Kidney International, Vol. 63, Supplement 85 (2003), pp. S115–S118

Heart valve calcification and calcium x phosphorus product in hemodialysis patients: Analysis of optimum values for its prevention

Margarita Rufino, Sagrario García, Alejandro Jiménez, Alejandra Alvarez, Rosa Miquel, Patricia Delgado, Domingo Marrero, Armando Torres, Daniel Hernández, and Victor Lorenzo

Nephrology Section, University Hospital of Canary Islands, Santa Cruz de Tenerife, Spain; and Research Unit, University Hospital of Canary Islands, Santa Cruz de Tenerife, Spain

Heart valve calcification and calcium x phosphorus product in hemodialysis patients: Analysis of optimum values for its prevention.

Background. Prevalence of valve calcification (VC) in end-stage renal disease (ESRD) patients is high and information regarding modifiable predictors is scarce. Our aim was to determine the prevalence of VC in our maintenance hemodialysis (HD) population, and the optimal Ca x P value that most accurately predicted the presence of VC after controlling for comorbidities.

Methods. This was a cross-sectional observational study of a cohort of 52 stable patients on maintenance HD for more than 12 months. Mean 12 months serum biochemical data (calcium, phosphorus, PTH, lipids) and M-mode 2D echocardiogram were used to evaluate the presence or absence of mitral and aortic VC and ventricular geometry.

Results. Twenty patients (38.4%) presented with VC. Patients with VC were more commonly diabetic and showed higher levels of serum phosphorus, Ca x P product, total and LDL cholesterol, and poor ventricular geometry, as compared to patients without VC. Moreover, they required higher doses of both $CaCO_3$ and $Al(OH)_3$. Logistic regression analysis showed that VC was independently influenced by age, Ca x P, and diabetes. ROC curves illustrated that a Ca x P >43 mg^2/dL^2 was the optimal value in terms of sensitivity and specificity for predicting the presence of VC in our patient population.

Conclusion. These findings highlight the importance of applying more vigorous measures for Ca x P control.

The prevalence of valve calcification (VC) in maintenance hemodialysis (HD) patients is eightfold more than that found in their counterparts in the general population (40% vs. 5%) [1, 2], and evolves rapidly from subclinical to severe dysfunction within a few years [3–5]. In adition, VC is strongly associated with myocardial and coronary calcification in dialyzed patients [6, 7].

Several factors have been reported to explain the higher prevalence of VC in the maintenance HD population. Hemodynamic alterations associated with the uremic state, or the dialysis procedure itself may lead to repetitive mechanical stress and local inflammation that may well promote the initiation of calcification [1]. Furthermore, dyslipidemia and a high calcium phosphorus product (Ca x P) have been related with dysthrophic soft tissue calcification and cardiovascular mortality in ESRD patients [5, 8–11].

The aim of the present study was to determine the prevalence of VC in our maintenance HD population and to establish the optimal Ca x P value that most accurately predicted VC after controlling for comorbidities.

METHODS

We performed a cross-sectional study of a cohort of 52 patients on maintenance HD for more than 12 months (59.7 ± 15.6 years, 63% men, 54% diabetics, time on maintenance HD 20.5 ± 17.9 months). All patients were in steady clinical condition, on thrice-weekly 3.5 to 4.5 hours of standard bicarbonate hemodialysis, with a prescribed urea reduction >65%. Patients were managed according to a standardized protocol.

An echocardiogram was performed at enrollment and the prior mean 12-month values of serum calcium, phosphorus, PTH (IRMA, Nichols Institute, CA, USA), cholesterol, triglycerides, and HbA1C (glycated hemoglobin) were recorded. Mean daily oral calcium intake from $CaCO_3$, the number of hypercalcemia episodes (>11 mg/dL), the proportion of patients on $Al(OH)_3$ and calcitriol therapy were also recorded.

Key words: valve calcification, calcium phosphorus product, maintenance hemodialysis.

Table 1. Demographic, biochemical and echocardiographic parameters in patients with and without VC

	Total	With VC	Without VC	*P* value
No. patients %	52	20 (38.4)	32 (61.6)	
Gender *M/F*	33/19	15/5	18/14	0.24
Age *years*	59.7 ± 15.6	63.4 ± 13.9	57.5 ± 16.4	0.17
Time on HD *months*	20.5 ± 7.9	20.5 ± 18.2	20.5 ± 18	0.98
Diabetics %	53.8	75	40.6	0.01
IVS *mm*	14.4 ± 3.3	16.6 ± 3.2	13.4 ± 2.9	0.002
LVM *g*	263.1 ± 84.7	319.2 ± 75.3	237.9 ± 77.3	0.004
LVMI g/m^2	151.4 ± 47.5	175.7 ± 44.7	140.5 ± 45.2	0.02
LVH %	66.6	77	62	0.24
Systolic blood pressure *mm Hg*	138.9 ± 13.2	142.4 ± 9.6	137.05 ± 14.7	0.18
Serum calcium *mg/dL*	9.5 ± 0.5	9.6 ± 0.6	9.4 ± 0.5	0.48
Serum phosphorus *mg/dL*	4.8 ± 1.4	5.7 ± 1.3	4.3 ± 1.1	0.0001
Ca x P mg^2/dL^2	46.2 ± 13.1	54.5 ± 11.7	41.04 ± 11.3	0.0001
iPTH *pg/mL*	168 ± 166.9	232.2 ± 231.8	127.3 ± 91.3	0.07
Hypercalcemic episodes	0.74 ± 1.12	0.8 ± 1.2	0.2 ± 0.5	0.052
Total cholesterol *mg/dL*	175.6 ± 37.1	188.7 ± 43.9	167.5 ± 29.9	0.04
Triglicerides *mg/dL*	153.9 ± 68.3	168.9 ± 72.7	144.2 ± 64.7	0.22
LDL-cholesterol *mg/dL*	87.8 ± 32.3	100.6 ± 33.9	79.3 ± 28.8	0.02
Albumin *g/dL*	3.7 ± 0.2	3.7 ± 0.2	3.7 ± 0.3	0.98
HbA1C %	6.5 ± 4.7	6.07 ± 2.09	6.7 ± 5.9	0.56
Ca binder dose *mg/day*	1209 ± 768	1551 ± 728	988 ± 720	0.01
Patients on $Al(OH)_3$ therapy %	30.8	60%	12.5%	0.001
Patients on calcitriol therapy %	42.3	55%	34.3%	0.14

Abbreviations are: IVS, interventricular septum; LVM: left ventricular mass; LVMI, left ventricular mass index; LVH, left ventricular hypertrophy; VC, valve calcification.

Ultrasonography

An M-mode two-dimensional echocardiogram was carried out to evaluate the presence or absence of mitral and aortic VC. Left ventricular geometry was measured following recommendations of the American Society of Echocardiography [12, 13].

Statistical analysis

All data are expressed as mean ± SD. Characteristics of the two groups were compared by two-tailed unpaired *t* test (continuous variables) or Chi-square test (categorical variables). Stepwise logistic regression analysis was performed with VC as the dependent variable. The optimal Ca x P value associated with the absence of VC was assessed by receiver-operator characteristic (ROC) curve. The best discrimination limit for Ca x P level was determined at the maximun of the Youden's index: J = sensitivity + specificity – 1. Significant differences were defined as $P < 0.05$. Statistical analysis was performed using the SPSS 10.0 for Windows (SPSS, Inc., Chicago, IL, USA); the NCSS 2000 (Kaysville, UT) and the Logxact software (Cytel, MA, USA) were used for exact logistic regression analysis.

RESULTS

Twenty patients had VC (4 aortic, 11 mitral, and 5 in both valves). Patients were grouped according to the presence or absence of VC. Table 1 shows that the group with VC had a significantly higher proportion of diabetics, higher levels of serum phosphorus, Ca x P, and total and LDL cholesterol. In addition, this group required higher doses of $CaCO_3$ and $Al(OH)_3$ for phosphorus control. Finally, parameters of ventricular geometry were more disturbed in the VC group.

Table 2. Stepwise logistic regression analysis models of independent predictors for VC

	Model 1	Model 2
Age *y*	1.14 (1.02–1.26) $P = 0.014$	3.61 (0.74–17.49) $P = 0.1$
Ca x P	1.21 (1.08–1.36) $P = 0.0001$	Not included
Serum phosphorus	Not included	6.83 (1.33–34.96) $P = 0.02$
Hypercalcemic episodes	NS	10.41 (1.68–64.32) $P = 0.01$
Diabetes	4.4 (1.27–15.05) $P = 0.02$	6.32 (1.32–30.3) $P = 0.02$

Model 1 includes the covariates that were significant predictors in the univariate model. In Model 2, serum phosphorus substituted Ca x P. The table shows odds ratio (95% confidence interval) and *P* values.

A subanalysis of diabetic patients showed similar statistical differences between patients with and without VC (data not shown).

In order to determine the predictors of VC (dependent variable), a stepwise logistic regression analysis was performed. We first introduced age, Ca x P product, diabetes, and hypercalcemia episodes as independent variables. Then, we added the other variables of the study one by one according to Table 1. VC was independently influenced by age, Ca x P, and diabetes (Table 2). That is, for each year of increasing age, and for each unit of

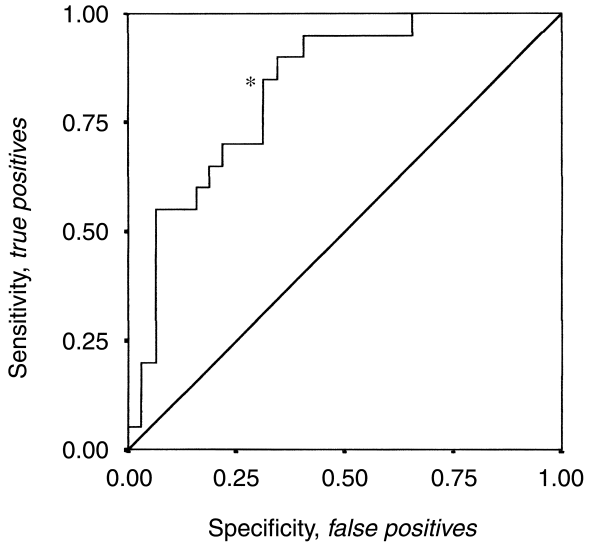

Fig. 1. ROC curve for Ca x P as predictor of VC presence. The optimal predictor cut-off value (*) was that of the highest sensitivity together with the lowest number of false positives. This value corresponds to Ca x P = 43.24 mg^2/dL^2.

increasing Ca x P, the likelihood of presenting with VC increased 14% and 21%, respectively. In addition, the probability of VC was 4.4 times higher in diabetics when compared with nondiabetic patients, and hypercalcemia episodes (two or more episodes) presented a probability of VC of 10.41 as compared with the absence or presence of only one episode. The other variables were not included in the equation.

This same statistical model applied only to the diabetic population showed that the best predictor factors for VC were odds ratio (OR) and confidence interval (CI) 95%; LDL-cholesterol 1.04 [1.01–1.07], $P = 0.03$; serum phosphorus 4.6 [0.94–22.55], $P = 0.057$; and age 1.14 [0.98–1.33], $P = 0.07$.

The sensitivity (probability that a patient with VC had Ca x P over a determined cut-off) and specificity (probability that a patient without VC had a Ca x P below that cut-off) of Ca x P were calculated for different cut-off levels and are represented by ROC in Figure 1. The best Younden's index was 0.48 and was shared by two cut-off values of Ca x P: a Ca x P >43.2 mg^2/dL^2 proved more sensitive (80%), but less specific (68.7%), and a Ca x P >55.7 mg^2/dL^2 was less sensitive (55%), but more specific (93.7%).

DISCUSSION

This cross-sectional study showed a high prevalence of VC in maintenance HD patients and an association between VC and age, diabetes, and mineral metabolism abnormalities. Of note, we found Ca x P to be a strong predictor of VC at lower values than previously reported.

The prevalence of VC in ESRD patients is remarkably high in all published series. Braun et al [2] reported a VC prevalence of 50% in maintenance HD patients. Huting et al [14] found mitral and aortic VC in 44% and 34%, respectively, in peritoneal dialysis patients. More recently, Ribeiro et al [15] described a similar prevalence of 44.5% and 52% of mitral and aortic calcification, respectively, in dialyzed patients. Taking into account differences in patient samples, our finding a VC prevalence of 38.5% does not conflict with these previous reports.

There are several studies that report predictors for cardiovascular morbidity-mortality in ESRD patients [9, 10], but few have distinctly evaluated predictors for VC [2, 14, 15]. Of the known factors that carry a high risk for VC [16], mineral metabolism alteration and dyslipemia are modifiable, and consequently, their identification is especially important.

Huting et al [14] observed that mitral VC was associated with the severity of predialysis hypertension, high Ca x P, reduced systolic function, and LV dilation. Ureña et al [4], in a multivariate analysis, found an association between aortic stenosis and increased age, calcitriol therapy, and hyperphosphatemia. Braun et al [2] reported a correlation between aortic VC and coronary heart disease, but other comorbidities were not evaluated. Ribeiro et al [15] reported that mitral VC was associated with age and high Ca x P, and aortic VC was related with age and duration of hypertension. Summarizing these studies, elevated Ca x P always appears to be a relevant risk factor for VC. Our multivariate statistical model also showed that a high Ca x P was the strongest predictor for VC after adjusting for comorbidities. In a second model, Ca x P product was substituted by serum phosphorus. In this model, hypercalcemia episodes, together with hyperphosphatemia, appeared as independent predictors but with less statistical significance. Serum calcium alone was not significant in either model.

Previous studies have reported a history of hypertension prior to starting dialysis as a predictor of VC [2, 15, 17]. However, LVH, a consequence of long-standing hypertension, was not a predictor in our study. This does not exclude a role for hypertension, and vigorous control of blood pressure is important in this population.

Regarding diabetes, we noted that this condition strongly correlated with VC, but HbA1C levels did not. However, LDL-cholesterol appeared to be a strong predictor of VC. It is tempting to hypothesize that, among diabetic patients, oxidative stress plays an important role in the genesis of VC.

Several limitations to our study should be noted. First, it is a cross-sectional and observational study, thus, only association, and not causality, can be established. Second, the qualitative evaluation of VC (presence or absence) is somewhat crude; currently, more sensitive methods provide a more accurate diagnosis of VC.

In spite of these limitations, our results support previous observations of increased prevalence of VC in ESRD patients. A Ca x P >43 mg^2/dL^2 proved to be the optimal value in terms of sensitivity and specificity to predict VC in our patient population. This value is lower than those previously recommended in the literature to prevent VC in ESRD patients [18], and is not easy to achieve in a clinical setting. For this reason, our findings highlight the importance of more vigorous Ca x P control measures. Additional prospective controlled studies are warranted to confirm these observational results and to better define optimal Ca x P values to reduce the risk of VC in the maintenance HD population.

ACKNOWLEDGMENT

The authors are grateful to Mr. Michael McLean for his transduction assistance.

Reprint requests to Margarita Rufino Hernández, C/ Ildefonso Cruz Rodríguez 2, Vivienda 1, 38098, Santa Cruz de Tenerife, Tenerife, Canary Islands, Spain.
E-mail: margaritarufino@hotmail.com

REFERENCES

1. London GM, Pannier B, Marchais SJ, Guerin AP: Calcification of the aortic valve in dialyzed patients. *J Am Soc Nephrol* 11:778–783, 2000
2. Braun J, Oldendorf M, Moshage W, *et al*: Electron beam computed tomography in the evaluation of cardiac calcification in chronic dialysis patients. *Am J Kidney Dis* 27(3):394–401, 1996
3. Otto CM, Lind BK, Kitzman DW, *et al*: Association of aortic valve sclerosis with cardiovascular mortality and morbidity in the elderly. *N Engl J Med* 341:112–117, 1999
4. Ureña P, Malergue MC, Goldfarb B, *et al*: Evolutive aortic stenosis in hemodialysis patients: Analysis of risk factors. *Nephrologie* 20:217–225, 1999
5. Baglin A, Hanslik T, Vaillant JN, *et al*: Severe valvular heart disease in patients on chronic dialysis. *Ann Intern Med* 148(8):521–526, 1997
6. Block GA, Port FK: Re-evaluation of risks associated with hyperphosphatemia and hyperparathyroidism in dialysis patients: Recommendations for a change in management. *Am J Kidney Dis* 35(6):1226–1237, 2000
7. Goodman WG, Goldin J, Kuizon BD, *et al*: Coronary artery calcification in young adults with end-stage renal disease who are undergoing dialysis. *N Engl J Med* 18;342(20):1478–1483, 2000
8. Raine AEG: Acquired aortic stenosis in dialysis patients. *Nephron* 68:159–168, 1994
9. Block GA, Hulbert-Shearon TE, Levin NW, Port FK: Association of serum phosphorus and calcium x phosphate product with mortality risk in chronic hemodialysis patients: A national study. *Am J Kidney Dis* 31:607–617, 1998
10. Ganesh SK, Stack AG, Levin NW, *et al*: Association of elevated serum PO4, Ca x PO(4) product, and parathyroid hormone with cardiac mortality risk in chronic hemodialysis patients. *J Am Soc Nephrol* 12(10):2131–2138, 2001
11. Guérin AP, London GM, Marchais SJ, Metivier F: Arterial stiffening and vascular calcifications in end-stage renal disease. *Nephrol Dial Transplant* 15:1014–1021, 2000
12. Koren MJ, Devereux RB, Casale PN, *et al*: Relation of left ventricular mass and geometry to morbidity and mortality in uncomplicated essential hypertension. *Ann Intern Med* 114:345–352, 1991
13. Devereux R, Reichek N: Echocardiographic determination of left ventricular mass in man: Anatomic validation of the method. *Circulation* 55:613–618, 1997
14. Huting J: Mitral valve calcification as an index of left ventricular dysfunction in patients with end stage renal disease on peritoneal dialysis. *Chest* 105:383–388, 1994
15. Ribeiro S, Ramos A, Brandao A, *et al*: Cardiac valve calcification in haemodialysis patients: Role of calcium-phosphate metabolism. Nephrol Dial Transplant 13:2037–2040, 1998
16. Cannata JB: ¿Se puede evitar el desarrollo de calcificaciones vasculares y cardiacas en los enfermos en diálisis crónica? *Nefrologia XXII*(Suppl 2):74–75, 2002
17. Yoshida M, Takamatsu J, Yoshida S, *et al*: Scores of coronary calcification determined by electron beam computed tomography are closely related to the extent of diabetes-specific complications. *Horm Metab Res* 31:558–563, 1999
18. Dm K, Andress DL: Control of hyperphosphatemia in renal failure: Role of aluminum. *Sem Dial* 9:310–315, 1996