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Progression of aortic calcification is associated with disorders of mineral metabolism and mortality in chronic dialysis patients

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ABSTRACT

Background. Previous studies have shown that simple imaging methods may be useful for detection of vascular calcifications in dialysis patients. Based on annual, plain chest X-rays during follow-up on dialysis, we studied the associations of mineral metabolism with the presence and progression of aortic calcification. In addition, we assessed the impact of aortic calcification on mortality.

Methods. Three hundred and eighty-four patients who started haemodialysis or peritoneal dialysis between 1997 and 2007 were included (age 61 ± 15 years, 64% male, 61% haemodialysis). Annual chest X-rays were screened for calcification in the aortic arch, and patients were categorized as having no, moderate or severe calcification.

Progression was defined as an increase in calcification category during follow-up on dialysis.

Results. At baseline, 96 (25%) patients had severe, 205 (53%) patients had moderate and 83 (22%) patients had no aortic calcification. For 237 of the 288 patients with no or moderate calcifications at baseline, X-rays were available for follow-up. During follow-up (mean 2.3 years), aortic calcification progressed in 71 patients (30%). We found that baseline plasma

calcium >9.5 mg/dL and iPTH >300 pg/mL were associated with progression [odds ratios of 3.1, 95% confidence interval (1.2–8.2) and 4.4 (1.4– 14.1), respectively]. Progression of aortic calcification was significantly associated with increased risk of all-cause mortality (hazard ratio: 1.9; 95% CI: 1.2–3.1) and cardiovascular mortality (hazard ratio: 2.7; 95% CI: 1.3–5.6).

Conclusions. Aortic calcification progressed in almost a third of the patients during dialysis. Hypercalcaemia and hyperparathyroidism were associated with an increased risk of progression. Progression of aortic calcification was significantly related to an increased mortality risk.

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death in dialysis patients; ~50% of these patients die from cardiovascular causes [1,2]. Traditional risk factors for CVD, such as advanced age, hypertension and smoking, cannot fully explain the high prevalence. In addition to these traditional risk factors, disorders of mineral metabolism, such as elevated calcium and phosphorus concentrations, are associated with increased cardiovascular morbidity and mortality, as was shown in previous studies [1,3–5].

It had been hypothesized that disturbances in mineral metabolism play a role in cardiovascular disease and mortality via the development of vascular calcifications [6–8].

In addition, a lack of calcification inhibitors, such as fetuin- A and matrix GLA protein (MGP), could play a role in the development of vascular calcification [9,10].

There are several methods to detect vascular calcifications.

Sophisticated CT techniques such as electron beam CT (EBCT) and spiral CT have proven to be adequate to quantify reproducibly calcifications in coronary arteries and the aorta [6,11,12]. A recent study of Bellasi et al.

showed that simple non-invasive measurements of calcifications may provide equally useful information [13]. In their study of 140 prevalent haemodialysis (HD) patients, these authors demonstrated a good correlation between simple imaging tests, i.e. X-rays of the lumbar abdominal aorta, and more sophisticated measurements obtained with EBCT. These less expensive and readily available methods might therefore be very useful in screening dialysis patients for vascular calcification [14].

In this study, we aimed to examine the associations of parameters of mineral metabolism with the progression of aortic calcification, based on annual, plain chest X-rays during follow-up on dialysis. We also assessed whether (progression of) aortic calcification was associated with an increased risk of all-cause and cardiovascular mortality.

MATERIALS AND METHODS.

Subjects.

Between January 1997 and August 2007, incident HD and peritoneal dialysis (PD) patients in 38 dialysis units in the Netherlands were consecutively invited to participate in the Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD), a large prospective multicentre cohort study. To be included, patients had to be 18 years or older, and dialysis had to be their first renal replacement therapy. All patients gave informed consent before inclusion, and the study was approved by local medical ethics committees. Patients were followed up from the start of dialysis treatment until transplantation, mortality, or 1 August 2007. In addition to the standard data collection, data on vascular calcificationswere retrospectively collected in four of the dialysis centres that participated in NECOSAD (n = 455). These centres were chosen for logistic reasons, i.e. the number of patients and the availability of X-rays.

Data collection procedures Information on demography, primary kidney disease and co-morbidity was collected from 0 to 4 weeks before the initiation of dialysis treatment.

Data on residual renal function, biochemistry and dialysis characteristics were collected at fixed times 3 (baseline visit) and 6 months after the start of dialysis, and at 6-month intervals thereafter.

Primary kidney disease and causes of death were classified according to the codes of the European Renal Association–European Dialysis and Transplant Association (ERA–EDTA) [14]. Cardiovascular mortality was defined as: code 0 (cause of death uncertain/not determined), 11 (myocardial ischaemia and infarction), 12 (hyperkalaemia), 14 (other causes of cardiac failure), 15 (cardiac arrest, cause unknown), 17 (hypokalaemia), 18 (fluid overload), 22 (cerebrovascular accident), 26 (haemorrhage from ruptured vascular aneurysm) and 29 (mesenteric infarction). All other codes were regarded as deaths of non-cardiovascular origin. Patients were classified as having no, intermediate or severe co-morbidity based on the number of co-morbid conditions according to Davies' co-morbidity index [15]. Residual renal function was expressed as residual glomerular filtration rate (rGFR), calculated as the mean of creatinine and urea clearance adjusted for body surface area (mL/min/1.73 m2).

Laboratory analyses In HD patients, blood samples were drawn before and after each monitoring dialysis session. Plasma calcium, phosphorus and albumin were measured using standard laboratory techniques depending on the participating centre. Calcium concentrations (mg/dL) were corrected for albumin concentrations (g/dL) using the following formula: corrected calcium = calcium + 0.8 × (4 − albumin) [16,17]. Baseline plasma concentrations were evaluated both as continuous variables and in reference to the targets advised in the KDOQI guideline for bone metabolism and disease in chronic kidney disease [16]. This guideline recommends serum concentrations of corrected calcium between 8.4 and 9.5 mg/dL (2.10 and 2.37 mmol/L), serum phosphorus between 3.5 and 5.5 mg/dL (1.13 and 1.78 mmol/L), calcium–phosphorus (Ca × P) product <55 mg2/dL2 (< 4.4 mmol2/L2) and iPTH concentrations between 150 and 300 pg/mL (15.8–31.6 pmol/L). In addition, analyses were repeated using the mean value of the concentrations at 3 and 6 months after the start of dialysis.

Serum fetuin-A, undercarboxylated matrix GLA protein (ucMGP), and high sensitivity C-reactive protein (hsCRP) measurements were available for 146 of the patients. Analysis of serum hsCRP was performed by means of particle-enhanced immunonephelometry using a standard 'CardioPhase hsCRP' for 'BNII' (Dade Behring Holding GmbH, D-65835 Liederbach, Germany). The nephelometry method for fetuin-A employs a high specificity antibody and has been described in detail elsewhere [18]. Serum ucMGP was measured with a novel method using Anti-ucMGP (VitaK BV, Maastricht, the Netherlands), which was described elsewhere [19].

Calcifications The baseline calcification score was determined between 6 months before and 12 months after the start of dialysis. Successive X-rays were collected once a year during follow-up on dialysis treatment. The presence of vascular calcification in the aortic arch was scored based on plain lateral chest X-rays. We excluded X-rays that were made while the patient was in a lying position or were made acutely at the emergency department, due to the non-standardized, inferior quality of the X-rays. The X-rays were scored by two of the investigators from this study (M.N. and L.E.), the majority of them independently. The two investigator were trained to score the X-rays by qualified, experienced radiologists from the Academic Medical Center of the University of Amsterdam. They did not have any information on the age, disease status, etc. of the patients while scoring the X-rays. There were only a few cases of disagreement between the observers, and in these cases, the calcification score was determined by mutual agreement or, in doubtful cases, in consultation with an independent third observer. In all cases of disagreement between the observers, consensus was eventually reached.

Patients were categorized as having no (score 0), moderate (1) or severe (2) aortic arch calcifications. Examples of chest X-rays demonstrating the calcification scores are shown in Figure 1. Progression of calcification was defined as an increase in the severity of calcification on the last available X-ray when compared with the baseline X-ray. Patients with a stable calcification burden or a decline of calcification score were combined as 'stable patients'.

[FIGURE 1]

[TABLE 1]

Statistical analysis Differences between groups of patients with no, moderate and severe calcification at baseline were calculated using standard descriptive statistics.

ANOVA tests were applied to examine differences in continuous variables. Chi-square tests with tests for trend (Cochran–Armitage trend test) were used to compare distributions of dichotomous or categorical data. A P-value of <0.05 was considered to statistically significant.

To study the associations between the parameters of mineral metabolism and the risk of progression of vascular calcification, we applied crude and adjusted logistic regression models. The multivariable statistical model comprised the variables age, sex, treatment modality (HD or PD), time between the first and last available X-ray, diabetes mellitus (as primary cause of kidney failure or as co-morbidity), and baseline plasma calcium, phosphorus and iPTH concentration. To calculate odds ratios (ORs) for Ca × P product, we applied a similar model with no adjustment for calcium and phosphorus. The subgroup of patients in whom fetuin-A, ucMGP and hsCRP were measured was analysed separately.

For this group, only unadjusted ORs were calculated because the sample size was too small to fit an appropriate multivariate model.

Survival curves for patients with no, moderate, and severe aortic calcification and for patients with and without progression of aortic calcification were created by means of Kaplan–Meier analysis. Hazard ratios (HRs) for all-cause and cardiovascular mortality risk associated with the presence and the progression of aortic calcification were calculated using crude and adjusted Cox proportional hazards regression. Mortality risks related to the presence of aortic calcification were calculated based on the time between the start of dialysis and censoring or death, and the multivariable model contained the variables age, sex, treatment modality and diabetes mellitus. In order to determine progression, patients had to meet two criteria. First, their initial aortic calcification score had to be below the ceiling score, so no or moderate aortic calcification at baseline. Second, they had to have at least two X-rays available for evaluation. For patients who fulfilled both criteria, the risk of dying (HR) started on the day that the last available X-ray was taken (left censoring). Once more, we adjusted for age, sex, treatment modality, diabetes mellitus and, in addition, the time between the first and the last evaluated X-ray.

All statistical analyses were performed using SAS statistical software version 9.1 (SAS Institute, Cary, NC, USA).

[FIGURE 2]

RESULTS

Patients

From a total of 455 patients, X-rays were collected. Differences in baseline patient characteristics, i.e. age, gender, treatment modality and mortality rate of the included patients, were not statistically significant from those of other patients included in NECOSAD (data not shown). For 27 patients, there were no appropriate X-rays available, and for 44 patients, X-rays were only available outside the time window defined as baseline. The remaining 384 patients were included in the analyses. The baseline calcification score was determined at a mean (SD) time of 1 (3.1)month after the start of dialysis. At baseline, there were 83 patients (22%) who did not show aortic calcifications in the aortic arch, 205 patients (53%) with moderate, and 96 patients (25%) with severe calcifications.

We found that fetuin-A and albumin concentrations were significantly lower and CRP levels significantly higher in patients with aortic calcifications as compared with patients without calcifications. Older patients had significantly more aortic arch calcifications. In addition, more heavily calcified patients were more often treated with HD ($P < 0.001$), and tended to have cardiovascular disease ($P < 0.001$). Baseline characteristics of patients with no, moderate and severe calcifications are summarized in Table 1.

Aortic calcification at baseline and mortality risk

The maximal follow-up time was 10 years (1997–2007). In the 83 patients without calcifications at baseline, the median follow-up time was 7.6 years, and 25 (30%) died during the study. Median follow-up

was 4.9 years in patients with moderate calcifications, and 80 patients (39%) died in this group. Finally, in the group with severe calcifications, median follow-up time was 2.6 years, and 58 patients (60%) died. Kaplan–Meier curves for survival in patients with no, moderate and severe calcification are shown in Figure 2A. Crude mortality risk was significantly different in the three groups, and the highest mortality risk was observed in patients with severe aortic calcification (log-rank $P < 0.001$).

Cox regression models were used to calculate crude and adjusted HRs for all-cause and cardiovascular mortality risk, which are presented in Table 2. In unadjusted analyses, we found that mortality risk was significantly increased in patients with severe calcifications (HR: 1.9; 95% CI: 1.4–2.6) when compared with patients who had no or moderate aortic calcifications. No statistically significant association was found after adjusting for age. In a survival analysis for cardiovascular causes of death specifically, similar results were obtained. Also, comparing the group with no aortic calcification with the groups with moderate and severe aortic calcification combined showed no statistically significant effects.

[TABLE 2]

Progression of aortic calcification

The median number of available X-rays per patient was 3 (range 1–9). For 237 of the 288 patients with no or moderate calcifications at baseline, X-rays were available for follow-up. For these patients, the change in calcification score between the first and the last chest X-ray was calculated.

The mean (SD) follow-up time between the first and the last X-ray was 2.3 (1.8)years. Seventy-one patients (30%) had progression of vascular calcification during follow- up. In addition, 5 patients with moderate and 7 patients with severe calcification at baseline had a decrease in calcification score. In Figure 3, these proportions are presented. Progression was seen in 37% of the subgroup of patients with at least 3 years between their first and their last X-ray ($n = 92$).

We studied the relationships between clinical variables, i.e. parameters of mineral metabolism, and the progression in vascular calcification using logistic regression analysis.

In the crude analyses, only higher age and longer time between the first and the last evaluated X-ray were significantly associated with higher risk of progression of aortic calcification. Higher concentrations of fetuin-Awere associated with a borderline significant OR of 1.26 (95% CI: 0.98–1.62), while ucMGP and hsCRP were not associated with progression. In the adjusted analyses, we found that baseline plasma calcium >9.5 mg/dL (OR: 3.1; 95% CI: 1.2–8.2), baseline plasma iPTH >300 pg/mL (OR: 4.4; 95% CI: 1.4–14.1), higher age (OR: 1.04; 95% CI: 1.01– 1.07), and longer time between the first and the last evaluated X-ray (OR: 1.05; 95% CI: 1.03–1.07) were significantly associated with an increase in calcification score over time. Results from the unadjusted and adjusted analyses are listed in Table 3. The analyses of the calcification progression were repeated applying calcium, phosphorus and iPTH concentrations averaged over the first 6 months on dialysis. These supplementary analyses did not alter our findings (data not shown). Additional adjustment for the use of coumarin derivates at baseline also did not affect our results in any way (data not shown).

Progression of aortic calcification and mortality risk

Kaplan–Meier curves for patients with and without progression of aortic calcification are displayed in Figure 2B ($n = 237$). The median follow-up time from the last evaluated X-ray was 2.2 years in the patients without progression, and 51 of 166 patients (31%) died in this group. In the patients with progression, median follow-up time from the last X-ray was 0.9 years, and 33 of 71 patients (46%) died.

Patients with progression had a significantly higher mortality risk than patients without progression (log-rank $P = 0.001$).

In both the unadjusted and the adjusted Cox regression analysis, progression of aortic calcification was significantly associated with increased risk of all-cause mortality (adjusted HR: 1.9; 95% CI: 1.2–3.1) and cardiovascular (adjusted HR: 2.7, 95% CI: 1.3–5.6) mortality. HRs for mortality risk related to progression of aortic calcification are listed in Table 4.

[FIGURE 3]

[TABLE 3,4]

DISCUSSION

In the current study, we assessed the associations of parameters of mineral metabolism with the progression of aortic calcification in incident dialysis patients based on annual chest X-rays during follow-up on dialysis. Elevated baseline plasma calcium (>9.5 mg/dL) and iPTH (>300 pg/mL) concentrations, higher age, and longer time between the first and the last evaluated X-ray were associated with a higher risk of progression of aortic calcification.

Moreover, we found that progression of aortic calcification was associated with significantly increased risk of both all-cause and cardiovascular mortality.

Vascular calcifications are common in the general population; 20–30% of people of 65 years or older have calcification in the aorta [20]. In ESRD patients, this proportion is substantially higher. We found that 78% of 384 incident HD and PD patients had moderate to severe vascular calcification in their aortic arch at the start of dialysis treatment. This percentage is in accordance with other studies that reported proportions ranging from 54% to 100% [21].

The major limitation to our study is the subjective method applied to assess aortic calcification. A 'weak'scoring system could potentially be a problem because it can lead to misclassification. Non-differential (random) misclassification leads to a dilution of the effects found. However, since we still found statistically significant effects in our study, this type of misclassification is apparently not a large problem. In addition, differential misclassification can occur when the people assessing the X-rays are not blinded, like in our study. This type of misclassification could potentially lead to bias [22]. However, in our study, the scorers could only see some general information like the date of birth and name of the patient. It is unlikely that this would lead to bias, especially when you adjust for these factors (i.e. age) in the statistical analysis. Differential misclassification could lead to bias if the scorers are able to see the information of interest for the research question, such as data on mineral metabolism or mortality. This was not the case in our study since the scorers were unaware of any clinical data.

Assessing aortic calcification on the basis of plain chest X-rays is less sensitive when compared with CT techniques.

In the studies of Block et al. [23] and Stompor et al.

[24], EBCTand multi-slice spiral CTwere applied to assess the calcification score. These CT techniques have proven to be adequate to quantify reproducibly calcifications in coronary arteries and the aorta. Because of the more precise quantification of these methods, the presence and progression of calcification are therefore more likely to be detected, which could explain the higher proportions of patients with progression.

A recent study of Bellasi et al. [13] showed that simple, non-invasive, semi-quantitative measurements of calcifications, i.e. scoring calcifications according to the method of Kauppila et al. [25] based on X-rays of the lumbar abdominal aorta, correlate well with more sophisticated measurements obtained with EBCT. It is currently unknown whether calcification of the aortic arch has the same predictive properties as calcification of the abdominal aorta. Additional studies are therefore needed to assess whether screening for aortic calcification based on chest X-rays correlates equally well with EBCT as screening for calcification based on lumbar aortic X-rays does.

Due to the retrospective design, we were not able to use CT measurements or X-rays of the abdominal aorta for our study since the availability of these measurements would introduce a bias in patient selection. We therefore chose to apply the current method based on chest X-rays which are available for almost every dialysis patient in the Netherlands.

On the other hand, a valuable strength to our study is the repeated evaluation of calcification scores, which made it possible to study the development of calcification over time. During dialysis treatment, one-third of

the patients who had no or moderate calcifications at the start of dialysis showed progression of vascular calcification.

Progression was associated with hypercalcaemia (>9.5 mg/dL), hyperparathyroidism (>300 pg/mL), higher age, and longer time between the first and the last evaluated X-ray. Althoughwe could not demonstrate any effects of hyperphosphataemia or elevated Ca × P product on progression, the greater part of our findings are in accordance with findings from previous studies that examined the progression of calcification in dialysis patients [12,23,24,26].

The majority of these studies had a shorter follow-up period than our study and found higher proportions of patients who showed progression during dialysis.

There were also 5 patients with moderate and 7 patients with severe calcification at baseline who showed a decrease in calcification score. This finding is remarkable since there are, to our knowledge, no previous studies that found decreasing aortic calcifications over time. Although we cannot elucidate this finding based on our results, we can speculate that this decrease is possible because calcification is not a passive but an active and regulated process in which extra osseous bone formation occurs in the vascular wall.

Our study may have some additional limitations. First, although the national guideline recommends making a chest X-ray annually, X-rays were not available for every patient and for each year. We believe that this did not considerably influence our results because we calculated the difference in calcification score independent of the time period between X-rays. Second, we were unable to draw any firm conclusions about the relationships with fetuin- A, ucMGP and hsCRP levels due to the small number of measurements that were available.

In conclusion, we found in this study that calcification of the aortic arch, as assessed based on plain chest X-rays, was common in dialysis patients, and it progressed in almost a third of patients during follow-up on dialysis. Hypercalcaemia and hyperparathyroidism were associated with a higher risk of progression. Moreover, progression of aortic calcification was significantly associated with an increased risk of both all-cause and cardiovascular mortality.

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CONFLICT OF INTEREST STATEMENT.

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REFERENCES.

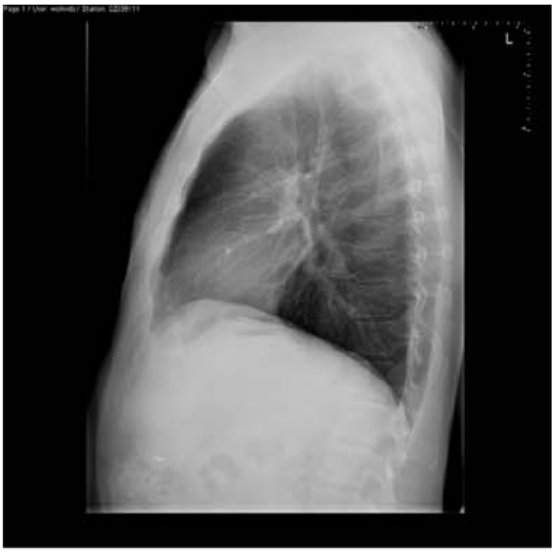
1. Noordzij M, Korevaar JC, Bos WJ et al. Mineral metabolism and cardiovascular morbidity and mortality risk: peritoneal dialysis patients compared with haemodialysis patients. Nephrol Dial Transplant 2006; 21: 2513–2520 2. Foley RN, Parfrey PS, Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. Am J Kidney Dis 1998; 32: S112–S119 3. Block GA, Klassen PS, Lazarus JM et al. Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. J Am Soc Nephrol 2004; 15: 2208–2218 4. Young EW, Albert JM, Satayathum S et al. Predictors and consequences of altered mineral metabolism: the Dialysis Outcomes and Practice Patterns Study. Kidney Int 2005; 67: 1179–1187 5. Ganesh SK, Stack AG, Levin NWet al. Association of elevated serum PO(4), Ca x PO(4) product, and

parathyroid hormone with cardiac mortality risk in chronic hemodialysis patients. J Am Soc Nephrol 2001; 12: 2131–2138 6. 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 1996; 27: 394–401 7. Goodman WG, Goldin J, Kuizon BD et al. Coronary-artery calcification in young adults with end-stage renal disease who are undergoing dialysis. N Engl J Med 2000; 342: 1478–1483 8. 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 2002; 39: 695–701 9. Ketteler M, Bongartz P, Westenfeld R et al. Association of low fetuin-A (AHSG) concentrations in serum with cardiovascular mortality in patients on dialysis: a cross-sectional study. Lancet 2003; 361: 827–833 10. Schurgers LJ, Teunissen KJ, Knapen MH et al. Novel conformationspecific antibodies against matrix gamma-carboxyglutamic acid (Gla) protein: undercarboxylated matrix Gla protein as marker for vascular calcification. Arterioscler Thromb Vasc Biol 2005; 25: 1629–1633 11. Moe SM, O'Neill KD, Fineberg N et al. Assessment of vascular calcification in ESRD patients using spiral CT. Nephrol Dial Transplant 2003; 18: 1152–1158 12. Jung HH, Kim SW, Han H. Inflammation, mineral metabolism and progressive coronary artery calcification in patients on haemodialysis.

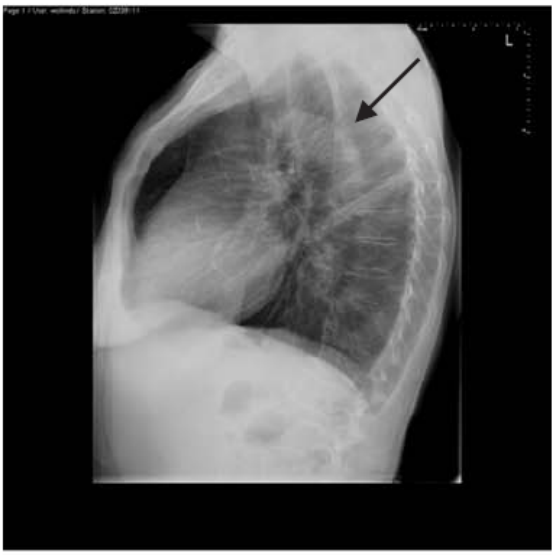
Nephrol Dial Transplant 2006; 21: 1915–1920 13. Bellasi A, Ferramosca E, Muntner P et al. Correlation of simple imaging tests and coronary artery calcium measured by computed tomography in hemodialysis patients. Kidney Int 2006; 70: 1623–1628 14. van Dijk PC, Jager KJ, de Charro F et al. Renal replacement therapy in Europe: the results of a collaborative effort by the ERA-EDTA registry and six national or regional registries. Nephrol Dial Transplant 2001; 16: 1120–1129 15. Davies SJ, Russell L, Bryan J et al. Comorbidity, urea kinetics, and appetite in continuous ambulatory peritoneal dialysis patients: their interrelationship and prediction of survival. Am J Kidney Dis 1995; 26: 353–361 16. National Kidney Foundation. K/DOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease. Am J Kidney Dis 2003; 42: S1–S202 17. Portale AA. Blood calcium, phosphorus, and magnesium. In: Favus MJ (ed). Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism. 4th edn. Philadelphia, PA, USA: Lippincott Williams & Wilkins, 1999; p115–p118 18. Hermans MM, Brandenburg V, Ketteler M et al. Association of serum fetuin-A levels with mortality in dialysis patients. Kidney Int 2007; 72: 202–207 19. Hermans MM, Vermeer C, Kooman JP et al. Undercarboxylated matrix GLA protein levels are decreased in dialysis patients and related to parameters of calcium-phosphate metabolism and aortic augmentation index. Blood Purif 2007; 25: 395–401 20. Witteman JC, Kannel WB, Wolf PA et al. Aortic calcified plaques and cardiovascular disease (the Framingham Study). Am J Cardiol 1990; 66: 1060–1064 21. Hujairi NM, Afzali B, Goldsmith DJ. Cardiac calcification in renal patients: what we do and don't know. Am J Kidney Dis 2004; 43: 234–243 22. Tripepi G, Jager KJ, Dekker FWet al. Bias in clinical research. Kidney Int 2008; 73: 148–153 23. Block GA, Spiegel DM, Ehrlich J et al. Effects of sevelamer and calcium on coronary artery calcification in patients new to hemodialysis.

Kidney Int 2005; 68: 1815–1824 24. Stompor TP, Pasowicz M, Sulowicz Wet al. Trends and dynamics of changes in calcification score over the 1-year observation period in patients on peritoneal dialysis. Am J Kidney Dis 2004; 44: 517–528 25. Kauppila LI, Polak JF, Cupples LA et al. New indices to classify location, severity and progression of calcific lesions in the abdominal aorta: a 25-year follow-up study. Atherosclerosis 1997; 132: 245–250 26. Sigrist MK, Taal MW, Bungay P et al. Progressive vascular calcification over 2 years is associated with arterial stiffening and increased mortality in patients with stages 4 and 5 chronic kidney disease. Clin J Am Soc Nephrol 2007; 2: 1241–1248

A. No calcification



B. Moderate calcification



C. Severe calcification

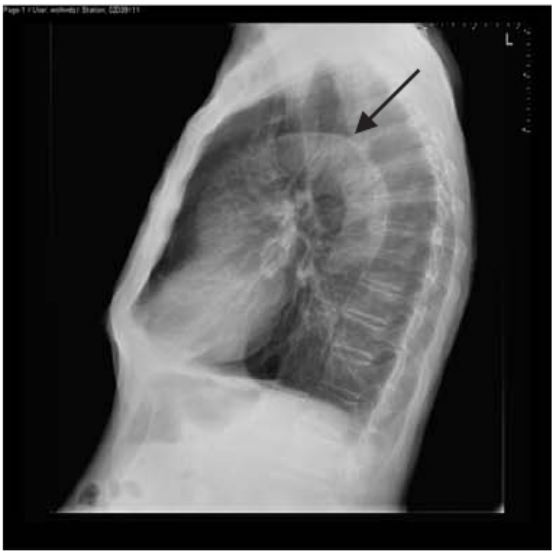


Fig. 1. Examples of aortic calcification scores based on plain lateral chest X-rays. **A**. No calcification. **B**. Moderate calcification. **C**. Severe calcification.

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Table 1. Baseline characteristics of patients with no, moderate and severe aortic calcification (AC) in the aortic arch (n = 384)

	No AC	Moderate AC	Severe AC	P-value
Number (%)	83 (22%)	205 (53%)	96 (25%)	
Age (years)	46 (16)	62 (13)	72 (9)	<0.0001
Sex (% male)	68	64	59	0.46
Modality (% HD)	45	62	76	0.0002
Primary kidney disease (%)				0.11
Diabetes mellitus	17	15	10	
Glomerulonephritis	11	13	4	
Renal vascular disease	10	14	21	
Co-morbidity score (%)				0.26
Low	63	53	51	
Moderate	33	39	38	
Severe	4	8	11	
Cardiovascular disease (%)	17	37	52	0.0001
Diabetes mellitus (%)[a]	25	27	31	0.78
rGFR (mL/min/1.73 m^2)	3.5 (2.3)	3.6 (2.3)	3.6 (3.5)	0.95
Smoking (%)				0.05
Former	26	48	47	
Current	23	17	25	
BMI (kg/m^2)	25.2 (5.7)	25.2 (5.0)	24.1 (3.6)	0.26
Blood pressure (mmHg)				
Systolic	142 (20)	149 (19)	146 (20)	0.06
Diastolic	83 (10)	82 (10)	78 (10)	0.009
Pulse pressure	60 (18)	66 (17)	68 (18)	0.008
Albumin (g/dL)	3.52 (6.21)	3.38 (5.31)	3.16 (4.12)	0.0001
Corrected calcium (mg/dL)	10.2 (1.1)	10.1 (1.2)	10.1 (0.9)	0.70
Phosphorus (mg/dL)	5.6 (1.7)	5.9 (1.7)	6.0 (1.8)	0.26
Ca × P product (mg^2/dL^2)	57.1 (17.8)	59.6 (17.9)	60.1 (18.7)	0.51
iPTH (pg/mL)	186 (220)	228 (243)	262 (266)	0.16
CRP (mg/L)[b]	8.5 (13.4)	12.1 (19.7)	30.4 (47.4)	0.002
Fetuin-A (g/L)[b]	0.69 (0.19)	0.63 (0.16)	0.58 (0.15)	0.03
ucMGP (nmol/L) [b]	191 (87)	176 (69)	172 (62)	0.54
Antihypertensive drugs (%)				
ACE inhibitors	20	19	16	0.74
AII receptor blockers	9	6	7	0.80
Beta-blockers	26	26	27	0.98
Calcium antagonists	30	29	22	0.33
Diuretics (%)	21	23	22	0.92
Coumarin derivates (%)	4	6	17	0.007
Phosphate binders (%)	95	94	88	0.19

Continuous variables are means (SD). P-values for ANOVA test (continuous variables) or chi-square test (categorical variables). To convert plasma albumin in g/dL to g/L, multiply by 10; calcium in mg/dL to mmol/L, multiply by 0.2495; and phosphorus in mg/dL to mmol/L, multiply by 0.3229.

[a]Diabetes mellitus as co-morbidity, not as the primary kidney disease.

[b]CRP and fetuin-A values were available for 146 patients and ucMGP values for 139 patients (22% no AC, 56% moderate AC and 22% severe AC).

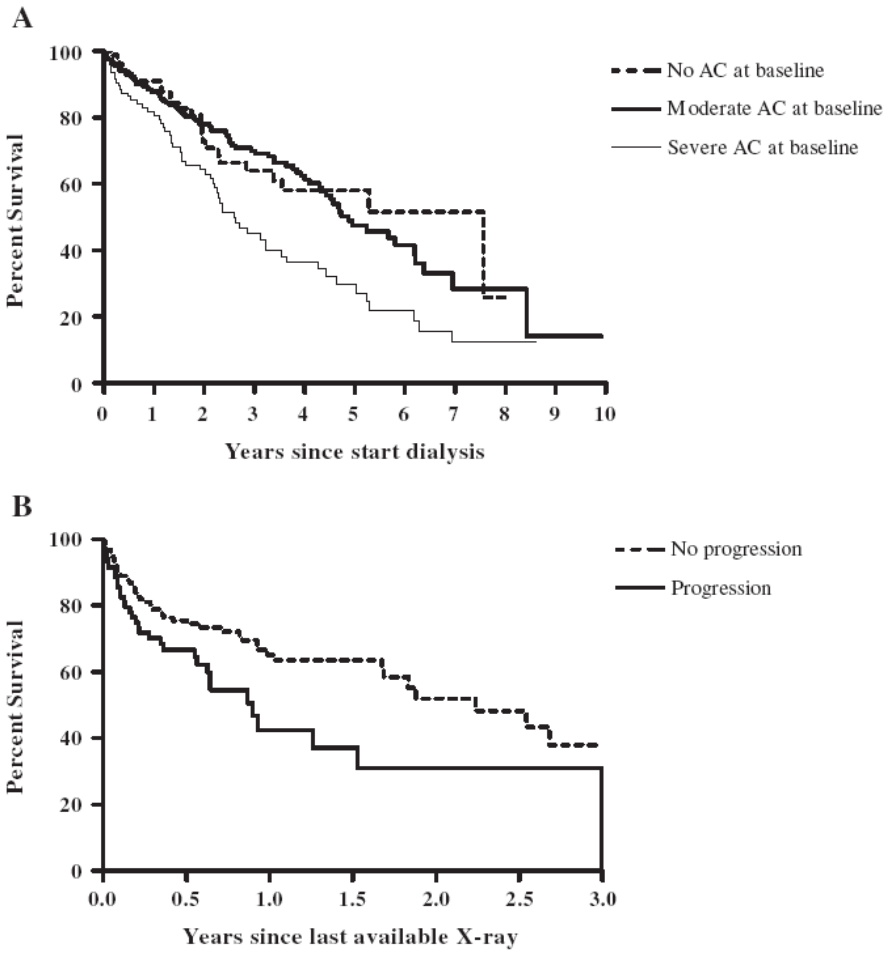

Fig. 2. Kaplan–Meier curves for mortality in patients with no, moderate and severe aortic calcifications (n = 384) (log-rank, P < 0.001) (**A**), and in patients with and without progression of aortic calcification (n = 237) (log-rank, P = 0.001) (**B**).

Table 2. Crude and adjusted hazard ratios (HR) for the risk of all-cause and cardiovascular mortality associated with the presence of aortic calcification (AC, n = 384)

	Crude HR (95% CI)	P-value	Adjusted HR (95% CI)	P-value
All-cause mortality				
No to moderate AC	1.0		1.0	
Severe AC	1.9 (1.4–2.6)	<0.001	1.2 (0.8–1.7)	0.40
Cardiovascular mortality				
No to moderate AC	1.0		1.0	
Severe AC	1.8 (1.1–2.9)	0.02	1.2 (0.7–2.1)	0.46

Multivariable model: adjusted for age, sex, treatment modality, and diabetes mellitus.

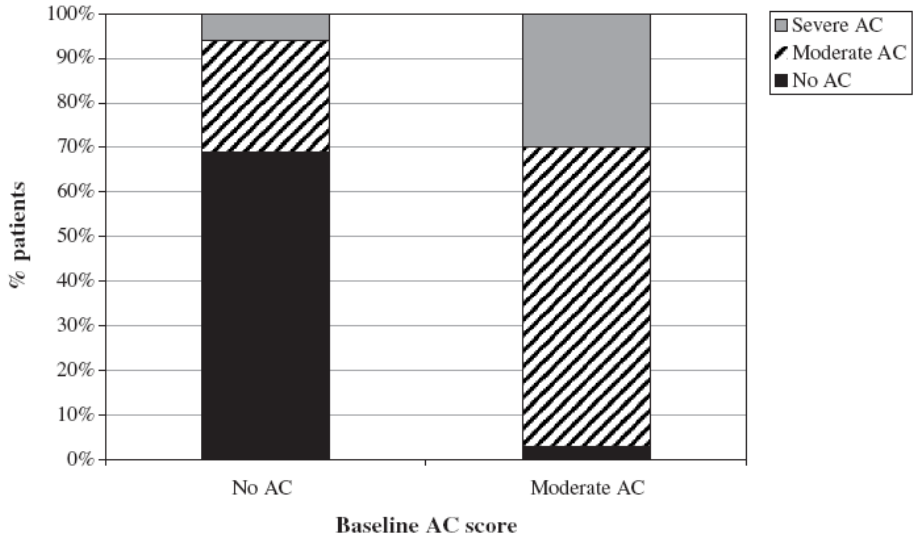

Fig. 3. Changes in aortic calcification score during follow-up (n = 237). Mean (SD) time between baseline calcification score and the last available score was 27 (22)months.

Table 3. Crude and adjusted odds ratios (ORs) for the risk of progression of aortic calcification (n = 237)

	Crude OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value
Calcium				
<8.4 mg/dL	2.19 (0.55)	0.27	1.77 (0.27)	0.55
>9.5 mg/dL	1.92 (0.93)	0.08	3.07 (1.15)	0.02
Phosphorus				
<3.5 mg/dL	0.55 (0.11)	0.47	0.38 (0.05)	0.34
>5.5 mg/dL	0.74 (0.42)	0.31	0.49 (0.23)	0.07
Ca × P product				
>55 mg^2/dL^2	1.09 (0.61–1.93)	0.77	1.00 (0.51–1.96)	0.9
iPTH				
<150 pg/mL	1.72 (0.75)	0.20	1.62 (0.58)	0.35
>300 pg/mL	1.79 (0.71)	0.22	4.36 (1.35)	0.01
Age (years)	0.97 (0.95–0.99)	0.01	1.04 (1.01–1.07)	0.004
Male gender	1.35 (0.74–2.46)	0.33	1.37 (0.65–2.93)	0.41
HD treatment	0.84 (0.48–1.47)	0.53	0.76 (0.33–1.73)	0.51
Time between X-rays (months)	1.04 (1.03–1.06)	<0.001	1.05 (1.03–1.07)	<0.001
Diabetes mellitus	1.13 (0.58–2.21)	0.72	1.43 (0.64–3.21)	0.39
Fetuin-A (0.1 g/L)	1.26 (0.97–1.63)	0.08	#	
ucMGP (nmol/L)	1.00 (0.99–1.00)	0.37	#	
hsCRP				
>10 mg/L	1.13 (0.45–2.84)	0.80	#	

Multivariable model: age, sex, treatment modality, time between the first and the last evaluated X-ray, calcium, phosphorus, iPTH, and diabetes mellitus. Plasma calcium in mg/dL may be converted to mmol/L by multiplying by 0.2495; phosphorus in mg/dL to mmol/L by multiplying by 0.3229. #hsCRP and fetuin-A values were available for 146 and ucMGP values for 139 patients. For these patients, only unadjusted ORs are reported because sample size was too small to fit a multivariable model.

Table 4. Crude and adjusted hazard ratios (HR) for the risk of all-cause and cardiovascular mortality associated with the progression of AC (n = 237)

	Crude HR (95% CI)	P-value	Adjusted HR (95% CI)	P-value
All-cause mortality				
No progression of AC	1.0		1.0	
Progression of AC	1.8 (1.1–2.7)	0.01	1.9 (1.2–3.1)	0.01
Cardiovascular mortality				
No progression	1.0		1.0	
Progression of AC	2.2 (1.2–4.2)	0.02	2.7 (1.3–5.6)	0.008

Multivariable model: adjusted for age, sex, treatment modality, diabetes mellitus, and the time between the first and the last evaluated X-ray.