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SCREENING OF VALVE CALCIFICATIONS IN HEMODIALYSIS AND PERITONEAL DIALYSIS PATIENTS

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Abstract

Valve calcifications (VC) are a major contributor of increased mortality in dialysis patients. The present study aimed to detect the presence of valve calcifications in peritoneal and hemodialysis patients patients and to evaluate potential risk factors.

Methods:

We conducted a cross-sectional study, enrolling 30 stable pts in peritoneal dialysis (60% males; mean age 57 +/-12.36 years and average duration of dialysis 22.5 +/-10 months) and 34 pts on hemodialysis (58.8% males; mean age mean age 50.8 +/-10.4 years and average duration of dialysis 26.5+/-10.9 months) who were in RRT more than 6 months- up to 36 months. Baseline echocardiography was performed to screen for calcification of valve. RRF was calculated by a standard technique.

Results: Valve calcifications were significantly more frequent in hemodialysis pts (p=0.007). Valve calcifications were found in 10 of pts (33.3%) in PD; mitral valve calcifications; aortic valve calcifications; and both valves calcifications in 8; 7; 5 pts respectively . 24 hemodialysis pts (70.6%) had valve calcifications; mitral valve calcifications; aortic valve calcifications and both valves calcifications in 14;9;9 pts respectively. Significant difference was found between patients on PD and HD for phosphate level [4.3+/-1.29 mg/dl vs 6.17+/-1.08 mg (p<0.001)]; RRF [4.03 +/-2.09ml/min vs 0.62 +/-0.89 ml/min (p<0.001)] and age (p=0.033) The presence of valve calcifications were significantly correlated with phosphate level (r=0,28, p=0.005) and negatively with RRF (r=-304, p=0.004). Multivariable analysis revealed increased age and lower RRF as independent predictors of VC in dialysis patients.

Conclusion:

Our study showed once again that presence of valve calcification is relatively high in dialysis patients. Residual renal function contributes significantly to the maintenance of phosphate balance and may explain the lower prevalence of valve calcification in PD pts in comparison with HD pts during the first years of RRT.

Key words: Valve calcification, Hemodialysis, Peritoneal dialysis, Phosphate, Residual renal function

Introduction

The cardiovascular disease is the primary cause of death in end-stage renal disease (ESRD) patients receiving long-term hemodialysis (HD) and peritoneal dialysis (PD) therapy. Vascular/valve calcifications are also important and highly prevalent complications among ESRD patients including the patients under PD therapy. The increased prevalence of risk factors for atherosclerosis [1], dysregulation of mineral metabolism with a high calcium load and the resulting poor calcium-phosphorus balance are [2], as well as the loss of inhibitors of calcifications are believed to be largely responsible for the excessive valve and vascular calcification in this population. Hyperphosphatemia is a frequent complication in PD patients as it is in HD patients. Several cross-sectional clinical studies have consistently reported a kind of association between hyperphosphatemia and vascular and valve calcification in ESRD patients. It has been linked to vascular calcification and increased cardiovascular mortality in the HD population [3]. Having a serum phosphorus level >1.78 mmol/L was associated with a time-dependent adjusted hazard ratios of 1.6 and 1.4 for all-cause mortality in PD and hemodialysis patients, respectively. Residual

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renal function is one of the key determinants of phosphorus control in PD patients and its importance outweighed that of PD clearance among those with preserved residual kidney function [4]. The more rapid rate of decrease in RRF and its smaller relative contribution to the total small-solute clearance in HD compared with PD patients are likely responsible for the poor data regarding the impact of RRF on phosphate in HD patients. Noordzij *et al.* found that 15% of the HD patients and 12% of the PD patients became anuric during the first 3 years of dialysis treatment, whereas Moist *et al.* reported proportions of 38% and 69%, respectively, during 18 months of dialysis therapy. However, an average of 3 - 4 years is required for incident PD patients to become anuric [5,6]. Based on the above mentioned studies, we aimed to detect the presence of valve calcifications in peritoneal and hemodialysis patients and to evaluate potential risk factors in both PD and HD patients who were on renal replacement therapy (RRT) with duration up to the first 3 years.

Methods

The Study of population: An observational cross-sectional study was conducted in the Dialysis Center of the University Hospital Center "Mother Teresa" from January - April 2012, enrolling all patients on chronic dialysis (HD and PD) older than 18 years. They were clinically stable (with no inflammatory or catabolic illnesses and were not hospitalized within the previous three months except for vascular access revision), and adequately dialyzed. Moreover, all HD patients had native fistulas or arteriovenous grafts, hemodialysed 3 times per week, 4 hours per treatment, with standard bicarbonate-containing dialysate bath, using high-flux dialysis membrane. The PD patients were on 4 - 5 exchanges/day with 2000ml using conventional lactate-buffered glucose-based PD solutions. Hemodialysis patients were dialyzed by default on 1.5 mmol/l dialysate calcium concentration and Ca concentration in PD solutions was 1.25 mmol/l.

The Echocardiography: Two-dimensional echocardiography was performed on HDI 5000 Sono CT machine with a 3.5-mHz multiphase array probe in subjects lying in the left decubital position. Two-dimensional assessment of the aortic and mitral valve together with continuous wave Doppler ultrasound was performed on the basis of the parasternal long-axis and short-axis views. All echocardiographies were performed according to the recommendations of the American Society and European Association of Echocardiography [7] and were analyzed by a single experienced echocardiographist who was blinded to all clinical details during the above mention period. Cardiac valve calcification was defined as a bright echoe of more than 1 mm on one or more cusps of the aortic or mitral valve or mitral annulus [8]. The intra-observer agreement for the echocardiographic detection of valve calcification was assessed by a repeated examination in 8 study subjects by the same observer and was 100% in our study.

*Laboratory measurements:*The method of quantifying residual renal function is done by 24 h urine collection, calculating GFR as the mean of urea and creatinine clearance and normalized by 1.73m^2 surfacing area. Serum biochemical parameters were collected one month before echocardiography

in each patient. Blood specimen for biochemical chemistry was drawn in the morning of the midweek dialysis day, after an overnight fast of at least 12 hours. The RRF level was set to zero when urine production was <200 ml/24 h.

Statistical analysis: Continuous variables were presented as mean ± standard deviation (SD). Dichotomous variables were presented in absolute numbers and percentages. Kendal's correlation coefficient was used for non parametric variables and Pearson correlation coefficient was used to analyze the correlation between continuous variables.

The comparisons between the two groups were tested by using a Student's *t*-test for continuous data and chi-square test for dichotomous data. Binary logistic regression analysis was performed to assess the relative importance of the different factors associated with valve calcifications. A *p*-value ≤ 0.05 was considered statistically significant. Statistical Package for Social Sciences (SPSS for windows, version 15.0, Chicago, IL) was used for all the analyses.

Results

In this study, it were enrolled 34 prevalent hemodialysis (59% males, mean age 50 ± 10.4 years), and 30 peritoneal dialysis patients (60% males mean age 57± 12.37 years) under dialysis treatment from 6 to 36 months. It was noted that ten of the 30 peritoneal study patients (33.3%) had echocardiographic evidence of valvular calcification, 8 patients had isolated calcification of the mitral

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valve, 7 patients had isolated calcification of the aortic and 5 other patients had calcification of both valves. In the hemodialysis group including 24 patients (70.6%) had valvular calcifications, 19 patients had mitral valve calcification, 14 patients had aortic valve calcification, and 9 patients had calcifications of both valves. The prevalence of valve calcification was 53.1%, being significantly higher in HD compared to the PD group (70.6% vs. 33.3 %; p=0.007, respectively). By utilizing the t-test for independent samples, it was found a statistical difference between groups (PD and HD) related to age (older in PD, p=0.033); related to Phosphorus level (lowest level in PD, p<0.001); related to Ca, P product (lowest level in PD, p<0.001); related to RRF (highest in PD, p<0.001) and related to Alb (lowest level in PD, p<0.001) (Table nr.1).

Table nr.1 Clinical characteristics and biochemical parameters of HD and PD patients in the study

	PD (n=30)	**HD (n=34)**	***P***
Age (years)	57±12.36	50.79±10.4	0.033
Serum phosphate (mmol/L)	1.38±0.41	1.99±0.35	0.0001
Residual renal Function (ml/min)	4.09±2.09	0.62±0.89	0.0001
PTH level (pmol/L)	43.47±37.5	61.3±42.8	NS
C Reactive Proteine (mg/L)	9.96±8.02	11.13±4.63	NS
Albumine (g/L)	32.4±3.6	39.2±3.6	0.001
Serum Calcium (mmol/L)	2.08±0.19	2.09±0.22	NS
Corrected Serum Calcium (mmol/L)	2.14±0.21	2.17±0.62	NS
CaxP product ($mmol^2/L^2$)	2.99±0.06	4.26±0.07	0.001
Ca CaCO3 (g/day)	1.4±0.4	0.96±0.3	NS
Aluminium based phosphtate binders (g/day)	0.7±0.46	0.8±0.32	NS
Sevelamer dose (mg/day)		2690±370	
Vitamin D dose (µg/week)	1.0±0.54	1.25±0.5	NS

It was found a significant relationship between the presence of valve calcifications and phosphate level (Kendall's correlation coefficient (r=0,28; p=0.005) and inversely with RRF (r=-0.304; p=0.004). Characteristics of patients with and without valve calcification are compared in Table nr.2.

Table nr.2 Characteristic of the patients with and without valve calcification

	Total (n=64)	**With valve calcification n=34 (53.1%)**	**Without valve calcification n=30 (46.9%)**
Age (years)	53.34 ±12.13	55.67±11.52	50.7±12.4
DM(yes) no (%)	9 (14.1)	4(11.8)	5(16.7)
D M (no) no (%)	55 (85.9)	30 (88.2)	25(83.3)
PD no (%)	30 (46.9)	10 (29.4)	20(67)
HD no (%)	34 (53.1)	24 (70.6)	10(33)
Serum phosphate (mmol/L)	1.77±0.65	1.90±0.46	1.61±0.8
RRF(ml/min)	2.24±2.34	1.07±1.47	3.57±2.45
CRP (mg/L)	10.69±6.52	11.49±5.97	9.97±7.09
Serum albumin (g/L)	3.60±0.50	3.67±0.49	3.52±0.5

Continuous values are expressed as mean ± SD. DM, diabetes mellitus ;CRP, C Reactive Protein; RRF, Residual Renal Function; PD, Peritoneal dialysis; HD, Hemodialysis

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The logistic regression analysis for presence of valve calcification when adjusted for age and diabetes, with type of therapy, serum phosphate, RRF, CRP, and serum albumin as variables in the model, revealed significant association between the presence of valve calcifications with age and RRF. For each year increase in age, the patient is 1.08 times more likely to have valve calcification (OR=1.08; CI95%: 1.001-3.07), and for each ml/min increase in RRF, the risk of valve calcification decrease for 58% (b=-0.858. OR=2,36; CI95%: 1.34-4.16), (Table nr.3).

Table nr.3 Binary logistic regression analysis showing important factors associated with valve calcification in peritoneal and hemodialysis patients

	B	S.E.	*P*	OR	CI95%
Age (year)	.084	.037	.022	1,08	1.001- 3.07
DM (yes vs no)	-.050	1.093	.964	.951	0.11-8.10
PD vs HD	.821	1.333	.538	2.273	0.17-10.99
Serum phosphate (mmol/L)	1.276	.806	.114	3.581	0.74-7.38
*RRF (ml/min)	-.858	.289	.003	2.359	1.34-4.15
CRP (mg/L)	-.002	.051	.968	.998	0.90-110
Serum albumin, g/L	.540	1.051	.607	1.716	0.22-13.44
Constant	-1.993	4.600	.665	.136	

Variable(s) entered on step 1: age, DM, groups, P, RRF, CRP, Alb
Abbreviations: DM, Diabetes mellitus; CRP, C Reactive Protein; RRF, Residual Renal Function; PD, Peritoneal dialysis; HD, Hemodialysis;
*Coefficient B here is negative representing an inverse correlation with OR= 1/2.359=0.42 is 58%.

While analyzing the relationship between the RRF and phosphorus levels in both groups it was found that there exists a significant negative correlation between them even though this difference was stronger among Peritoneal dialysis patients (Pearson correl coef.: r = -0.704; p=0.0001) than among Hemodialysis patients (Pearson correl coef.: r=-0.520; p=0.002) (Figure nr.1).

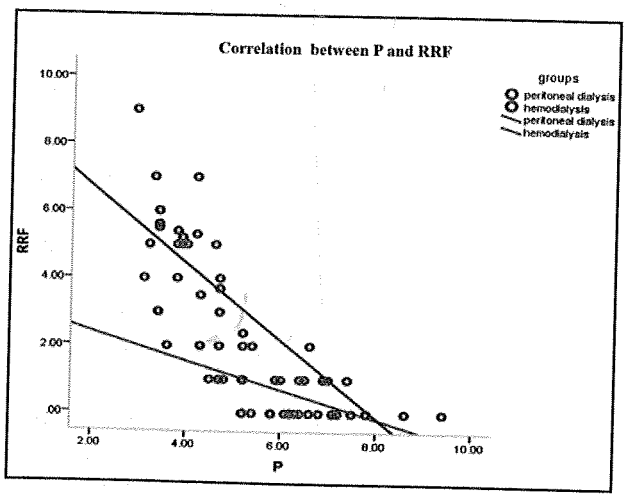

Figure nr.1 Relationship between Residual renal function and Phosphate level in HD and PD patients

Discussion

The treat goal study revealed that after 3 years in dialysis 85 % of patients had vascular calcifications [9]. Based on this study we analyzed stable patients who had up to 3 years in RRT with the intention of verifying whether there existed a difference in presence of valve calcifications between two therapies PD vs HD and which were the contributing factors. In our group study, 53.1% of the patients had valve calcification, 29.4% being part of the PD group and 70.6% belonging to HD group. It was also found a significant difference between the presences of valve calcifications in peritoneal dialysis (33.3%) compared to hemodialysis patients (70.6%) [p=0.007]. In addition, it was found a difference regarding the age of patients (older in PD, p=0.033); to level of P (lowest level in PD, p<0.001); to Ca x P product (lowest level in PD, p<0.001); to RRF (highest in PD, p<0.001) and related to Alb (lowest level in PD, p<0.001). The Age Factor is of a paramount importance in the occurrence of CAC, and vascular calcification has been shown to intensify in parallel with the advancing age [9]. Logistic regression analysis confirmed the importance of age in the presence of valve calcification of our patients. It should be noted that the mechanisms of vascular and valve calcification are not completely

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understood, but are likely multifactorial. Disturbances in mineral metabolism with resulting hyperphosphatemia were suggested to play a major contributory role to vascular and valve calcification in ESRD patients. In this study, it was found that exist a significant correlation between the presence of valve calcifications and Phosphate level (p=0.005). The elimination characteristics of phosphate in HD and PD are unlike the urea nd other small-molecular weight toxins much more similar to those of typical middle molecules. Its negative charge, the aqueous cover that increases its effective molecular weight and the slow intra-/ extracellular solute transfer rate are main phosphate characteristics that explain this, although Phosphate molecule is only 96Da alone [10]. We found a negative significant relationship between the presence of valve calcifications and RRF (r=-304; p=0.004) and an increased risk of valve calcification with every ml/min decreased of RRF (Table nr.3). Residual renal function (RRF) contributes significantly to the maintenance of phosphate balance. Urinary phosphate excretion is highly correlated with RRF among PD patients and a strong correlation between RRF and serum phosphate concentration has been reported [4]. It is well known that RRF declines with time on PD. In the short term, the declining renal clearance may be mitigated by an increase in peritoneal clearance [11], but in anuric patients, increased peritoneal clearance may not be able to compensate because of the limited numeric variability in peritoneal clearance [12]. This relationship is not as well described in HD patients, with only 1 single-center report suggesting improved serum phosphate levels with preservation of RRF [13]. When we studied the relationship between the RRF and phosphate level in both groups it was found that existed a significant negative correlation between them, although this negative correlation was stronger in Peritoneal dialysis patients (r=-0.704; p=0.0001) than in Hemodialysis patients (r=-0.520; p=0.002); (Figure nr.1]. Improved control of serum phosphate adds yet another reason to focus on preservation of RRF and also provides another possible mechanistic link helping to explain the important relationship between RRF and valve calcifications in Hemodialysis and Peritoneal dialysis patients. In addition, a better preservation of RRF in Peritoneal dialysis group may give explanation to the finding of the lower frequency of valve calcifications in peritoneal dialysis patients during the first years under therapy treatment.

Conclusions

Our study showed once again that presence of valve calcification is relatively high in dialysis patients. The prevalence was significantly higher in HD patients compared with PD patients. By multivariate analysis, significant risk factors for VC were older age and residual renal function.

Residual renal function contributes significantly to the maintenance of phosphate balance mainly in PD patients, and may explains the lower prevalence of valve calcification in PD patients in comparison with HD patients during the first years under therapy treatment. Further prospective, longitudinal studies are needed to evaluate whether a decline in RRF with time on dialysis is independently associated with an increase of vascular calcifications in dialysis patients.

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