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Vascular calcification in the uremic patient: A cardiovascular risk?

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Background. Several factors suggest that the presence of vascular calcification (VC) is associated with a high risk of cardiac events in uremic patients. The aim of this study was to analyze the influence of VC on cardiac morbidity and mortality in our hemodialysis (HD) patients.

Methods. We studied 79 patients on HD: 43 males, mean age 48 ± 15 years old, mean time on HD 83 ± 63 months. The presence of VC was evaluated by radiologic series. Other cardiovascular risk factors analyzed were arterial hypertension, diabetes mellitus, obesity, cigarette smoking, anemia, and dyslipidemia. All patients underwent M-mode, two-dimensional, Doppler echocardiography. Patients were followed for two years. During this time, clinical information collected included predialysis blood pressure, incidence of ischemic heart disease, episodes of congestive heart failure, and mortality due to cardiovascular event.

Results. VC was observed in 55.7% of patients. Left ventricular hypertrophy, diastolic dysfunction, and cardiac valve calcification were significantly associated with VC. Ischemic heart disease (71.4% vs. 28.6%) and episodes of cardiac failure (0.41 vs. 0.18 per year; $P < 0.05$) appeared more frequently in the patient group with VC. VC was present in 80.6% of patients who developed episodes of heart failure. Eight patients died from cardiac disease; each of them had VC.

Conclusion. The presence of VC can help to identify those HD patients with a higher cardiovascular risk.

End-stage renal disease (ESRD) patients have a substantially greater risk of cardiovascular death than the population with normal kidney function [1]. In the last decade vascular calcification has emerged as a process with important clinical consequences, and the presence of coronary artery calcification has been clearly defined as a risk factor for cardiovascular morbidity and mortality [2, 3].

Diffuse media calcification of arterial vessels with no relation to atheromatosis is very prevalent in ESRD, even in young patients [4–6]. Recently, clinical studies have supported the association between VC and cardiac changes in these patients [2].

Alterations in the calcium-phosphate metabolism and the treatment of these abnormalities contribute to the development of VC in ESRD patients. VC may be one of the mechanisms by which hyperphosphatemia and elevated Ca x P product influences cardiac mortality in this population [7–10].

VC induces stiffening of the vessel wall and reduces vascular compliance, which has found to be predictive of cardiovascular mortality in these patients [2, 11].

VC in the media of medium- and small-sized vessels in ESRD patients is very marked and may displace intimae, causing luminal narrowing. This may also be applicable to coronary arteries contributing to cardiovascular complications [12].

Finally, soft tissue calcification also includes myocardium and cardiac valve calcification, with important consequences in the cardiac function [5, 13, 14].

We undertook this prospective study to analyze the influence of VC on cardiac morbidity and mortality in our HD patients.

METHODS

We included 79 patients, 43 males and 36 females, with a mean age of 48 ± 15 years old and mean time on hemodialysis of 83 ± 62 months.

Cardiovascular risk factors analyzed were arterial hypertension (54 patients, 68%), diabetes mellitus (8 patients, 10%), obesity (17 patients, 21.5%), and cigarette smoking (25 patients, 31.6%). Other factors assessed were hematocrit, serum cholesterol, triglycerides, total/HDL-cholesterol, and lipoprotein(a).

VC was studied by radiograph series that included the thorax, abdomen, pelvis, and the extremities. VC was diagnosed when they were found in any of the examined areas.

Echocardiography was performed using M-mode two-dimensional, Doppler color ultrasonography. The

Key words: cardiovascular disease, end-stage renal disease.

Table 1. Cardiovascular risk factors

	Vascular calcification (VC)	No VC	*P* value
Hypertension *54 patients*	30	24	NS
Diabetes *8 patients*	7	1	<0.05
Obesity *17 patients*	9	8	NS
Smoking *25 patients*	11	14	NS
Hematocrit %	31 (4)	32 (2)	NS
Serum cholesterol *mg/dL*	257 (75)	182 (64)	NS
Serum triglicerides *mg/dL*	175 (93)	214 (144)	<0.05
Lipoprotein (a) *mg/dL*	51 (44)	22 (9)	NS

Table 2. Echocardiographic parameters

	VC	No VC	*P* value
PWT *cm*	1.39 (0.4)	1.21 (0.3)	<0.05
IVST *cm*	1.35 (0.4)	1.23 (0.3)	<0.05
LVM g/m^2	218 (93)	178 (57)	<0.05
EF %	70 (6)	72 (5)	NS
PAMV *m/s*	0.96 (0.4)	0.74 (0.2)	<0.05
PEMV *m/s*	0.75 (0.4)	0.85 (0.5)	NS
E/A ratio	0.71 (0.2)	1.1 (0.5)	<0.05
IVRT *m/s*	144 (32)	144 (40)	NS
Mitral valve calcification %	82.8	17.2	<0.001
Aortic valve calcification %	84.6	15.4	<0.001
Diastolic dysfunction %	70.2	29.8	<0.001

Abbreviations can be found in the text.

same experienced cardiologist always carried out the technique in a midweek interdialysis day. Left ventricular (LV) dimensions were presented according to recommendations of the American Society of Echocardiography. The following parameters were assessed: posterior wall thickness (PWT); interventricular septal thickness (IVST); LV mass (LVM) calculated by the Penn convention formula and indexed to body surface area; ejection fraction (EF); peak early and peak atrial mitral velocities (PEMV, PAMV); E/A ratio of transmitral velocities; isovolumetric relaxation time (IVRT); and presence of calcification in cardiac valves.

Patients were prospectively followed over two years. Clinical variables that appearing during this follow-up period and were considered in the study included ischemic heart disease, the occurrence of myocardial infarction, and angina pectoris (intradialysis thoracic pain was not included). Episodes of heart failure were diagnosed by the presence of recurrent or persistent dyspnea associated with two of the following things: raised jugular venous pressure, bibasilar crackles, pulmonary venous hypertension, or interstitial edema on chest radiograph. Predialysis arterial pressure and survival were also considered.

Statistical analysis

Baseline characteristics were described using median ± interquartile range. Nonparametric statistical tests were used to compare quantitative variables, while Chi-square test was used for qualitative variables. A *P* value less than 0.05 indicated statistical significance.

RESULTS

Vascular calcification was observed in 44 of the 79 patients (55.7%). Table 1 shows the different cardiovascular risk factors of the patients grouped according to the presence of VC.

Patients with VC showed significant differences in PWT, IVST, and LVM. The presence of VC was associated with diastolic dysfunction, higher PAMV, and a lower E/A ratio (pattern of abnormal LV relaxation) (Table 2).

VC appeared statistically associated with mitral and aortic valve calcification.

Table 3. Clinical outcome and VC

	VC 44 patients	No VC 35 patients	*P* value
Ischemic disease *21 patients*	15	6	0.07
Heart failure *31 patients*	25	6	<0.01
Survivors *65 patients*	35	30	NS
Cardiac death *8 patients*	8	0	<0.05

Clinical outcome

Predialysis arterial pressure did not differ in both groups of patients: 140/77 in the VC group versus 134/73. Twenty-one of the 79 patients (26.6%) developed ischemic heart disease during the follow-up period (Table 3). Most of these patients (15) belonged to the group with VC.

Thirty-one patients (39%) presented with at least one episode of congestive heart failure during the two years of follow-up. These episodes occurred with a significantly higher frequency in the group of patients with VC (25 patients, 80.6%) (Table 3). The number of episodes per year was also higher in VC patients (0.41 vs. 0.18).

Fourteen patients died from different causes, and eight, all of them presenting with VC, died from cardiovascular disease. The proportion of deaths attributed to cardiac causes was 57%.

DISCUSSION

We found a prevalence of VC greater than 50% in our ESRD patients undergoing regular HD. This prevalence would most likely have been even higher if new and more sensitive radiologic techniques, such as electron-beam CT, had been used [9]. The presence of VC was associated with echocardiographic abnormalities. A higher degree of LV hypertrophy and more evident alterations in ventricular filling occurred in patients with VC. Guerin et al [2] observed a significant decrease in stroke volume and E/A ratio of transmitral velocities in ESRD subjects with VC. In the same study, VC was associated with increased stiffening of large arteries. The contribution of functional and structural changes in the large

arteries to the genesis of LV hypertrophy has been previously documented [15].

The association of VC and cardiac valve calcification has been frequently observed [4, 5, 13, 16]. The mechanisms responsible for VC in ESRD patients remain uncertain. It is possible, however, that alterations in mineral metabolism play an important role in its development. [2, 3, 5, 8, 10, 13].

When we analyzed cardiovascular risk factors in our patients (Table 1), diabetes appeared to be statistically significant. However, the number of diabetics was small. Only eight patients were diabetic, and seven of them had VC.

During the follow-up period, 21 (26.6%) patients developed symptoms of ischemic heart disease and 31 (39%) patients developed cardiac failure. The prevalence of VC in the group of patients with ischemic heart disease was 71.4% (15 patients) (Table 3). We think this is a very high percentage, and that perhaps the number of patients was not large enough to reach statistical significance. Coronary-artery calcification is common and severe in ESRD patients [3–5, 9]. It has also been associated with cardiovascular events in individuals unaffected by renal disease [17]. Coronary-artery calcification has not been evaluated in this study; however, we think that it may be present in most of our patients with VC.

At the end of the follow-up period, 25 (56.8%) of the 44 patients with VC had presented with at least one episode of heart failure. Risk factors that have previously been found to predict heart failure include diastolic dysfunction, age, ischemic heart disease, anemia, hypoalbuminemia, and arterial hypertension [18]. Our patients with VC presented a high prevalence of ischemic heart disease and significant abnormalities in diastolic function. The abnormal left ventricular relaxation produces an increase in the end-diastolic pressure, which can result in pulmonary congestion and congestive heart failure.

The proportion of deaths attributed to cardiac causes in our patients during the two years of follow-up was 57%; all of the patients who died of cardiac causes had VC. LV hypertrophy, ischemic heart disease, and congestive heart failure have been previously identified as risk factors for death in ESRD patients [18–20]. Moreover, recent epidemiologic studies have shown that arterial stiffness is a major predictor of cardiovascular mortality in HD patients, and the presence of VC is associated with increased stiffness of large arteries [20].

CONCLUSION

Our study confirms that VC is a common finding in hemodialysis patients. Echocardiography demonstrates that VC is associated with left ventricular hypertrophy, diastolic dysfunction, and the presence of calcium deposits in the cardiac valves. VC was also associated with more episodes of heart failure and ischemic heart disease. Vascular calcification should be considered a marker of cardiovascular risk in hemodialysis patients. More studies are necessary to learn how to avoid VC, or how to modify its evolution and complications.

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REFERENCES

1. Foley RN, Parfrey PS, Sarnak MJ: Clinical epidemiology of cardiovascular disease in chronic renal disease. *Am J Kidney Dis* 32 (Suppl 3):S112–S119, 1998
2. Guerin AP, London GM, Marchais SJ, Metivier F: Arterial stiffening and and vascular calcifications in end-stage renal disease. *Nephrol Dial Transplant* 15:1014–1021, 2000
3. 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* 342:1478–1483, 2000
4. 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* 27:394–401, 1996
5. Raggi P, Boulay A, Chasan-Taber S, *et al*: Cardiac calcification in adult hemodialysis patients. A link between end-stage renal disease and cardiovascular disease? *J Am Coll Cardiol* 39:695–701, 2002
6. Davies MR, Hruska A: Pathophysiological mechanisms of vascular calcification in end stage renal disease. *Kidney Int* 60:472–479, 2001
7. Block GA: Prevalence and clinical consequences of elevated Ca x P product in hemodialysis patients. *Clin Nephrol* 54:318–324, 2000
8. 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* 37: 1331–1333, 2001
9. Raggi P: Effects of excess calcium load on the cardiovascular system measured with electron beam tomography in end-stage renal disease. *Nephrol Dial Transplant* 17:332–335, 2002
10. Amin N: The impact of improved phosphorus control: Use of sevelamer hydrochloride in patients with chronic renal failure. *Nephrol Dial Transplant* 17:340–345, 2002
11. Blacher J, Demuth K, Guerin AP, *et al*: Influence of biochemical alterations on arterial stiffness in patients with end-stage renal disease. *Arterioscler Thromb Vasc Biol* 18:535–541, 1998
12. Meema HE, Oreopoulos DG, Rapoport A: Serum magnesium level and arterial calcification in end-stage renal disease. *Kidney Int* 32:388–394, 1987
13. Salgueira M, Jarava C, Moreno Alba R, *et al*: Calcificaciones valvulares cardiacas en pacientes en hemodiálisis análisis de factores predisponentes. *Nefrologia* 18:221–226, 1998
14. Llach F: Cardiac calcification: Dealing with another risk factor in patients with kidney failure. *Sem Dial* 12:293–295, 1999
15. London GM, Guerin AP, Marchais SJ, *et al*: Cardiac and arterial interactions in end stage renal disease. *Kidney Int* 50:600–608, 1996
16. Christian RC, Fitzpatrick LA: Vascular calcification. *Curr Opin Nephrol Hypertens* 8:443–448, 1999
17. Arad Y, Spadaro LA, Goodman K, *et al*: Prediction of coronary events with electron beam computed tomography. *J Am Coll Cardiol* 36:1253–1260, 2000
18. Harnett JD, Foley RN, Kent GM, *et al*: Congestive heart failure in dialysis patients: Prevalence, incidence, prognosis and risk factors. *Kidney Int* 47:884–890, 1995
19. Silberberg JS, Berre PE, Prichard SS, Sniderman AD: Impact of left ventricular hypertrophy on survival in end stage renal disease. *Kidney Int* 36:286–289, 1989
20. Parfrey P, Foley R: The clinical epidemiology of cardiac disease in chronic renal failure. *J Am Soc Nephrol* 10:1606–1615, 1999