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Evaluation of the relationship between cardiac calcification and cardiovascular disease using the echocardiographic calcium score in patients undergoing peritoneal dialysis: a cross-sectional study

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ABSTRACT

Introduction: An echocardiographic calcium score (ECS) predicts cardiovascular disease (CVD) in the general population. Its utility in peritoneal dialysis (PD) patients is unknown.

Methods: This cross-sectional study assessed 125 patients on PD. The ECS (range 0–8) was compared between subjects with CVD and those without.

Results: Among the subjects, 54 had CVD and 71 did not. Subjects with CVD were older (69 years vs. 56 years, $p < 0.001$) and had a higher prevalence of diabetes mellitus (DM) (81.5% vs. 45.1%, $p < 0.001$). They had lower diastolic blood pressure (72 mmHg vs. 81 mmHg, $p < 0.001$), lower phosphate (1.6 mmol/L vs. 1.9 mmol/L, $p = 0.002$), albumin (30 g/L vs. 32 g/L, $p = 0.001$), parathyroid hormone (34.4 pmol/L vs. 55.8 pmol/L, $p = 0.002$), total cholesterol (4.5 vs. 4.9, $p = 0.047$), LDL cholesterol (2.4 mmol/L vs. 2.8 mmol/L, $p = 0.019$) and HDL cholesterol (0.8 mmol/L vs. 1.1 mmol/L, $p = 0.002$). The ECS was found to be higher in subjects with CVD than in those without (2 vs. 1, $p = 0.001$). On multivariate analysis, only DM and age were independently associated with CVD..

Conclusion: The ECS was significantly higher in PD patients with CVD than in those without, reflecting a higher vascular calcification burden in the former. It is a potentially useful tool to quantify vascular calcification in PD patients.

Keywords: calcification, cardiovascular disease, echocardiography, end-stage renal disease, peritoneal dialysis

INTRODUCTION

Cardiovascular disease (CVD) causes significant mortality and morbidity in patients with end-stage renal disease (ESRD).[1] Although traditional risk factors such as age, gender, smoking, hyperlipidaemia and family history are important determinants of cardiovascular risk, additional factors such as systemic inflammation, protein energy wasting, and mineral and bone disorders of chronic kidney disease are at play in the setting of ESRD. These factors have yet to be incorporated into well-established risk prediction models tailor-made for ESRD patients.[2] Furthermore, the diagnosis of ischaemic heart disease (IHD) in ESRD is a challenge because symptoms of fluid overload mimic those of cardiac ischaemia and might lead to over-investigation. Regarding the treatment of IHD in ESRD, the decision to revascularise is relatively straightforward in patients who fail medical therapy, but less so in those with asymptomatic high-risk coronary lesions.[3]

Vascular calcification is a predictor of cardiovascular morbidity and mortality in ESRD.[4-13] The presence of calcification, as detected by electron beam computed tomography (EBCT), has been shown to correlate with obstructive coronary lesions and adverse outcomes.[14,15] Current revascularisation practice in patients with ESRD is guided by data drawn from the general population, but tools to stratify cardiovascular risk in ESRD may result in further refinements that may prove beneficial. In particular, coronary artery calcification in the general population increases the risk of procedural failure and complications after coronary interventions; this may potentially argue against overzealous percutaneous or surgical interventions in patients with ESRD in whom calcification is highly prevalent.[16]

In the general population, an echocardiographic calcium score (ECS), which assesses calcification at four cardiac sites, namely the papillary muscles, mitral annulus, aortic valve leaflets and the aortic root, correlates with coronary and non-coronary calcium burden and obstructive coronary artery disease as detected by EBCT. Furthermore, it predicts myocardial

infarction and all-cause mortality.[17-20] Unlike EBCT, transthoracic echocardiography is readily available and does not involve radiation. To the best of our knowledge, it has not yet been utilised in patients with ESRD.

We hypothesise that the ECS has similar diagnostic value in peritoneal dialysis (PD) patients. In this cross-sectional study, we used the ECS to assess calcification in PD patients. The ECS was compared between subjects with established CVD and those without.

METHODS

The study was conducted in a regional hospital caring for more than 300 patients on PD. Recruitment for the study started on 1 July 2016 and ended on 31 December 2016. The study took place at the dialysis clinic when patients visited for routine follow-up. Patients undergoing PD who were older than 18 years and had received dialysis for at least three months were included. An echocardiogram was performed after obtaining informed consent. Patients with the following characteristics were excluded: inability to provide informed consent, chronic rheumatic heart disease, congenital heart disease, active malignancy, liver cirrhosis, systemic lupus erythematosus, suboptimal echocardiography, history of undergoing long-term haemodialysis, and history of kidney transplantation or parathyroidectomy. The study was approved by the local research ethics committee (IRB approval number KW/EX-16-121[101-11]) and is in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Transthoracic echocardiography was performed with a ProSound F37 ultrasonography machine (Hitachi Aloka Medical America, Wallingford, Connecticut, USA) capturing the parasternal long axis, parasternal short axis, apical four-chamber, apical five-chamber, apical two-chamber and apical three-chamber views. Definitions are summarised in Table I and are

described as follows: mitral annular calcification is a well-defined echogenic structure situated at the junction of the atrioventricular groove and the posterior mitral leaflet. Its size is assessed by measuring its anteroposterior diameter in the parasternal long-axis view. Aortic root calcification is a focal or diffuse area of increased echogenicity or thickening of the aortic root in the parasternal long axis view. Aortic valve sclerosis or calcification refers to increased echogenicity or thickening of the most heavily involved aortic valve leaflet measured in the parasternal long axis view. Papillary muscle calcification refers to a well-defined echogenic spot involving one or both papillary muscles in any view. The echocardiograms were recorded and stored dynamically as a digital file, which was labelled with a unique identifier. Two independent and blinded echocardiographers individually assessed the echocardiograms in a retrospective manner.

Table I. Echocardiographic calcium scores.

Grade	Aortic root calcification	Aortic valve sclerosis	Mitral annular calcification	Papillary muscle calcification
0	Absent	Absent	Absent	Absent
1	Present	Mild ≥ 2 mm	Mild < 5 mm	Present
2	–	Moderate ≥ 4 mm	Moderate 5–10 mm	–
3	–	Severe ≥ 6 mm	Severe ≥ 10 mm	–

Cardiovascular disease (CVD) was defined as any of the following: IHD, cerebrovascular disease and peripheral vascular disease (PVD). IHD was defined as any of the following: classical angina, acute coronary syndrome, percutaneous coronary interventions or coronary artery bypass graft surgery, and stress-testing or imaging documenting the presence of coronary artery disease. Cerebrovascular disease included symptomatic and asymptomatic brain infarcts and transient ischaemic attacks. PVD was defined as symptoms, signs and

complications related to ischaemia of arterial origin in the upper or lower limbs or arterial stenosis or occlusion documented by imaging.

Demographic, clinical and laboratory data within three months of echocardiography were collected for each subject.

Sample size estimation was performed using an online sample size calculator (Epitools AusVet, Canberra, Australia) for two-tailed *t*-tests. We assumed the prevalence of CVD to be 40% and the standard deviation of ECS to be 1. We set $\alpha = 0.05$ and $\beta = 0.2$. We estimated that 53 subjects with CVD and 80 subjects without CVD were needed to detect a one-unit difference in ECS between the two groups. The total required sample size was thus 133.

Statistical analysis was performed with IBM SPSS Statistics version 23.0 (IBM Corp, Armonk, NY, USA). Numeric data were summarised as mean ± standard deviation (SD) for normal data, and median with the interquartile range (IQR) specified in parentheses for non-parametric data. Categorical data were summarised as proportions. Interobserver agreement for ECS was assessed using the intraclass correlation coefficient (ICC). Univariate comparisons were made using the two-tailed *t*-test or Mann-Whitney *U* test for continuous variables and the Pearson chi-square test or Fisher's exact test for categorical variables. Bivariate relationships were assessed using the Pearson correlation and Spearman correlation for normal data and non-parametric data, respectively. Multivariate analyses were performed using logistic and linear regression models. In all analyses, a p-value < 0.05 was considered statistically significant.

RESULTS

The medical records of 170 patients were screened. Three patients were excluded because of the presence of systemic lupus erythematosus, liver cirrhosis and chronic rheumatic heart disease. 42 subjects were subsequently excluded because of suboptimal echocardiography. The sample population was thus 125, of whom 54 (43.2%) had CVD and 71 (56.8%) did not (Fig. 1). Demographic, clinical and laboratory data are summarised in Tables II and III. There were 82 men and 43 women in the cohort, and their mean age was 61 ± 13 years. Diabetes mellitus (51.2%) was highly prevalent as the cause of ESRD. Other major causes of ESRD included hypertension (11.2%) and immunoglobulin A nephropathy (9.6%), but a significant proportion of the subjects had unknown aetiology (15.2%). 41 (32.8%) subjects were either current or ex-smokers, whereas 84 (67.2%) subjects had never smoked. The median duration of dialysis was 32 (IQR 16–54) months. Subjects were well dialysed with a median weekly Kt/V of 2.01 (IQR 1.86–2.39). The mean blood pressure was 138 ± 16/77 ± 11 mmHg. The dialysate calcium concentration was 1.75 mmol/L in 57 (45.6%) subjects and 1.25 mmol/L in 68 (54.4%) subjects. 80 (64%) subjects were on statin therapy, and 101 (80.8%) subjects were on either angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. Median calcium carbonate and active vitamin D analogue dosages were 20 (IQR 0–30) mmol per day or 2 (IQR 0–3) g per day and 0.5 (IQR 0–1) mcg per week, respectively. None of the subjects were on warfarin or novel oral anticoagulants. Of the 76 subjects with diabetes mellitus, 26 (59%) of those with CVD and 16 (50%) of those without CVD received insulin therapy (p = 0.488). The median intact parathyroid hormone (iPTH) level was 44.5 (IQR 24.1–78.5) pmol/L. Mean/median cholesterol levels were as follows: total cholesterol 4.7 ± 1.2 mmol/L; low-density lipoprotein (LDL) cholesterol 2.7 ± 1.0 mmol/L; high-density lipoprotein (HDL) cholesterol 0.9 (IQR 0.8–1.3) mmol/L and triglycerides 1.8 (IQR 1.2–2.9) mmol/L. Among

subjects with CVD, 24 (44.4%) had IHD, 37 (68.5%) had cerebrovascular disease and 12 (22.2%) had PVD.

Table II. Characteristics of subjects with and without cardiovascular disease (CVD).

Characteristic	No. (%)			p-value
	Total (n = 125)	History of CVD (n = 54)	No history of CVD (n = 71)	
Echocardiographic calcium score	1.5 (1.0, 2.5)	2.0 (1.5, 3.0)	1.0 (1.0, 2.0)	0.001
Demographic and clinical parameters				
Age* (yr)	61 ± 13	69 ± 11	56 ± 13	0.001
Male gender	82 (65.6)	39 (72.2)	43 (60.6)	0.174
Body mass index* (kg/m^2)	24.4 (21.9, 26.7)	24.3 ± 3.2	24.5 ± 3.8	0.769
Smoking status	41 (32.8)	17 (31.5)	24 (33.8)	0.784
Duration of dialysis* (mth)	32 (16, 54)	38 (19, 55)	29 (14, 53)	0.356
Diabetes mellitus	76 (60.8)	44 (81.5)	32 (45.1)	0.001
Atrial fibrillation	10 (8.0)	9 (16.7)	1 (1.4)	0.002
Systolic BP* (mmHg)	138 ± 16	138 ± 19	137 ± 13	0.758
Diastolic BP* (mmHg)	77 ± 11	72 ± 12	81 ± 9	0.001
Pulse pressure* (mmHg)	61 ± 13	67 ± 14	57 ± 12	0.001
Weekly total Kt/V*	2.01 (1.86, 2.39)	1.93 (1.78, 2.29)	2.10 (1.90, 2.40)	0.103
Dialysate calcium concentration				0.277
1.25 mmol/L	68 (54.4)	26 (48.1)	42 (59.2)	
1.75 mmol/L	57 (45.6)	28 (51.9)	29 (40.8)	
Prescriptions				
Warfarin	0 (0)	0 (0)	0 (0)	NA
Statins	80 (64.0)	39 (72.2)	41 (57.7)	0.095
ACEI/ARB[*]	101 (80.8)	40 (32.0)	61 (85.9)	0.096
Cinacalcet	8 (6.4)	4 (7.4)	4 (5.6)	0.688
Paricalcitol	2 (1.6)	0 (0)	2 (2.8)	0.214
Active vitamin D analogues	63 (50.4)	22 (40.7)	41 (57.7)	0.060
Calcium carbonate	93 (74.4)	42 (77.8)	51 (71.8)	0.450
Current calcium carbonate dose (mmol/day)*	20 (0, 30)	20 (10, 30)	20 (0, 30)	0.517
Current active vitamin D analogue dose (mcg/wk)*	0.5 (0, 1.0)	0 (0, 1.0)	0.5 (0, 1.0)	0.065

**Distributions are expressed as mean ± standard deviation or as median (25th percentile, 75th percentile). Comparisons were made using either the two-tailed t-test or Mann-Whitney U test, with $p < 0.05$ being considered statistically significant. ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; BP: blood pressure; NA: not applicable*

Table III. Biochemical and haematological parameters of subjects with and without cardiovascular disease (CVD).

Parameter	Mean ± SD/Median (Q1, Q3)*			p-value
	Total (n = 125)	History of CVD (n = 54)	No history of CVD (n = 71)	
Serum calcium (mmol/L)	2.39 ± 0.17	2.38 ± 0.17	2.39 ± 0.17	0.792
Serum phosphate	1.6 (1.4, 2.1)	1.6 ± 0.5	1.9 ± 0.6	0.002
Calcium X phosphate product ($mmol^2/L^2$)	3.8 (3.2, 5.0)	3.7 ± 1.1	4.5 ± 1.6	0.002
Serum albumin (g/L)	31 ± 5	30 ± 4	32 ± 6	0.001
Alkaline phosphatase	89 (67, 122)	84 (72, 108)	92 (63, 127)	0.589
Intact parathyroid hormone (pmol/L)				
Current	44.5 (24.1, 78.5)	34.4 (17.0, 61.5)	55.8 (31.5, 89.3)	0.002
Peak	54.8 (30.9, 85.2)	40.6 (25.0, 68.9)	61.8 (40.2, 98.7)	0.005
Haemoglobin (g/dL)	10.5 ± 1.3	10.5 ± 1.3	10.5 ± 1.3	0.752
CRP (mg/L)	1.6 (0.7, 4.0)	1.8 (0.9, 4.2)	1.6 (0.6, 3.9)	0.601
Total cholesterol (mmol/L)	4.7 ± 1.2	4.5 ± 1.2	4.9 ± 1.1	0.047
LDL cholesterol (mmol/L)	2.7 ± 1.0	2.4 ± 0.9	2.8 ± 1.0	0.019
HDL cholesterol (mmol/L)	0.9 (0.8, 1.3)	0.8 (0.7, 1.0)	1.1 (0.8, 1.4)	0.002
Triglyceride (mmol/L)	1.8 (1.2, 2.9)	1.8 (1.1, 3.4)	1.7 (1.3, 2.4)	0.444

**Distributions are expressed as mean ± standard deviation or as median (25th percentile, 75th percentile). Comparisons were made using either the two-tailed t-test or Mann-Whitney U test, with $p < 0.05$ being considered statistically significant. CRP: C-reactive protein; HDL: high-density lipoprotein; LDL: low-density lipoprotein*

The median ECS in the study population was 1.5 (IQR 1.0–2.5), with the maximum and minimum ECS being seven and zero, respectively. Only 7 (5.6%) subjects had an ECS of 0. The ICC between the scores of the two independent observers was 0.712 (95% confidence interval [CI] 0.590–0.798).

There were 54 subjects with CVD and 71 subjects without CVD (Tables II & III). Subjects with CVD were older (69 years vs. 56 years, $p < 0.001$). They had a higher prevalence of diabetes mellitus (81.5% vs. 45.1%, $p < 0.001$) and atrial fibrillation (16.7% vs. 1.4%, $p = 0.002$). Their diastolic blood pressure was significantly lower (72 mmHg vs. 81 mmHg, $p < 0.001$) and pulse pressure was significantly larger (67 mmHg vs. 57 mmHg, $p < 0.001$).

Biochemically, they had lower serum phosphate (1.6 mmol/L vs. 1.9 mmol/L, p = 0.002), parathyroid hormone (34.4 pmol/L vs. 55.8 pmol/L, p = 0.002), albumin (30 g/L vs. 32 g/L, p = 0.001), total cholesterol (4.5 mmol/L vs. 4.9 mmol/L, p = 0.047), LDL cholesterol (2.4 mmol/L vs. 2.8 mmol/L, p = 0.019) and HDL cholesterol (0.8 mmol/L vs. 1.1 mmol/L, p = 0.002) levels. The ECS was significantly higher in subjects with CVD (2.0 vs. 1.0, p = 0.001). There was no difference in either dialysis intensity or duration between the groups (Table II).

Five variables (age, serum albumin, diastolic blood pressure, diabetes mellitus and ECS) with the smallest p-values were included as covariates in a logistic regression model using CVD as the dependent variable (Table III). Only diabetes mellitus and age were independently associated with CVD. The odds of having CVD for every one-year increase in age were 1.094 (95% CI 1.044–1.147). The odds of having CVD associated with diabetes mellitus were 3.841 (95% CI 1.363–10.824).

Table III. Multivariate logistic regression model of important factors associated with cardiovascular disease in patients on peritoneal dialysis.

Factor	Unit increase	Odds ratio (95% CI)	p-value
ECS	1	1.128 (0.825–1.541)	0.451
Age	1 yr	1.094 (1.044–1.147)	0.001
Diabetes mellitus	Presence	3.841 (1.363–10.824)	0.011
Pulse pressure	1 mmHg	1.035 (0.998–1.073)	0.065
Serum albumin	1 g/L	0.945 (0.867–1.030)	0.197

Factors with $p \leq 0.001$ on univariate analysis were included in the multivariate logistic regression model. $p < 0.05$ was considered statistically significant. CI: confidence interval; ECS: echocardiographic calcium score

DISCUSSION

The Kidney Disease: improving Global Outcomes (KDIGO) guidelines recommend the assessment of valvular calcification by echocardiography to stratify cardiovascular risk in dialysis patients, but how this should be carried out is not specified.[21] We were able to detect a higher ECS in the CVD group despite similar intensities of dialysis between the groups as reflected by total weekly Kt/V values (Table II).

Our analysis showed that malnutrition might be associated with CVD. Although multiple studies in the past have shown a robust correlation between high phosphate levels and mortality, we found significantly lower phosphate levels in the CVD group. We hypothesise that decreased dietary intake in the CVD group might have led to lower phosphate, parathyroid hormone and cholesterol levels.[22,23] There was no difference in the prevalence of statin usage in the CVD and non-CVD groups.

Age and diabetes mellitus remained strong independent factors associated with CVD. Interestingly, these two factors are known to cause both intimal and medial arterial calcification.[24] There was no significant difference in the prevalence of insulin use between the CVD and non-CVD groups (59% vs. 50%, respectively, p = 0.488).

Vascular stiffness, a predictor of cardiovascular mortality, is closely linked to vascular calcification.[8] It is therefore not surprising that subjects in the CVD group had lower diastolic blood pressures resulting from the loss of vascular compliance

Clinical practices might affect the development of vascular calcification. Indeed, there is emerging evidence suggesting that calcium loading is a major risk factor for cardiovascular mortality in the dialysis population. The use of 'low-calcium' dialysate should be made routine to retard coronary artery calcification, improve calcium and phosphate balance, and reduce cardiovascular mortality.[25-32] Calcium-containing phosphate binders are another potential source of calcium loading. There are data showing that the use of non-calcium phosphate

binders can retard coronary calcification and reduce mortality.[33,34] The ECS, being a semi-quantitative tool, could be useful to monitor vascular calcification and its progression.

This study has limitations. Being cross-sectional in design, its finding of a higher ECS in subjects with CVD does not prove causality. On the other hand, a Type 2 error cannot be excluded in multivariate analysis owing to the small sample size. Despite the operator-dependent nature of echocardiography, the inter-observer agreement was respectable, with the ICC being 0.712 (1.000 for perfect agreement). Importantly, the ECS focused on cardiac calcification only, ignoring parameters such as left ventricular ejection fraction and left ventricular hypertrophy, which have prognostic implications. Although the dialysis vintage did not differ between the CVD and non-CVD groups, our study did not document the exact duration of chronic kidney disease before the commencement of dialysis, which could affect the development of CVD. To investigate the prognostic implication of the ECS, subjects recruited in this study could be followed up to assess outcomes such as cardiovascular morbidity and mortality.

In conclusion, the ECS was significantly higher in PD patients with CVD than in those without. Although it was not found to be an independent determinant of CVD in this undersized studyit is a potentially useful tool to quantify vascular calcification in PD patients.

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FIGURE

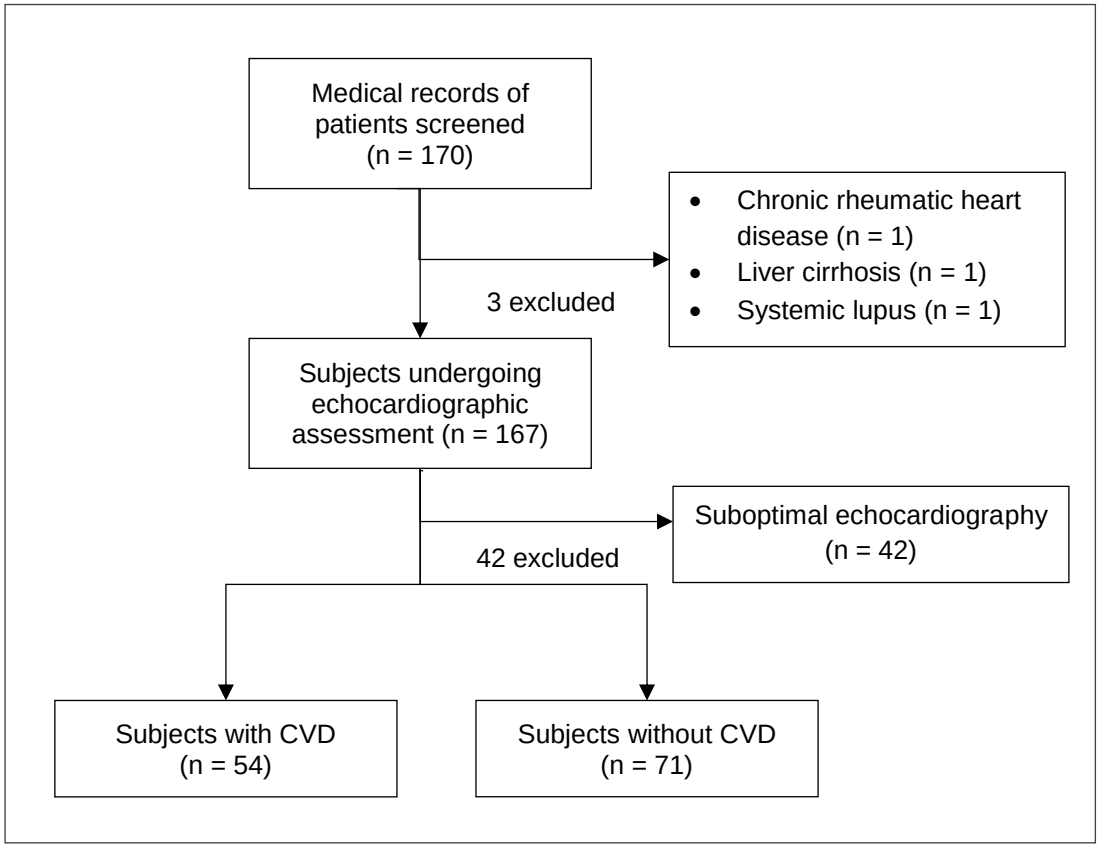

Fig. 1 Flowchart shows subject recruitment. CVD: cardiovascular disease