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CLINICAL STUDY

Valvular calcification and left ventricular modifying in peritoneal dialysis patients

Damir Rebić[1], Senija Rašić[1], Aida Hamzić-Mehmedbašić[1], Jasminka Džemidžić[1], and Emir Kurtalić[2]

[1]Clinic for Nephrology and [2]Clinic for Angiology, University Clinical Center of Sarajevo, Sarajevo, Bosnia and Herzegovina

Abstract

Background: Cardiac valve calcification (CVC) and left ventricular (LV) alterations are frequent complication in end-stage renal disease (ESRD). We determined the prevalence of CVC and LV hypertrophy (LVH) in ESRD patients before renal replacement therapy and 12 months after peritoneal dialysis (PD). *Methods*: A prospective longitudinal of 50 incident PD patients was studied. Demographic and clinical data were recorded and blood assayed at baseline and after 1-year of follow-up. CVC and LVH were evaluated by M-mode two-dimensional echocardiography. *Results*: CVC of the mitral and aortic valves and of both valves were noted in 30, 18 and 10% of patients, respectively. After 12 months of PD regimen, 20% patients had aortic, 24% mitral and 8% had calcification of both valves. After one year of PD, LVH was 62 and 36% in patients with and without CVC, respectively ($p < 0.05$). Endothelin-1 is an independent predictor of CVC at the baseline, while nitric oxide is inversely an independent predictor at the end of follow-up. *Conclusions*: CVC is associated with LVH in PD patients. These findings identified a potential role for monitored markers to be incorporated into therapeutic strategies aimed at detection and treatment of cardiovascular complications and prevention strategies.

Keywords

Biomarkers, cardiac valve calcification, end-stage renal disease, left ventricular alterations, peritoneal dialysis

History

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Introduction

Cardiovascular disease is a major cause of mortality in end-stage renal disease (ESRD) patients. The US Renal Data System reported that 38.3% of prevalent dialysis patients died from cardiovascular causes between 2008 and 2010.[1] Similar results exist in the Registry of the Bosnian Society of Nephrology that mortality was due to cardiovascular causes in 63.8% of the dialysis cases.[2]

Cardiac valve calcification (CVC) is an independent predictor for all-cause and cardiovascular mortality. It is associated with valve dysfunction, hypertension, myocardial ischemia, infective endocarditis, and heart failure. The prevalence of CVC is high (40%) in ESRD patients, and several factors have been reported to explain this increased prevalence.[3] Left ventricular (LV) hypertrophy (LVH) independently predicts cardiovascular mortality in ESRD patients as well the prevalence of LVH has been demonstrated in up to 75% of this patient population.[4]

Echocardiography is a simple and also very useful tool for assessing cardiac structure and function, non-invasively. According to the LV mass (LVM) and relative wall thickness (RWT), LV geometry may be classified into four groups: normal geometry, concentric remodeling, concentric LVH, and eccentric LVH.

Address correspondence to Dr Damir Rebić, Clinic for Nephrology, University Clinical Center of Sarajevo, Bolnička 25, 71000 Sarajevo, Bosnia and Herzegovina. E-mail: damir.rebic@gmail.com

The combination of fluid overload and hypertension contributes to eccentric and concentric LV hypertrophy in dialysis patients.[5] In the absence of coronary heart disease, as compared with eccentric LVH, concentric LV geometry characterizes a more severe impairment of the cardiovascular system. Concentric LV geometry is in fact associated with more marked vascular alterations in arterial hypertension in ESRD and predicts a more severe outcome.

The aims of the present study were to determine the presence of CVCs, LVH and geometric patterns in the patients before renal replacement therapy (RRT) and 12 months after peritoneal dialysis (PD) treatment and to compare the results with those in the literature. We also aimed to determine the most important factors related to the development of CVC in these patients.

Materials and methods

The study protocol was approved by the Human Research Ethics Committee of the local University. Informed consent was obtained from all study participants.

Study population

This is the prospective longitudinal study. Patients were considered eligible for study inclusion when they had been in 5-stage chronic kidney disease (CKD) before the commencement of dialysis treatment. The same patients are observed 12 months after the treatment of PD. The exclusion criteria

were anuria, underlying malignancy, chronic liver disease, systemic lupus erythematosus, carotid artery stenosis, chronic rheumatic heart disease or congenital heart disease, or incomplete data. On the basis of the inclusion and exclusion criteria, 50 ESRD patients were recruited at the dialysis unit, and they represented 89% of the total PD population at the unit. All patients were undergoing dialysis using the conventional lactate-buffered glucose-based PD solutions. They underwent 4 to 5 dialysis changes with 2 L of solution. The baseline of laboratory findings is complemented with echocardiography at the very beginning of dialysis treatment and after 12 months of PD. The patients were free from taking diuretic therapy prior to diuresis level measurement and sampling.

Echocardiography

Two-dimensional echocardiography was performed (Toshiba 270 SSA, New York, NY) using a 3.75 MHz transducer on all patients lying in the left decubitus position. Two-dimensional assessment of the aortic valve and mitral valve, together with continuous-wave Doppler ultrasound, was performed on the basis of the parasternal long-axis, parasternal short-axis, and apical views. Echocardiography was performed according to the recommendations of the American Society of Echocardiography,[6] and images were analyzed by a single experienced cardiologist who was blinded to all of the clinical details. LVH was defined according to Framingham's criteria (LVM/body surface area (BSA) $>110\,g/m^2$ in females and LVM/BSA $>134\,g/m^2$ in males).[7] LV geometry was evaluated based on LVM index (LVMi) and RWT. RWT was calculated by the standard formula, as follows: RWT = 2 × posterior wall thickness/LV end-diastolic diameter;[8] a normal value was assumed to be lower than 0.45. Concentric LVH was defined as LVH and elevated RWT, while LVH and normal RWT indicated eccentric LVH. Normal LVMi but elevated RWT was defined as concentric remodeling.

Valvular calcification was defined as bright echoes of >1 mm on one or more cusps of the aortic valve or mitral valve or mitral annulus. Sensitivity and specificity for echocardiographic detection of calcium in the mitral valve or mitral annulus and aortic valve were reported to be 76 and 89 to 94%, respectively.[9]

Measurement of RRF and dialysis adequacy

The daily urine and dialysis fluid were collected at the time of baseline blood collection for measurement of residual renal function (RRF), dialysis, and total weekly urea and creatinine clearance. RRF was measured as the average of 24-h urine urea and creatinine clearance.[10] Total weekly urea clearance and creatinine clearance were measured using standard methods.[11]

Statistical analysis

All data were expressed as the mean standard deviation (SD) or as median and interquartile range. The distribution of variables was tested by the Shapiro–Wilk test. Significant change in the variables from baseline to 12 months after treatment was tested by paired *t*-test for the variables that followed normal distribution or by the Wilcoxon signed-rank test for the variables that had skewed distribution. The difference between two groups was analyzed by the Mann–Whitney test. A multiple regression analysis was applied to examine the relationship between echocardiography and a set of clinical and laboratory parameters. A *p*-value of <0.05 (two-sided) was regarded as statistically significant. SPSS (Chicago, IL) for Windows (Version 16.0) was used for statistical analysis.

Results

The characteristics of the study patients are shown in Table 1. The underlying cause of ESRD was diabetic nephropathy in 24 (48%), hypertensive nephrosclerosis in 9 (18%), chronic glomerulonephritis in 7 (14%), pyelonephritis in 7 (14%), and not identified in 3 (6%) patients. Overall, 80% of the patients were using calcium-containing phosphate binders, and 38% of the patients were receiving vitamin D preparations.

Comparison of various parameters in patients with and without LVH is provided in Table 2. In ESRD patients, LVH was diagnosed in 39 patients (78%); most of these (22%) had concentric LVH. Eccentric LVH and concentric remodeling were identified in 15 (30%) and two patients (4%), respectively. The ejection fraction (EF) was found to be $50.1 \pm 9.4\%$ in the whole group; and E/A ratio is 0.9 ± 0.1, respectively. LVH was observed in 68% after 12 months on PD treatment. Among 34 PD patients with LVH, 38% had concentric LVH, 22% had eccentric LVH, and 2% had concentric remodeling. LV function was determined as significantly better after 12 months of PD (EF $56.9 \pm 10.0\%$, E/A ratio 1.1 ± 0.1; $p < 0.05$). Age, gender, daily urine volume, RRF, *Kt/V* urea weekly, systolic and diastolic blood pressure (BP) were significantly different between the two groups after 1 year of PD. On the other hand, endothelin-1 (ET-1), CaxP, and C-reactive protein (CRP) were higher in the group with LVH. Also, serum albumin was lower in the LVH group during follow, but not significantly.

The clinical and biochemical characteristics of patients with and without CVCs during the monitoring period are presented in Table 3. Among the 50 ESRD patients, nine (18%) had aortic valve calcification and 15 (30%) had mitral valve calcification. Five (10%) had calcification of both the aortic and mitral valves. There were no patients with valvular stenosis. After 12 months of PD regimen, 10 (20%) patients had aortic valve calcification and 12 (24%) had mitral valve calcification. Four (8%) patients had calcification of both the aortic and mitral valves. LVH was found in 79% of the patients with CVC but only in 44% without CVC before RRT. After one year of PD, LVH was 62 and 36% in patients with and without CVC, respectively ($p < 0.05$).

At the beginning of the study, the model was statistically significant (Chi square = 47.9; $p < 0.001$) and could explain between 62% (R^2 Cox and Snell) and 82% (R^2 Nagelkerkea) variance results and correctly classified 92% of cases. The model after 12 months was statistically significant (Chi square = 37.0; $p < 0.001$) and was able to explain between 52% (R^2 Cox and Snell) and 77% (R^2 Nagelkerkea) variance results and accurately classified 90% of cases (Table 4).

Table 1. Characteristics of study subjects.

Characteristic	Value	
	Baseline	End of follow-up
Age (years) (median [IQR])	60.5 (19–76)	
Gender (m/f) (*n*)	25 (50%)	
Smokers (*n*)	18 (45%)	16 (32%)
Diabetes (*n*)	26 (52%)	
BMI (kg/m^2)	25.9 ± 3.7	25.8 ± 2.6
SBP (mmHg; mean ± SD)	147.4 ± 20.1	134.2 ± 14.4[b]
DBP (mmHg; mean ± SD)	89.2 ± 12.6	79.4 ± 9.8[a]
Hemoglobin (g/dL; mean ± SD)	101.9 ± 10.3	109.8 ± 8.9
Serum albumin (g/L; mean ± SD)	30.9 ± 2.6	30.9 ± 2.6[b]
Serum calcium (mmol/L; mean ± SD)	2.2 ± 0.2	2.2 ± 0.1
Phosphorous (mmol/L; mean ± SD)	1.8 ± 0.3	1.6 ± 0.2[b]
Ca × P (mean ± SD)	3.9 ± 0.6	3.6 ± 0.6[b]
iPTH (pg/mL; mean ± SD)	225.5 (97.8–387.0)	205.0 (102.0–336.0)
CRP (mg/L; mean ± SD)	11.1(6.1–16.4)	5.9(3.5–8.9)[a]
Total cholesterol (mmol/L; mean ± SD)	6.5 ± 1.6	5.9 ± 1.2[b]
Triglyceride (mmol/L; mean ± SD)	2.4 ± 1.3	2.0 ± 0.4
HDL (mmol/L; mean ± SD)	1.0 ± 0.3	1.3 ± 0.3[b]
LDL (mmol/L; mean ± SD)	4.7 ± 1.4	3.8 ± 0.8[a]
Homocysteine (μmol/L; median [IQR])	25.2 (20.2–30.1)	21.0 (16.7–23.4)[b]
Nitric oxide (μmol/L; median [IQR])	40.72 (19.4–56.7)	45.95 (33.5–60.0)[a]
Endothelin-1 (pg/ml; median [IQR])	4.0 (2.27–6.3)	4.68 (2.9–6.6)[a]
Urine volume (mL/day; mean ± SD)	545.6 ± 378.5	538.0 ± 425.2
RRF (ml/min per 1.73 m^2; mean ± SD)	5.5 ± 3.8	6.5 ± 5.0[b]
Total weekly *Kt/V* (mean ± SD)	1.9 ± 0.8	2.1 ± 0.9[b]
Medication use		
Erythropoietin (*n*; %)	36 (72)	43 (86)
Antihypertensive drugs (*n*; mean ± SD)	2.0 ± 1.0	1.5 ± 1.0
ACEI or ARB (*n*; %)	32 (64)	29 (58)
Vitamin D analogs (*n*; %)	19 (38)	22 (44)
Calcium-based phosphate binders (*n*; %)	40 (80)	37 (74)

Notes: IQR, interquartile range; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic BP; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.
[a]Significant differences, $p < 0.01$.
[b]Significant differences, $p < 0.05$.

Discussion

In this longitudinal study of ESRD patients, we showed for the first time that definitely loss of kidney function was associated with an increased risk for valvular calcification, but this association was partly lost when controlling a series hemodynamic and non-hemodynamic risk factors using adequate PD treatment.

Cardiovascular diseases are the most frequent cause of mortality in patients with ESRD. CVC and LVH are independent predictors of cardiovascular mortality and have frequently been noted in PD patients.[12] In this patient group, cardiac structure and function are frequently abnormal and 74% of patients with CKD stage 5 have LVH at the initiation of RRT. Cardiac changes, such as LVH and impaired LV systolic function, have been associated with an unfavorable prognosis. Despite the prevalence of underlying cardiac abnormalities, symptoms may not manifest in many patients.[13]

Abnormalities in LV size and function are common in dialysis patients due to a variety of reasons, such as volume overload, anemia, secondary hyperparathyroidism, chronic inflammation, and malnutrition.[14]

In a study by Wang et al.,[15] they showed that in adult chronic PD patients, the prevalence of LVH was noted to be as high as 94.8%. Similarly, in another study, 86.4% of the patients overall had LVH; among these, 56.3% had concentric LVH, 30.1% had eccentric LVH, 6.8% had concentric remodeling, and only 6.8% of the patients had normal LV geometry.[16] In our PD patients, the prevalence of LVH was 78% at baseline with significant reduction in LVMi and significant improvement of systolic and diastolic LV function after 12 months of PD treatment. Among our patients normal LV geometry was observed in 22% of patients at baseline and in 38% after 12 months on PD. Similarly, in another study it has been proven that regression of LVH in dialysis patients is possible.[14] Namely, LVM and LVMi are modifiable factors, and their reduction decreases cardiovascular risk, especially in the dialysis population.[17] Important indicators of LVMi changes are hemodynamic and non-hemodynamic factors. In PD patients, the most prominent hemodynamic parameters are hypertension of high prevalence, volume overload and anemia.

Soft-tissue calcifications, including CVCs, are common in both hemodialysis (HD) and PD patients. Specifically, prevalences of 38.2 and 44.4% of mitral and aortic calcification, respectively, were described in HD patients,[18] while mitral CVC was found in 26.3% of PD patients and aortic CVC in 57.8%.[12]

Data, herein, reported show a frequent present calcification of mitral and aortic valves in patients before starting treatment with PD. These findings suggest the presence of different mechanisms underlying the damage on heart valves.

Table 2. Clinical and biochemical characteristics of all patients with and without left ventricular hypertrophy at baseline and 1 year later on PD.

	Baseline		End of follow-up	
Characteristic	LVH (−) (11)	LVH (+) (39)	LVH (−) (16)	LVH (+) (34)
Age (years) (median [IQR])	46.5 (19–68)	57 (43–76)[a]	44.3 (19–68)	60.5 (49–76)[b]
Gender (m/f) (*n*)	7/4	17/22[a]	10/7	14/20[b]
Smokers (*n*)	1	14[a]	0	13[b]
Diabetes (*n*)	6	17[a]	9	14[b]
BMI (kg/m^2)	23.9 ± 3.4	26.5 ± 3.6	24.6 ± 2.2	26.4 ± 1.9
SBP (mmHg; mean ± SD)	128.2 ± 8.7	152.8 ± 19.1[a]	123.6 ± 9.2[c]	137.4 ± 14.6[b,c]
DBP (mmHg; mean ± SD)	79.1 ± 9.4	92.1 ± 12.0[a]	71.8 ± 24.1	82.1 ± 10.4[b,c]
Hemoglobin (g/dL; mean ± SD)	108.8 ± 10.7	99.9 ± 9.4[a]	111.0 ± 8.3[c]	110.1 ± 9.1[c]
Serum albumin (g/L; mean ± SD)	34.9 ± 4.3	29.5 ± 3.8	31.4 ± 2.1	30.9 ± 2.8
Serum calcium (mmol/L; mean ± SD)	2.3 ± 0.1	2.2 ± 0.2	2.2 ± 0.1	2.3 ± 0.1
Phosphorous (mmol/L; mean ± SD)	1.5 ± 0.2	1.8 ± 0.3[a]	1.4 ± 0.2	1.7 ± 0.2[b,c]
Ca × P (mean ± SD)	3.3 ± 0.6	4.0 ± 0.5[a]	3.0 ± 0.4[c]	3.8 ± 0.5[b]
iPTH (pg/mL; mean ± SD)	173.6 ± 133.0	290.0 ± 210.3	136.6 ± 103.2	313.3 ± 246.8[b]
CRP (mg/L; mean ± SD)	5.7 ± 3.5	13.9 ± 8.4[a]	3.1 ± 1.5	9.0 ± 12.8[b,c]
Total cholesterol (mmol/L; mean ± SD)	5.7 ± 1.9	6.7 ± 1.5[a]	4.9 ± 1.0[c]	6.0 ± 0.8[b,c]
Triglyceride (mmol/L; mean ± SD)	2.0 ± 1.5	2.5 ± 1.2	1.4 ± 0.4[c]	1.8 ± 0.3[bc]
HDL (mmol/L; mean ± SD)	1.4 ± 0.3	1.0 ± 0.2[a]	1.7 ± 0.2[c]	1.2 ± 0.3[b]
LDL (mmol/L; mean ± SD)	3.8 ± 1.9	5.0 ± 1.2[a]	2.9 ± 0.5[c]	4.0 ± 0.6[bc]
Homocysteine (μmol/L; median [IQR])	20.2 (19.7–26.5)	26.6 (21.6–31.4)	14.8 (13.8–19.9)[c]	22.2 (18.0–23.4)[b,c]
Nitric oxide (μmol/L; median [IQR])	63.2 (59.7–106.2)	28.5 (14.8–46.8)[a]	98.2 (63.9–106.2)[c]	43.9 (33.0–49.1)[b,c]
Endothelin-1 (pg/mL; median [IQR])	2.6 (2.2–4.0)	7.0 (4.1–8.8)[a]	2.3 (2.0–2.9)[c]	5.8 (4.0–8.0)[b,c]
Urine volume (mL/day; mean ± SD)	750.0 ± 463.1	487.9 ± 335.9	959.1 ± 508.8	413.2 ± 320.4[b]
RRF (mL/min per 1.73 m^2; mean ± SD)	7.2 ± 4.2	5.0 ± 3.5	10.7 ± 6.3[c]	4.8 ± 3.7[b,c]
Total weekly *Kt/V* (mean ± SD)	2.0 ± 0.9	1.77 ± 0.43	2.4 ± 0.7	2.1 ± 0.3[b]
Medication use				
Erythropoietin (*n*)	4	32	13	30
Antihypertensive drugs (*n*; mean ± SD)	1.5 ± 1.0	2 ± 1.0	1 ± 0.5	2 ± 1.0
ACEI or ARB (*n*)	2	30	4	25
Vitamin D analogs (*n*)	8	11	10	12
Calcium-based phosphate binders (*n*)	6	34	11	26

Notes: IQR, interquartile range; LVH, left ventricular hypertrophy; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic BP; iPTH, intact parathyroid hormone; CRP, C-reactive protein; HDL, high-density lipoprotein; LDL, low-density lipoprotein; RRF, residual renal function; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker

[a]Significant difference between without and with LVH at baseline.

[b]Significant difference between without and with LVH after 1 year.

[c]Significant difference in the same group before (basal) and 12 months after PD treatment.

Significant differences, $p < 0.01$; $p < 0.05$.

Compared with the initial results, a significant smaller number of patients have valve calcification in the relatively short period of 1-year of follow-up: 24% in the mitral valve and 20% in the aortic valve. The four (8%) patients had calcification of both the aortic and mitral valves. The similar or even higher rates of valve calcification have been reported in several studies in prevalent HD and PD patients.[18,19] However, the reduction recorded valvular calcification is only based on regression in mitral valves calcification. The number of patients with aortic calcifications at the end of the study is even slightly higher.

As a regression of valvular calcifications was seen in spite of uremic milieu, it seems that the metabolic changes induced by renal failure and secondary hyperparathyroidism may be the major mediators of CVC, rather than renal failure *per se*. Roosens and coworkers obtained similar results in animal models.[20]

Our longitudinal data also provided some suggestion that valvular calcification and the calcification milieu (e.g. inflammation and high Ca × P) may represent part of the process linking loss of renal function and LVH in patients before dialysis therapy and warrant further longer period of observation. In contrast to other studies,[21,22] which showed that increased transaortic flow velocities or pressure gradients promote LVH in HD patients with aortic valvular calcification and stenosis, our data suggest that the relationship between valvular calcification and LVH in PD patients is unlikely to be explained by valvular stenosis, because neither patient had valvular stenosis. As shown in our study, disorders of balance of vasoactive substances, lower RRF, increase calcification markers, dyslipidemia, and anemia all were associated with valvular calcification and were each associated with LVH. CRP is recognized as an independent factor for the development of valvular calcification after 12 months of PD. This suggests that apart from traditional risk factors for LVH, vasoactive substances showed important relations with CVC and LVH in PD patients. Also, the results of our study suggest the positive effect of PD on the process of cardiovascular remodeling. Recently, similar results are presented Rroji and associates.[23] Furthermore, it is worth mentioning that there was no significant difference of values serum calcium and intact parathyroid hormone in the patients with and without CVCs at the end of the monitoring period.

The other factor that explained greater LVH and dilation and more diastolic dysfunction among PD patients with valvular calcification than those without may relate to an increased arterial stiffening.[24] A study of HD patients reported greater LVH and more diastolic dysfunction among

Table 3. Clinical and biochemical characteristics of all patients with and without valve calcification at baseline and 1 year later on PD.

	Baseline		12 months on PD	
Variable	CVC (−) (21)	CVC (+) (29)	CVC (−) (24)	CVC (+) (26)
Age (years) (median [IQR])	42 ± 13	58 ± 18	40 ± 11	60 ± 16[b]
Gender (m/f) (*n*)	15/6	10/19	16/8	9/17
Smokers (*n*)	8/12	18/12[a]	8/15	18/9[b]
Diabetes (*n*)	22.75 ± 2.9	27.56 ± 3.5[a]	23.94 ± 1.6	26.98 ± 1.7 < 0.05[b,c]
BMI (kg/m^2)	2/14	16/18[a]	0/26	16/6[b]
SBP (mmHg; mean ± SD)	137.50 ± 15.3	156.82 ± 19.6[a]	123.68 ± 10.1[c]	136.92 ± 10.3[b,c]
DBP (mmHg; mean ± SD)	80.63 ± 11.2	95.91 ± 9.1[a]	76.84 ± 7.5	80.0 ± 10.0[b]
Hemoglobin (g/dL; mean ± SD)	109.1 ± 11.1	96.6 ± 7.8	125.1 ± 10.0[c]	109.2 ± 9.6[b,c]
Serum albumin (g/L; mean ± SD)	33.6 ± 4.1	28.2 ± 3.1[a]	32.0 ± 2.1	30.5 ± 2.0[b]
Serum calcium (mmol/L; mean ± SD)	2.2 ± 0.2	2.15 ± 0.2	2.26 ± 0.1	2.3 ± 0.1
Phosphorous (mmol/L; mean ± SD)	1.7 ± 0.3	1.9 ± 0.2[a]	1.5 ± 0.2	1.8 ± 0.1[b,c]
Ca × P (mean ± SD)	3.8 ± 0.7	3.98 ± 0.6	3.35 ± 0.5	3.96 ± 0.3[b,c]
iPTH (pg/mL; mean ± SD)	224.0 ± 219.7	308.5 ± 208.7[a]	241.4 ± 215.6	277.8 ± 156.2
CRP (mg/L; mean ± SD)	8.1 ± 5.8	16.1 ± 9.4[a]	3.5 ± 2.7[c]	6.8 ± 3.2[b,c]
Total cholesterol (mmol/L; mean ± SD)	5.82 ± 1.1	7.10 ± 1.8	5.03 ± 1.3[c]	6.28 ± 1.6[c]
Triglyceride (mmol/L; mean ± SD)	2.07 ± 1.5	2.73 ± 1.2	1.83 ± 0.3	2.44 ± 4.0[b,c]
HDL (mmol/L; mean ± SD)	1.23 ± 0.3	0.93 ± 0.2[a]	1.56 ± 0.3[c]	1.14 ± 0.3[b,c]
LDL (mmol/L; mean ± SD)	3.78 ± 1.2	5.18 ± 1.5[a]	3.31 ± 0.7[c]	3.95 ± 0.7[b,c]
Homocysteine (μmol/L; median [IQR])	22.9 (19.8–30.0)	28.0 (23.7–33.6)	16.8 (13.3–19.3)[c]	20.9 (18.9–26.3)[b,c]
Nitric oxide (μmol/L; median [IQR])	55.2 (45.7–69.4)	42.2 (34.9–56.8)[a]	56.8 (46.6–72.4)	49.5 (33.0–66.2)[b,c]
Endothelin-1 (pg/mL; median [IQR])	3.2(2.6–6.9)	4.1 (3.1–4.7)[a]	3.0 (2.1–5.0)	3.4 (2.3–4.9)[c]
Urine volume (mL/day; mean ± SD)	609.09 ± 311.3	424.00 ± 327.6[a]	535.00 ± 396.7	226.15 ± 208.8[b,c]
RRF (mL/min per 1.73 m^2; mean ± SD)	6.8 ± 4	3.9 ± 2[a]	7.4 ± 2.7	3.7 ± 1.6[c]
Total weekly *Kt/V* (mean ± SD)	2.0 ± 0.3	1.88 ± 0.76	2.2 ± 1.6	2.1 ± 0.2[c]
LVH (%)	44	79	36	62
LVMi (g/m^2)	149.52 ± 34.9	176.58 ± 36.0[a]	119.5 ± 29.6[c]	173.75 ± 35.3[b,c]
EF (%)	56.59 ± 7	44.32 ± 7.9[a]	62.37 ± 8.2[c]	48.38 ± 6.9[b,c]
E/A ratio	1.04 ± 0.1	0.89 ± 0.1[a]	1.14 ± 0.1	1.02 ± 0.0[b]
Medication use				
Erythropoietin (*n*)	14	22	18	25
Antihypertensive drugs (*n*; mean ± SD)	2.0 ± 0.5	1.5 ± 1.0	1.5 ± 1.0	2.5 ± 1.0
ACEI or ARB (*n*)	12	20	16	13
Vitamin D analogs (*n*)	11	8	14	8
Calcium-based phosphate binders (*n*)	13	27	11	26

Notes: IQR, interquartile range; CVC, cardiac valve calcification; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic BP; iPTH, intact parathyroid hormone; CRP, C-reactive protein; HDL, high-density lipoprotein; LDL, low-density lipoprotein; RRF, residual renal function; LVH, left ventricular hypertrophy; LVMi, LV mass index; EF, ejection fraction; E/A, the ratio of the early (E) to late (A) ventricular filling velocities; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.
[a]Significant difference between non-CVC and with CVC at baseline.
[b]Significant difference between non-CVC and with CVC after 1 year.
[c]Significant difference in the same group before (basal) and 12 months after PD treatment.
Significant differences, $p < 0.01$; $p < 0.05$.

Table 4. Multiple logistic regression analysis for valvular calcification before and after one year on PD treatment.

Dependent variable	Predictors	*B*	SE	*p*	OR (95% CI)
Valvular calcification before RRT	Serum albumin	−1.111	0.459	0.015	0.329 (0.134 to 0.809)
	Hemoglobin	−0.155	0.074	0.037	0.857 (0.741 to 0.991)
	Endothelin-1	0.56	2.933	0.048	2.119 (1.927 to 2.408)
	LDL	1.402	0.652	0.032	4.063 (1.131 to 4.591)
	Age	0.171	0.078	0.029	1.186 (1.018 to 1.383)
Valvular calcification after 12 months on PD	Female	−3.137	1.546	0.042	0.043 (0.002 to 0.898)
	BMI	0.434	0.204	0.033	1.544 (1.035 to 2.304)
	CRP	0.453	0.171	0.008	1.572 (1.124 to 2.200)
	Nitric oxide	−0.622	0.048	0.031	0.902 (0.886 to 1.109)
	Hemoglobin	−0.310	0.093	0.001	0.733 (0.611 to 0.880)

Note: RRT, renal replacement therapy; SE, standard error; CI, confidence interval; OR, odds ratio; LDL, low-density lipoprotein; BMI, body-mass index; CRP, C-reactive protein.

those with vascular calcification.[25] Given the positive correlations between valvular and vascular calcification in patients with ESRD, we speculate that the association between valvular calcification and LVH in our PD patients may also be partly explained by arterial stiffening and will need further investigation.

The valve calcification and LVH in our patients at the very beginning of PD treatment are indicative of the present

morphological changes on LV structure and valves in these patients. The mentioned results are agreement with previous reports by other authors.[12,15]

At the beginning of PD treatment the patients who had CVC and LVH, accompanied by higher ET-1 serum values and lower NO concentration levels, compared to after 1 year of PD treatment. The relation between the ET1 and CVC had not been previously described in a PD population. The conducted research established that ET1 is significantly independent predictor of valve calcifications at the baseline, while NO is significantly inversely independent predictor at the end of the follow-up.

According to the results of this study, the level ET1 represents one of the most important factors to be closely associated with the formation CVC in PD patients. Several previous studies suggest that the production of ET-1 is increased in patients with the advanced atherosclerosis and that this contributes to the exacerbated endothelial-dependent vasodilatation in experimental models with accelerated atherosclerosis, as well as humans.[26] ET1 plays an important role in maintaining BP and arterial stiffness, which contributes to the development of oxidative stress and inflammation, in the long term, cardiovascular remodeling.

The biological basis of a possible adverse effect of hypoalbuminemia on cardiac structure and function is unclear.[27] Serum albumin levels were found to be inversely associated with the progression of LV dilation, especially in PD patients. In the present study, serum albumin was lower in the LVH group, which can be explained by hypervolemia-induced dilution, but no statistically significant. Hypoalbuminemia is also a major risk factor for mortality in ESRD patients, and an important link between inflammation and CVC in PD patients has been reported. The presence of inflammation and malnutrition (as compared with no evidence of inflammation or malnutrition) was associated with at least a doubling in the prevalence of CVC.[28] In our study, patients with CVC had significantly lower serum albumin at the end follow-up. The decreased serum albumin level at the beginning of PD treatment was an independent predictor of CVC.

During the first year, RRT and reduction in hemoglobin levels by 1 g/L increases LVH incidence.[29] Our results support the view that reducing cardiovascular remodeling, although not necessarily in the physiological ranges, might be achieved through anemia treatment (epoetin substitution) by a reduction in BP, at least under certain circumstances. The hemoglobin level was found to be an independent predictor of valvular calcifications and at the start and end of the study.

Also, using multivariate analysis at the end monitoring period age, BMI and female gender are proved as independent risk factors of valvular calcifications, probably due to the strong correlation between observed variables. These data agree with the results presented by Wang and co-workers.[15]

Our study has some limitations. First, it has a small sample and relatively short time of follow-up. Second, echocardiography instead of electron-beam computed tomography was used to detect valvular calcification and does not allow quantification of calcium in the heart valves and other vasculature. Third, patients are not specifically separated as patients with diabetes mellitus and there is a need to include patients after kidney transplantation. Therefore, we would suggest a multicentric study with a larger number of PD patients and a longer time of follow-up for the evaluation of the findings. Our study shows that the adequate PD treatment contributes significantly to the maintenance of hemodynamic and non-hemodynamic balance and may explain the lower prevalence of valve calcification in PD patients compared with ESRD patients in the period up to first year under renal replacement therapy.

In summary, heart valve calcification is a frequent and rapid phenomenon that seems to affect mitral and aortic valves in different ways and to different magnitudes. CVC is associated with LVH. Intensive monitoring of risk factors of cardiovascular disease and cardiovascular parameters in PD patients is necessary in order to prevent and reverse unwanted changes to the cardiovascular system. PD treatment, together with regulation of potentially reversible risk factors, significantly prevents the process valvular calcification and cardiac remodeling.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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