 8.2[a]	13.2±7.4[b]
Ca^{++} (mg/dl)	9.3± 2.7[a]	10.2± 3.1[a]	8.2±3.3[b]
P (mg/dl)	5.5± 1.1[a]	5.4± 1.3[a]	3.2±0.9[b]
iPTH (pg/ml)	640.2± 113.9[a]	635± 104.2[a]	28.5±14.7[b]
CAC s median-range	632(441-906)[c]	542(317-772)	-----

Different letters indicates statistically significant differences among groups , p<0.05.

CAC scores were significantly higher in HD (65.5%) and CAPD (62.5%) patients than that of the control group ($p<0.05$). Furthermore, the HD group had highest CAC score, median calcification score 632 (range 441-906) compared to CAPD median calcification score 542 (range 317-772) but, it was not statistically significant ($p>0.05$; Table II). Despite having been on renal replacement therapy for prolonged periods of time, 3 CAPD and 4 HD patients did not show any coronary calcification. There was no single statistically significant correlation between zero calcification score and duration of dialysis, serum Hcy, İPTH, Ca, P levels and age of the patients ($p>0.05$). The baseline characteristics of dialysis groups were roughly the same and CAC score was zero in the control group. Although serum Hcy levels were at least twice higher in dialysis patients when compared to the control group ($p<0.05$), the mean Hcy levels did not significantly differ in both HD and CAPD groups ($p>0.05$). In patients with prolonged dialysis treatment, serum Hcy levels were found to be higher than those of the patients with shorter dialysis duration; but neither HD nor CAPD technigues seemed to be superior to each other ($p>0.05$). When the relationship between dialysis duration and CAC scores was investigated, we found out that the more the duration at the dialysis the more CAC score increases. But, there was no single statistically significant difference in serum Hcy levels and CAC scores between the two dialysis groups as well.

Dıscussıon

Cardiovascular diseases are the most important cause of early mortality and morbidity in patients with chronic renal failure [15]. These patients have a high cardiac mortality rate. The recently published guidelines strictly recommend that CRF patients should be treated as a possible candidate for cardiac events. One of the detrimental factors contributing to the high mortality risk in these patients is dyslipidemia. All forms of lipid abnormalities are frequently seen in CRF [16-18]. However most frequently seen lipid disorders are hypertriglyceridemia and decrease in HDL levels. Data from current studies revealed that although dyslipidemia is quite common in HD and CAPD groups rather than in the control groups, no statistically significant difference is found between the twodialysis modalities. The mechanisms by which lipids mediate vascular calcification have recently been explored. In 1994 Sarig *et al*. [19] showed that cholesterol was found located in the center of calcified atherosclerotic plaques by using confocal microscope. This suggested that cholesterol constitutes the core of the calcium mineral crystals. Our findings were not in paralel with the findings of Ozdemir *et al*. [20] who compared the relationship between plasma total cholesterol, LDL, Lp(a) and carotid intima media thickness and found that CAPD patients have a more atherogenic profile than that of the HD patients. However, other studies with similar designs revealed that there is no significant difference between these two techniques with respect to atherogenicity [16,17,21-23]. These findings suggest that the process of atherosclerosis begins early in the predialysis period [18,19].

In this current study, Hcy levels were found to be higher in CRF group than those of control group. There was no statistically significant difference between HD and CAPD groups ($p>0.05$). Recent studies showed that hyperhomocysteinemia is an independent risk factor for coronary artery disease in CRF [24-26]. Furthermore, it was suggested that the increase in serum Hcy levels positively correlated with an increase in atherosclerotic vascular disease [24,27-30]. The incidence of hyperhomocysteinemia is increased in renal failure [24]. A two-to four-fold increase is frequently seen in patients with renal failure [24,31-33]. Although research concerning serum Hcy increase in patients on dialysis treatment is intensively carried out; there is limited number of studies comparing both CAPD and HD, accordingly [34]. In a comparison study it was shown that CAPD patients had lower Hcy levels as compared to HD patients [33]. In our study there was no statistically significant difference between the groups ($p>0.05$).

CAC plays an important role in the developement of atherosclerotic disease and it is an independent risk factor for symptomatic and asymptomatic CAD for patients with renal failure [35,36]. Data observed from several studies revealed that CAC begins in the earlier disease course especially in younger patients undergoing dialysis. This may be due to several factors, including dialysis quality, high serum phosphorus, high Ca x P levels, elevated iPTH, increased inflammatory markers and calcium deposition triggered by the prescription of calcium containing phosphate binders.

In our study, three patients in CAPD and four patients in HD groups showed no calcification, even in those undergoing dialysis for a prolonged period of time. The question here is whether specific and undetected factors protecting these patients from the development of calcification is implicated or not. If so, are they modifiable (medical management of bone and mineral balance and/or lipid management, biochemistry, choice of dialysis and hormonal factors). or non-modifiable factors (i.e. age, gender, genetic factors, diabetic status and residual renal function). The development and progression of vascular calcification is a multifactorial process. Potentially differing factors may exert their maximum influence at either the predisposition, initiation and continuation phase of the process. Further work is required to identify factors promoting progression of vascular calcification in those who are susceptible.

The results of previous studies comparing mortality rates of patients in both groups have been inconsistent [10-22]. Therefore there is still an ongoing debate about the mortality and morbidity rates of the patients on HD or CAPD. Moreover other risk factors, such as comorbidity or nutritional status, might have accounted for different outcomes in patients on PD and in patients on HD, rather than the dialysis modality of choice itself [12,16,17], Two studies comparing PD and HD post-transplant failure have been published [22, 23]. They found that there were no significant differences in survivals between the two groups, although the median survival rates tended to be shorter in the HD group. They concluded that there is no difference in outcomes between patients returning to PD or to HD after renal transplant failure and also, the principal risk factor for patients returning to dialysis seems to be the presence of comorbidity and the specific dialysis modality.

In a study of 5327 patients undergoing percutaneous coronary interventions, Best *et al*.[37], demonstrated that in patients with mild CRF with an estimated creatinine clear-

ance of 50 to 69 ml per minute, there is a>2-fold increase in the 1-year mortality rate (1.5% vs 3.6%). Moreover, the degree of renal dysfunction appeared to be associated with a gradient of risk, because the more severe the CRF, the greater the mortality rate. The risk ratio for death was 1.46 in patients with a creatinine clearance of 50 ml per minute, and 3.7 in patients with a creatinine clearance of 30 ml per minute. The risk ratio for patients undergoing dialysis was 8.91, making CRF one of the most powerful predictors of mortality, with a clear gradient of effect. Another study has similarly demonstrated that CRF is a risk factor for cardiovascular events [38].

Data obtained in this this study suggests that overall patient survival is similar on either modality. Furthermore, in the absence of randomized controlled trials, comprehensive patient description is an absolute prerequisite before outcomes can be compared.

Conclusions

In conclusion, renal failure is an independent risk factor for the development of CAD per se. Dyslipidemia, hyperhomocysteinemia and elevated CAC scores are frequently common in ESRD patients when compared to the general population. Vascular calcification seems to begin earlier than the onset of chronic renal failure and as renal functions deteriorate calcification accelerates. The major factor that determines the severity and frequency of calcification appears to be the renal function. Which dialysis modality is less atherogenic? These two modalities should not be considered as competitive techniques, instead they should be accepted as different methods successfully being used to rehabilitate uremic patients. Thus, all dialysis centers should establish an integrated HD and CAPD programmes in order to improve the poor outcome. To detect the exact onset of clinical atherosclerosis and to understand the influence of dialysis modality on vascular calcification, prospective large, randomized, case-controlled studies are required.

Conflict of interest statement. None declared.

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