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Original Article

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Vascular calcification and cardiovascular function in chronic kidney disease

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Abstract

Background. Vascular calcification and arterial stiffening are independent predictors of all causes and cardiovascular mortality in chronic kidney disease (CKD). Few data are currently available comparing vascular calcification and its attendant functional cardiovascular consequences between CKD stage 4 patients and both peritoneal dialysis (PD) and haemodialysis (HD) (CKD stage 5) patients.

Method. We studied 134 subjects (60 HD, 28 PD and 46 CKD 4). Vascular calcification was quantified using multi-slice spiral CT scanning of a 5 cm standardized segment of superficial femoral artery. Pulse wave analysis and pulse wave velocity were assessed using applanation tonometry, to determine arterial compliance. Further digital arterial pulse wave analysis was used to measure systemic haemodynamic variables. All medications were recorded and biochemical variables were time averaged for the 6 months prior to entering the study.

Results. Forty-seven percent of CKD 4 patients demonstrated vascular calcification as compared with CKD 5 (71% PD and 73% HD, $P = 0.02$). HD patients had higher calcification scores (median 121) than either PD (median 21) or CKD 4 (median 0) ($P = 0.008$). There were no significant differences in baseline characteristics between the groups. Comparing tertiles of patients (based on calcification score), increased calcification score was associated with a reduction in arterial compliance (mean PWV 8.9 ± 1.1, 11 ± 3.6, 11.3 ± 3.7 m/s, $P = 0.005$). The degree of calcification did not influence systolic blood pressure (BP), diastolic BP or heart rate. However, more heavily calcified patients demonstrated significantly higher mean pulse pressures (58 ± 19, 74 ± 22 and 72 ± 25 mmHg, $P = 0.001$), lower total peripheral resistance (1.5 ± 1, 1.3 ± 0.8, 0.9 ± 0.4, $P = 0.01$) and higher stroke volume (84 ± 25, 95 ± 29, 106 ± 39 ml, $P = 0.01$). More heavily calcified patients were significantly older and predominantly male.

Conclusion. This study has successfully utilized a novel technique for the quantification of calcification. We have demonstrated vascular calcification and associated cardiovascular dysfunction in CKD 4, PD and HD with significant differences between the groups. Thirty percent of individuals show no calcification, even those established on renal replacement therapy for a prolonged period of time. Further work is required to identify factors which promote progression of arterial calcification in those who are susceptible.

Keywords: arterial stiffness; calcification; cardiovascular mortality; chronic kidney failure; haemodialysis; haemodynamics; peritoneal dialysis; phosphate binder

Introduction

Arterial calcification and arterial stiffening are independent predictors of all-cause and cardiovascular mortality in chronic kidney disease (CKD) stage 5 patients [1]. It is well recognized that cardiovascular (CV) mortality is responsible for around 50% of all deaths in the dialysis population [2]. The reasons for this high incidence of CV mortality are incompletely understood, but in the large part cannot be explained by traditional risk factors [3]. In fact, the CKD population have a reverse association with some traditional risk factors; obesity, hypercholesterolaemia and hypertension have been associated with a reduction in the relative risk of death in epidemiological studies of dialysis patients [4]. Inflammation, malnutrition, oxidative stress and abnormal mineral metabolism are risk factors for vascular disease specific to CKD [5].

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The presence of ectopic calcifications in CKD has been frequently described in the literature since the 1970s [6]. The development of imaging techniques such as electron beam computerized tomography (EBCT) and multi-slice spiral CT scanning have allowed accurate quantification of calcification *in vivo*. Recent studies using these techniques have highlighted the extent of coronary artery calcification among patients with CKD 5, particularly focusing on those receiving haemodialysis (HD) as a treatment modality [7,8]. There is limited data available on the prevalence of arterial calcification in CKD 4 patients or peritoneal dialysis (PD).

Previous studies using semi-quantitative methods for assessing calcification in peripheral vessels have found peripheral calcification to be functionally significant in HD [1]. However, the direct functional consequences of vascular calcification remain unclear. It has been demonstrated that vascular calcification results in haemodynamic alterations such as reduced compliance of large conductance arteries and autonomic dysfunction [9]. However, few studies have looked at both structural and functional changes associated with calcification of the vasculature.

The aim of this study was to determine the prevalence and severity of vascular calcifications in a cross-sectional study of matched CKD 4 and 5 subjects. In addition, we set out to assess the association between prevalent vascular calcification and arterial compliance, cardiac performance and peripheral cardiovascular performance.

Method

Subjects

We studied 134 subjects (60 HD, 28 PD and 46 CKD 4). All subjects were recruited from Derby City General Hospital. All patients were eligible to enter the study unless they had undergone a previous transplantation or had an amputated limb. All eligible patients registered under the care of the renal consultants were approached to take part in this study (total population of 158 HD, 71 PD and 62 CKD 4 in May 2003, at the start of recruitment).

CKD 4 patients were defined as having at least two creatinine clearance measurements made, with values between 15–30 ml/min. Dialysis modality was a matter of free patient choice, unless a medical imperative existed that prevented the use of PD. PD patients were all treated with bicarbonate/lactate mix-buffered PD fluids (Baxter, physioneal®). Nine out of 28 patients were on automated PD and the others were on continuous ambulatory PD (3–5 exchanges per day). All patients had been established on dialysis for at least 6 months. All HD patients received three dialysis sessions of at least 4 h duration per week (maximum 5 h per session). HD was performed using Hospal Integra (Mirandola, Italy) monitors and low flux polysulphone dialysers (1.5–2.0 m^2, LOPS 15–20®, Braun Medical Sheffield, UK). All HD patients were dialysed using bicarbonate-based 1.25 mmol/l calcium and 134 mmol/l sodium containing dialysate. Patients were all dialysed at the main dialysis centre at Derby City General Hospital.

Four patients were excluded from pulse wave studies due to a diagnosed arrhythmia. Information on patient characteristics, past medical history, co-morbid conditions and current medication were recorded from medical notes, in addition to direct questions regarding current conditions and phosphate binding medication. The Local Regional Ethics Committee granted approval for the project and written consent was received from all participants.

Biochemistry

Blood samples were collected at monthly intervals for HD patients and at regular clinic visits for PD and CKD 4 patients as part of routine treatment follow up. Serum phosphate, calcium, albumin-corrected calcium (CCa), albumin, parathyroid hormone (PTH), lipid profile and C-reactive protein (CRP) were analysed in on-site biochemistry laboratories using standard autoanalyser techniques (Roche diagnostics modular IIP®). Serum iPTH was measured using the immunometric, Immulite® 2000 assay (normal range 7–53 pg/ml). The results presented here were time-averaged results from the preceding 6 months, prior to the CT scan, and other assessments.

Measurement of vascular calcification

In order to quantify the presence and extent of arterial calcification, each patient underwent a multi-slice spiral CT scan. All studies were performed using GE Medical Systems lightspeed16® multi-slice spiral CT scanner. Images were acquired when the patient was supine; no contrast was used. A standardized section of the superficial femoral artery (SFA), 20 cm above the tibial plateau, 5 cm in length was imaged in 2.5 mm slices; care was taken to ensure that none of the slices overlap. This image allowed accurate, reproducible quantification of calcium load in this section of artery. The investigator scored each of the 20 slices individually. The score has been found to be reproducible from CT scanner to CT scanner regardless of the scan protocol [10]. The calcification was considered to be present if an area $\geq 1\,mm^2$ displayed a density greater than 130 Hounsfield units (HU). Scoring was undertaken using GE Medical Systems® Advantage Workstation software and carried out as described by Agatston *et al.* [11].

Haemodynamic parameters

A SphygmoCor® (AtCor Medical Pty Ltd, New South Wales, Australia) system was used to assess pulse wave analysis (PWA) and pulse wave velocity (PWV). Three blood pressure (BP) recordings were taken using an automated AND® UA-767 oscillometric device. A 3-lead electrocardiograph (ECG) was attached to the subject and the surface distance between pulse points was measured using tape measure while the patient was supine. PWV was measured utilizing applanation tonometry gated to the ECG, which calculates the velocity of the pulse waveform between two points, a known distance apart, on the arterial tree. PWV was assessed at carotid and radial pulses (C-R) and also radial and dorsalis pedis pulses (R-D). PWA was undertaken at the radial pulse. A single observer undertook all haemodynamic

measurements. In order to validate results obtained using this technique, the interobserver error between an experienced operator and the investigator was assessed. Each observer made two PWA measurements on 47 consenting subjects. Regression analysis demonstrated a strong correlation between the two observers ($R^2 = 0.83$, $P < 0.0001$).

Systemic haemodynamic function was assessed non-invasively using a Finometer® (TNO Instruments Amsterdam, The Netherlands). Continuous beat-to-beat measurements of cardiac output, stroke volume and peripheral vascular resistance were measured over a minimum of 8 min. Cuffs attached to the Finometer® were placed on the middle finger and on the upper arm of the patient [9]. All data were subsequently downloaded to a PC-based analysis program (Beatscope™), allowing averaging of results over defined time periods and a display of variables as percentage change from baseline. All analysis was averaged over the period of 300 heartbeats.

Statistical analysis

Results are displayed as mean ± SD for normally distributed data; those with non-normal distribution are presented as median (range) and (95% confidence interval). Column statistics were generated using GraphPad, prism® V0.3 statistical software. Comparisons of unpaired data were performed using unpaired *t*-tests for parametric data and Mann–Whitney U-tests for non-normally distributed data, such as the biphasic distribution of calcification. Comparisons of more than two sets of unmatched data were performed by one way ANOVA using the Tukey test or Kruskal–Wallis tests dependent upon the distribution. Chi-squared tests were used to analyse nominal data. Correlation plots were analysed by linear regression, coefficient of determination was calculated from Pearson correlation. Stepwise linear regression analysis and binary logistic regression analysis was undertaken using SPSS v12.0.1.

Results

The characteristics of the study population are shown in Table 1. The three groups were well matched for age, gender, diabetic status, smoking status, body mass index and dialysis vintage (where appropriate). Relevant serum biochemistry and relevant prescribed medications of the study population are also shown. The CKD 4 group were characterized by higher total and LDL cholesterol, lowest PO_4, CCa and Ca×P product, also the lowest use of calcium-based phosphate binders. PD patients had higher CCa than the other two groups and the highest PTH (not significant). On the other hand, the HD group was characterized by the highest use of both calcium-based and non-calcium-based phosphate binders, the highest PO_4 and Ca×P product. Overall, this patient population was characterized by good mineral control, with mean time averaged serum phosphate, corrected calcium and calcium×phosphate product being 1.6 ± 0.3 mmol/l, 2.4 ± 0.1 mmol/l and 3.9 ± 0.9 $mmol^2/l^2$, respectively.

Calcification of the SFA was found to be highly prevalent in all three groups, as shown in Table 2. Significantly more HD (73%) and PD (71%) patients demonstrated calcification than CKD 4 patients (47%, $P = 0.02$). Overall, HD patients had the highest arterial calcification score (median calcification score 121, range 0–2279) compared to PD (median score 21, range 0–990) and CKD 4 subjects (median score 0, range 0–915) ($P = 0.008$), shown in Figure 1. When analysing patients with vascular calcification alone (86/134), HD patients had a higher calcification score than both PD and CKD 4 patients, although this result did not reach statistical significance.

Arterial stiffness, as measured by PWV, demonstrated no significant difference between the three groups; however, CKD 4 patients had slower R-D PWV than the other two groups indicating more elastic arteries (Table 2). Augmentation was significantly higher in HD than PD subjects ($P = 0.04$), but the same as those in the CKD 4 group. With the exception of heart rate, there were no significant differences between any of the other cardiovascular variables recorded and the stage of renal failure or dialysis modality.

In order to further investigate the associations between haemodynamic function and vascular calcification, we divided our population into tertiles (with respect to calcification score). Table 3 shows functional assessments of the cardiovascular system by calcification tertile. Those subjects in the 3rd tertile, with the highest calcification scores, were characterized by a faster R-D PWV ($P = 0.005$), higher stroke volume ($P = 0.01$), lower total peripheral resistance (TPR) ($P = 0.01$) and higher pulse pressure ($P = 0.001$). Those subjects in the 3rd tertile were predominantly male and significantly older than the other two groups. All other measured variables showed no difference between the three calcification tertiles.

In univariate analysis of the relationship between all haemodynamic variables and vascular calcification, R-D PWV was the only positive association found ($r = 0.34$, $P = 0.004$), as illustrated in Figure 2. Table 4 shows the results from the univariate analysis between vascular calcification, recorded patient characteristics and biochemical variables. In order to identify possible determinants of vascular calcification severity, a multivariate regression analysis was performed using all the factors in Table 1 (except dialysis vintage) as independent variables and the vascular calcification score as the dependent variable. Independent variables that entered the equation are shown in Table 5. When the analysis was repeated using only data from dialysis patients, and including dialysis vintage as an independent variable, similar results were obtained (data not shown). To investigate factors that may predispose patients to develop vascular calcification, binary logistic regression analysis was performed using the same independent variables, but with the presence or absence of calcification as the dependent variable. Further multivariate regression analysis was performed to investigate possible haemodynamic variables

Table 1. Descriptive summary of all patient variables, biochemical parameters and relevant prescribed medications included in the study, by modality

	CKD 4 ($n=46$)	PD ($n=28$)	HD ($n=60$)	Significance *P*-value
Age (years)	60 ± 14	61 ± 14	60 ± 15	ns
Male gender	26 (56%)	17 (60%)	42 (70%)	ns
Diabetes mellitus	10 (21%)	8 (29%)	16 (27%)	ns
Smokers	6 (13%)	4 (14%)	6 (10%)	ns
Dialysis vintage (months)	n/a	34 ± 23	36 ± 25	ns
Body mass index (kg/m^2)	25 ± 9	25 ± 11	23 ± 9	ns
Creatinine clearance (ml/min)	19 ± 6	8 ± 3	2 ± 5	0.0001
Dialysis adequacy (Kt/V)*	–	2.5 ± 0.5	1.2 ± 0.2	–
Previous CV co-morbidities†	11 (23%)	12 (42%)	12 (20%)	ns
Total cholesterol (mmol/l)	5.1 ± 0.9	4.5 ± 1.0	4.3 ± 1.0	0.002 <0.05[a] <0.001[b] ns[c]
HDL cholesterol (mmol/l)	1.3 ± 0.3	1.3 ± 0.3	1.3 ± 0.3	ns
LDL cholesterol (mmol/l)	2.7 ± 0.9	2.6 ± 0.9	2 ± 0.7	0.0003 ns[a] <0.001[b] <0.05[c]
Serum phosphate (mmol/l)	1.49 ± 0.3	1.59 ± 0.3	1.70 ± 0.4	0.01 ns[a,c] <0.01[b]
Serum albumin corrected calcium (mmol/l)	2.38 ± 0.1	2.51 ± 0.1	2.46 ± 0.1	<0.001 <0.001[a] <0.001[b] ns[c]
Calcium × phosphate product (mmol^2/l^2)	3.5 ± 0.6	4.0 ± 0.7	4.2 ± 1.1	0.001 ns[a,c] <0.01[b]
PTH (pg/ml)	196 ± 105	293 ± 267	287 ± 278	ns
Albumin (g/l)	34 ± 2.8	27 ± 3.7	33 ± 4.2	$P<0.001$
C reactive protein (mg/l)	10 ± 16	15 ± 40	21 ± 29	ns
Use of vitamin D	17 (37%)	17 (61%)	33 (55%)	ns
Lipid lowering therapy	15 (33%)	13 (46%)	18 (30%)	ns
Use of non-calcium-based phosphate binders	1 (2%)	16 (57%)	26 (43%)	<0.001
Use of calcium-based phosphate binders**	17 (37%)	13 (46%)	37 (61%)	0.04
Dose of calcium-based binder (mg/day)	1941 ± 1025	1982 ± 817	2303 ± 1343	ns
Calcium channel blockers	23 (50%)	11 (39%)	13 (21%)	ns
Use of ACE inhibitors	17 (37%)	11 (89%)	11 (18%)	ns
Use of β blockers	20 (43%)	3 (10%)	15 (38%)	0.01

Results are expressed as mean ± SD or number of observations (percentage of total). Results are analysed using one-way ANOVA, with Tukey post-test for normally distributed data or Chi-squared tests for non-parametric data.
[a]Comparison between CKD 4 and PD.
[b]Comparison between CKD 4 and HD.
[c]Comparison between PD and HD.
*Kt/V in PD is 'weekly' and in HD is 'per single session'.
**Some patients are prescribed both calcium-containing and non-calcium-containing phosphate binders.
†CV co-morbidities are defined as any previous description of ischaemic heart disease, heart failure, cerebral vascular disease or peripheral vascular disease recorded in the patient's medical notes.

associated with vascular calcification. Factors listed in Table 2 were used as independent variables and vascular calcification score as the dependent variable. Variables entering the equation are shown in Table 6.

Discussion

This observational study presents data comparing arterial calcification, arterial stiffening and associated functional haemodynamic parameters between CKD 4 and CKD 5 patients. These data demonstrate that the process of arterial calcification has begun in almost 50% of subjects prior to the initiation of dialysis. In addition, morphological change of the arterial wall caused by arterial calcification is associated with stiffening of the arterial tree, and the process is highly prevalent in CKD 4.

Multi-slice CT, used as an assessment tool to quantify calcification score of the SFA, is a simple, sensitive, low radiation dose alternative to coronary artery and aortic measurements. The section of artery chosen for this study is ideal as it avoids major bifurcations and arterial branching, and therefore, obvious sites for turbulent flow and the development of atheroma. In addition, calcification load is measured in arteries of functional interest. When we compared our results to recently published studies using

Table 2. Measured variables of all patients in study, with respect to modality

	CKD 4 ($n=46$)	PD ($n=28$)	HD ($n=60$)	Significance *P*-value
Calcification score	0 (0–915) {53–196}	21 (0–990) {77–321}	121 (0–2279) {272–572}	0.008 ns[a,c] <0.01[b]
No patients calcified	22 (47%)	20 (71%)	44 (73%)	0.02
Calcification score of calcified patients	112 (2–795) {113–339}	142 (2–990) {124–452}	360 (1–2279) {390–761}	ns
Systolic blood pressure (mmHg)	144 ± 26	142 ± 25	155 ± 29	ns
Diastolic blood pressure (mmHg)	79 ± 14	80 ± 16	81 ± 16	ns
Pulse pressure (mmHg)	66 ± 22	62 ± 16	72 ± 26	ns
Heart rate (bpm)	65 ± 13	74 ± 15	71 ± 12	0.01 <0.05[a] ns[b,c]
Augmentation (mmHg)	16 ± 10	11 ± 8	16 ± 11	0.04 ns[a,b] <0.05[c]
Augmentation index (p1/p2)	142 ± 18	103 ± 21	140 ± 25	ns
C-R PWV (m/s)	9.0 ± 1.6	9.4 ± 1.5	9.2 ± 1.7	ns
R-D PWV (m/s)	9.4 ± 3.1	10.8 ± 2.4	10.8 ± 3.8	ns
Cardiac output (l/min)	6.4 ± 2.2	6.8 ± 3	7.6 ± 2.9	ns
Stroke volume (ml)	92 ± 31	84 ± 28	103 ± 36	ns
Total peripheral resistance (MU)	1.3 ± 0.4	1.1 ± 0.4	1.0 ± 0.5	ns

Results are expressed as median (range) (95% confidence interval). Results are analysed using one-way ANOVA, Kruskal–Wallis test and Dunn's post-test for not normally distributed data or Tukey post-test for normally distributed data. Chi-squared tests are used for non-parametric data.
[a]Comparison between CKD 4 and PD.
[b]Comparison between CKD 4 and HD.
[c]Comparison between PD and HD.

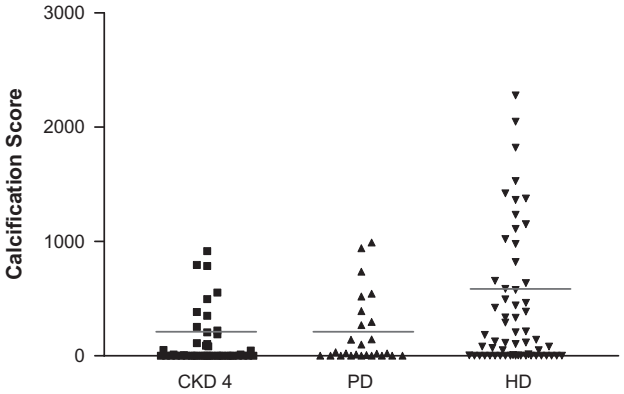

Fig. 1. Scatter plot of calcification scores in CKD 4, PD and HD patients, measured in the SFA. Mean calcification scores for each group are shown with a line.

multi-slice spiral CT of the coronary arteries, we found comparable magnitude of calcification scores [12]. It is not possible to differentiate between intimal and medial calcification using 16 slice spiral CT [8]. However, although intimal and medial calcifications have different pathologies, they do co-exist [1].

A bimodal distribution of vascular calcification is consistently observed in quantitative studies of vascular calcification. Interestingly, our data show that 27% of HD and 29% of PD patients showed no evidence of vascular calcification, even those initiated on dialysis for a prolonged period of time. These patients demonstrate lower PWV, lower stroke volume and higher peripheral resistance. These figures are consistent with other studies that have used quantitative methods of measuring calcification. Moe *et al*. found that 28% of HD and 32% of transplant subjects had no evidence of coronary calcification using multi-slice CT [8]. Chertow *et al*. in the Treat to Goal study, found that 17% of HD subjects had no coronary calcification and 20% had no aortic calcification using EBCT [13]. Stompor *et al*. found that 29% of their PD population studied remained calcium-free after 12 months [12]. London *et al*. found 36% of HD patients to be free of vascular calcification using plain radiography [1]. In addition, this final group had a lower CV mortality than an age-matched cohort. The question arises whether there are specific factors that protect this patient group from the development of calcification. If so, are they modifiable (medical management of bone and mineral balance and/or lipid management, biochemistry, choice of dialysis and hormonal factors) or non-modifiable factors (i.e. age, gender, genetic factors, diabetic status and residual renal function).

The development and progression of vascular calcification is a multifactorial process. Potentially differing factors may exert their maximum influence at either the predisposition, initiation and continuation phases of the process. The multivariate analysis performed on these data attempts to elucidate which factors might be most significant to the development of vascular calcification and which to the progression (using the severity as a surrogate of true progression data). Older age, male gender, presence of diabetes and high Ca×P product (albeit with borderline significance) all contribute to the presence of vascular

Table 3. Table of haemodynamic variables shown with respect to calcification tertiles

	1st tertile	2nd tertile	3rd tertile	Significance
Calcification score	≤0	1–200	≥200	–
Systolic blood pressure (mmHg)	141 ± 26 (84–213)	154 ± 28 (102–230)	152 ± 26 (91–250)	ns
Diastolic blood pressure (mmHg)	82 ± 16 (48–138)	80 ± 15 (45–114)	79 ± 15 (57–160)	ns
Pulse pressure (mmHg)	58 ± 19 (10–114)	74 ± 22 (37–134)	72 ± 25 (20–154)	$P = 0.001$
Heart rate (bpm)	75 ± 17 (46–113)	76 ± 12 (46–97)	73 ± 13 (49–108)	ns
Augmentation (mmHg)	13 ± 10 (−2–45)	14 ± 9 (−1–39)	18 ± 10 (0–47)	ns
Augmentation index (p1/p2)	141 ± 25 (99–199)	134 ± 20 (97–172)	141 ± 21 (94–198)	ns
C-R PWV (m/s)	8.9 ± 1.5 (5.9–13)	9.2 ± 1.9 (6.1–15.9)	9.4 ± 1.6 (5.5–12.3)	ns
R-D PWV (m/s)	8.9 ± 2.5 (4.4–14.4)	11 ± 3.6 (4.3–21.4)	11.3 ± 3.7 (5.7–20.4)	$P = 0.005$
Cardiac output (l/min)	6.2 ± 2.1 (3.3–12)	7.2 ± 2.6 (2.5–13.8)	7.7 ± 3.2 (3.6–17.6)	ns
Stroke volume (ml)	84 ± 25 (47–157)	95 ± 29 (33–173)	106 ± 39 (45–218)	$P = 0.01$
Total peripheral resistance (MU)	1.5 ± 1 (0.6–5.4)	1.3 ± 0.8 (0.5–3.5)	0.9 ± 0.4 (0.3–1.8)	$P = 0.01$
Age (years)	52 ± 14 (26–74)	62 ± 14 (32–85)	67 ± 12 (28–86)	$P < 0.0001$
Dialysis vintage (months)	18 ± 25 (0–86)	21 ± 23 (0–84)	28 ± 28 (0–101)	ns
Male	18 (46%)	28 (71%)	39 (81%)	$P < 0.001$

Results are expressed as mean ± SD or number of observations (%). Results are analysed using one-way ANOVA, with Tukey post-test for normally distributed data or Chi-squared tests for non-parametric data.

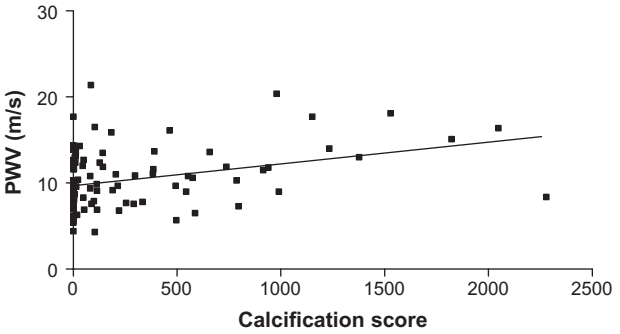

Fig. 2. Correlation plot of R-D PWV and vascular calcification scores, for all patients in the study. Pearson's: $r = 0.34$, $P = 0.0004$. Regression: $r = 0.33$, $P = 0.004$.

Table 4. Univariate correlations between vascular calcification, recorded demographics and recorded biochemical parameters

	r	*P*-value
Age (years)	0.22	0.01
Dialysis vintage (months)	0.26	0.002
CRP	0.24	0.01
Total cholesterol	−0.24	0.005
Albumin	−0.26	0.001

calcification. Only about 50% of the variance is explained within this model. Increasing age is consistently associated with the presence of vascular calcification in observational cohorts [1,7,14,15]. In contrast, male gender, diabetes and Ca×P have all been identified individually, but not consistently, as factors related to the process of vascular calcification [12,16].

Only albumin and cholesterol were negatively correlated with the severity of vascular calcification. This suggests that a characteristic state of low albumin/cholesterol as seen in malnutrition, inflammation or atherosclerosis complex is most important, as suggested by Wang *et al.* [17]. There was no relationship identified between PO_4, CCa, intact PTH, phosphate binder type or dose and degree of calcification. It may be important that as a whole, the group was characterized by good mineral control and relatively low use of calcium-based phosphate binders. This is consistent with recently published data which showed that patients with poor control of Ca and PO_4 were more likely to develop progressive vascular calcification when exposed to calcium-based phosphate binders than those with tight control [18]. A recent study by Mehrotra and colleagues has brought into sharp focus the complexity of the role of circulating inhibitors of vascular calcification that play in CKD patients [19]. Further clarification awaits longitudinal prospective study of vascular calcification; this is currently underway at our institution.

The PD population in this study (with the same percentage population demonstrating calcification as HD) had a lower arterial calcification score. This result did not reach statistical significance, presumably due to smaller patient numbers in the PD group. This PD population was characterized by lower serum phosphate, lower Ca×P product, higher PTH (not significantly) and a smaller percentage taking calcium-based phosphate binders. In addition, the PD patients retain a degree of residual renal function. We have recently demonstrated that HD is associated with higher Ca and PO_4 levels during the long intradialytic period compared with short intradialytic period. Such cyclical changes in serum mineral levels, which are not characteristic of PD, may be important in the pathogenesis of vascular calcification [20]. It will be of interest to see whether longitudinal data in this cohort continue to show less calcification in the PD group.

Although measurements made with the Finometer are well validated, the technique used a three-tube viscoelastic tube model to calculate parameters derived from the finger arterial waveform. It is possible that

Table 5. Variables entering the equation as determinants of the presence or absence of vascular calcification in binary logistic regression analysis[†] (left-hand column) and variables entering the equation as determinants of the severity of vascular calcification in stepwise linear regression analysis[‡] (right-hand column) using calcification score as the dependent variable

	Presence verses absence of calcification (Nagelkerke $R^2 = 0.48$)[†]		Degree of calcification present (Model $R^2 = 0.24$)[‡]	
	B co-efficients	Significance	Standardized co-efficient (β)	Significance
Age (years)	0.098	<0.001	–	–
Gender	−2.108	<0.001	–	–
Diabetes mellitus	1.578	0.009	–	–
Ca × P product ($mmol^2/l^2$)	0.615	0.053	–	–
Total cholesterol (mmol/l)	–	–	−0.34	0.001
Albumin (g/l)	–	–	−0.31	0.003

Table 6. Haemodynamic variables entering the equation as correlates of the presence or absence of vascular calcification in binary logistic regression analysis[†] (left-hand column) and haemodynamic variables entering the equation as correlates of the severity of vascular calcification in stepwise linear regression analysis[‡] (right-hand column) using calcification score as the dependent variable

	Presence verses absence of calcification (Nagelkerke $R^2 = 0.35$)[†]		Degree of calcification present (Model $R^2 = 0.22$)[‡]	
	B co-efficients	Significance	Standardized co-efficient (β)	Significance
Pulse pressure (mmHg)	0.051	0.001	–	–
Heart rate (bpm)	−0.039	0.008	–	–
R-D PWV	0.276	0.009	0.41	>0.001
Stroke volume (ml)	–	–	0.20	0.043

higher vascular calcification load may introduce significant variance from the assumptions made in the model and introduce these observed differences as systematic errors. However, we have previously used this methodology successfully [9].

Vascular calcification has profound effects on cardiovascular function. Calcification is associated with reduced arterial compliance, as illustrated by multivariate analysis of this data. This appears to be associated with an altered systemic haemodynamic state. Furthermore, we have recently reported that both the presence of vascular calcification and increased arterial stiffness are associated with a reduction in baroreflex sensitivity, potentially influencing short-term dysregulation of blood pressure [9].

In conclusion, functionally significant vascular calcification is highly prevalent in HD, PD and those approaching the need for renal replacement therapy; the determinants of progression are the subject of ongoing investigation. Further understanding of this process will require prospective studies to allow alteration of current therapies and investigation of new approaches to deal with this important patho-physiological entity.

Conflict of interest statement. CWM has an unrestricted educational group from Genzyme Pharmaceuticals and has received personal honoraria from Genzyme Pharmaceuticals.

(See related articles by Taniwaki *et al*. NDT 20: 2472–2478 and McIntyre NDT 21: 251–254)

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