Screening of vascular calcifications in patients with end-stage renal diseases

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Abstract. Vascular calcifications (VC) are a major contributor to the massively increased mortality in hemodialysis (HD) patients. The present study aimed to detect arterial media and intima calcifications in HD patients and to evaluate potential risk factors.

214 patients aged 59.0 ± 11.0 years on HD for 6.39 ± 4.59 years were studied. VC were scored based on to plain radiographs. Potential risk factors were assessed.

Out of the 214 patients studied, only 14% did not display any detectable VC. Using plain radiographs calcifications could be detected in 136 (63.6%) patients. Calcified plaques on carotid arteries were detected in 168 (78.4%) patients. There was the highest frequency of patients with the most pronounced calcifications. Calcifications of heart valves were detected in 89 (44.1%) patients. Univariante analysis indicate that risk to develop VC is present in older patients, patients with longer dialysis vintage, thicker intima media, higher lumen diameter and mitral valve calcifications. Multivariate multinomial logistic regression analysis revealed these factors as independent predictors of VC in dialysis patients.

Our data confirm a high prevalence of VC in HD patients, their association with older ages, longer dialysis vintage, and presence of valvular calcifications and early markers of atherosclerosis.

Key words: Hemodialysis — Arterial calcifications — Atherosclerosis — Cardiovascular disease — Conventional radiography — Echosonography

Introduction

Cardiovascular disease is common among patients with end-stage renal disease (ESRD), accounting for approximately half of the deaths in those treated with regular hemodialysis (HD) (Go et al. 2004; Brancaccio and Zoccali 2006). Arterial disease due to vascular calcifications (VC) and left ventricular hypertrophy are two principal risk factors for the high rate of cardiovascular mortality. There are two types of arterial calcifications: atherosclerotic vascular lesions with calcium accumulation in the intimal layer of arteries, usually together with localized accumulations of lipid, macrophages and fibrous tissue; medial calcifications – Moenckeberg's sclerosis, typically affects the medial wall of arteries, not usual in general population, but only in diabetic and uremic patients (Kimura et al. 1999; Davies and Hruska 2001; O´Hare et al. 2002; Goodman 2004; Yildiz et al. 2004).

The underlying cause of VC remains uncertain, but there is now strong evidence that it is an active cellular and regulated process. Beside traditional risk factors, hyperparathyroidism, isolated hyperphosphataemia, administration of calcium-containing phosphate binders and vitamin D analogues, inflammation, deficiency in circulating inhibitors of calcification and adynamic bone disease have all been proposed to contribute to VC (Hayden et al. 2005; Shanahan 2005; Qunibi 2005).

Consequences of medial VC include diminished arterial compliance and arterial wall thickening, which can adversely

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affect systemic blood pressure and modify hemodynamic stresses upon the myocardium and large arteries (London et al. 2002; Tozawa et al. 2002). Consequences of intimal VC include reductions in blood flow, vascular occlusion and thrombosis (O´Hare et al. 2002; Tozawa et al. 2002; Yildiz et al. 2004; Okamoto et al. 2006). Calcifications of the myocardium and cardiac valves represent additional serious cardiovascular complications (Wang et al. 2005).

The arterial tree has considerable variability in the susceptibility and the type of calcification. In older patients with ESRD, calcification in the aortic wall and radial artery consistently involves both the intima and media, whereas in younger patients, isolated mediasclerosis predominates especially in blood vessels of lower extremities (Moe et al. 2002).

Several radiographic techniques have been used to detect soft-tissue and VC in patients with chronic renal failure, but none has gained widespread acceptance as a method to reliably assess the prevalence, extent or progression of VC in this patient population. Conventional radiographs often reveal calcifications within medium-sized and large arteries (Adragao et al. 2004; Goodman 2004; Hernandez et al. 2005). Improvements in the spatial resolution achievable with ultrasound have led to the widespread use of this noninvasive method for evaluating the cardiovascular system. Measurements of intimal medial wall thickness in large arteries can be obtained, and atherosclerotic plaques can be visualized in the aorta, common femoral arteries and common carotid arteries. Localized calcium deposits can be detected in the walls of arteries and in atherosclerotic plaques (O´Hare et al. 2002; London et al. 2003; Goodman 2004). Echocardiography can also be used to document the presence of calcium deposits within cardiac valves, and to assess the impact of this abnormality on valve motion and function (Goodman and Salusky 2001; Bellasi and Raggi 2007). Electron-beam computed tomography (EBCT) and spiral computed tomography have been developed as noninvasive, sensitive, but very expensive techniques to screen for the presence of coronary artery calcifications (Moe et al. 2002; Moe and Chen 2008). Braun et al. (1996) showed that coronary artery calcium score revealed by EBCT was from 2.5-fold to 5-fold higher in the dialysis patients as compared with non-dialysis patients with coronary artery disease .

The aim of this study was screening of VC in patients undergoing chronic HD using sensitive, non-invasive radiographic methods and evaluation of the risk factors for their appearance.

Materials and Methods

Population

This single-center cross-sectional study included 214 patients, 116 males and 98 females, on HD for at least six months (mean 6.39 ± 4.59 years) and with a mean age of 59.0 ± 11.0 years. Patients were maintained on bicarbonate HD, three times per week for 12–15 h. Etiologies for ESRD were hypertensive nephrosclerosis, 118 (54.6%); glomerulonephritis, 31 (14.4%); autosomal-dominant polycystic kidney disease, 20 (10.2%); pyelonephritis 22 (10.2%), tubulointerstitial disease and obstructive nephropathy, 3 (1.4%); diabetic nephropathy, 12 (5.6%) and Balkan endemic nephropathy, 8 (3.7%). The following phosphate binders and vitamin D medications were given: calcium carbonate, 159 (75%); aluminum hydroxide, 21 (10%); calcium carbonate/aluminum hydroxide, 24 (11%); no phosphate binder, 8 (4%); 1,25-OH-vitamin D3, 146 (69%); 1α-OH-vitamin D3, 14 (6.6%); warfarin, 5 (2.4%); calcium antagonists, 89 (42%). Cumulative dose of calcium carbonate for six months was 686.2 ± 280.4 g. Viral hepapitis B was detected in 21(9.7%) and viral hepatitis C infection in 61 (28.2%) patients. Due to local circumstances, no patient used lipid lowering drugs, and anti-hypertensive drugs were prescribed as necessary to maintain a post-weekend pre-dialysis blood pressure below 140/90 mmHg. The study protocol was approved by the Ethics Committee of the Zvezdara University Medical Centre (Belgrade, Serbia) and each patient gave informed consent.

Calcification assessment

Common carotid arteries were investigated by B-mode ultrasonography (using the ALOCA SSD 2000 system equipment with 7.5 MHz linear transducers). A trained sonographer evaluated intima media thickness (IMT) and carotid plaques in both common carotid arteries 4 cm from the bulbs, within carotid bulbs and the first 2 cm of the internal and external carotid arteries (Kawagishi et al. 1995). Plaques were defined as echogenic structures showing protrusion into the lumen with focal widening that was 50% greater than the IMT of adjacent sites. Highly echogenic plaques producing bright white echoes with shadowing were considered to be calcifications (Hunt et al. 2001). Such plaques were defined as representing arterial intima calcification (AIC) pattern. To determine the intraobserver variability of IMT measurements, one experienced investigator examined 30 randomly selected patients twice within 14 days. Intraobserver variability was 8%.

Arterial media calcifications (AMC) were detected by plain radiography of the pelvis, both hands and the region of the vascular access. The presence of linear VC was defined as a pattern indicating AMC. Extent of calcifications on plain radiography was analyzed semi-quantitatively by an overall score (Adragao plus region of vascular access score). X-rays of pelvis and one hand were divided into 4 sections by a median vertical line and horizontal line just above the upper rim of the femoral heads and the metacarpal bones, respectively. The presence of linear VC in

each quadrant was counted as 1 point, thus a maximum of 8 points could be achieved (Hunt et al. 2001). In addition to the Adragao score, calcifications detected by X-ray of the fistula arm (fistula itself, ulnar and radial artery) were counted as 1 point each. The investigations were performed by three experienced physicians blinded to patient's information.

Baseline echocardiography was performed with an Aspen-Acuson device equipped with a 2.5 MHz probe allowing M-mode, two-dimensional, and pulsed Doppler measurements. Measurements were made according to the recommendations of the American Society of Echocardiography (Feigenbaum 1994). To determine the intraobserver variability of echocardiographic detection of valvular calcification, one experienced investigator examined 30 randomly selected patients twice within 14 days. Intraobserver variability was 4%.

Biochemistry

Average values of plasma total protein, total cholesterol and triglycerides during the previous year were assessed as traditional risk factors and average values of plasma calcium, phosphorus, intact parathormon (iPTH) and calcium x phosphate product, C-reactive protein (CRP), as non-traditional factors. Inhibitors of VC (fetuin-A and matrix-Gla protein (MGP)) were also detected. All parameters were analyzed by standard laboratory procedures using an automated analyzer. iPTH was assessed by chemiluminescence's assay (Diagnostic Product Corporation, USA). Serum analysis for high sensitivity CRP was performed by particle-enhanced immunonephelometry using a standard 'CardioPhase hsCRP' for 'BNII' (Dade Behring Holding GmbH, Liederbach, Germany). The nephelometric method for association of serum fetuin-A was adopted from a serum ELISA method (Dade Behring Holdings, Liederbach, Germany). The ELISA measurement of undercarboxylated MGP (ucMGP) was conducted as previously described (Schurgers et al. 2005).

Statistics

Statistical calculations were performed using the SPSS software. Data were expressed as percentages for discrete factors, and mean values for continuous variables. Statistical analyses include descriptive statistics and exploratory analyses. Mantel-Haenszel Common Odds Ratio Estimate test was used for risk estimation for VC. Multinominal logistic regression analyses were used to determine odds ratios for calcifications associated with clinical and biological parameters. In all comparisons, $p < 0.05$ was considered statistically significant.

Results

Prevalence of calcification patterns

Out of the 214 patients studied, only 30 did not display any detectable VC (14%). Using plain radiographs calcifications of pelvis, hands and vascular access, calcifications could be detected in 136 (63.6%) patients (Figure 1). Calcified plaques on carotid arteries were detected in 168 (78.4%) patients. Mean value of IMT was 0.79 ± 0.09 mm and lumen diameter 7.27 ± 0.86 mm. There was the highest frequency of patients with the most pronounced calcifications (AIC plus AMC) (Figure 2). Calcifications of heart valves were detected in 89 (44.1%) patients. Mitral valves calcifications were detected in 68 (33.8%), and aortic valves calcifications in 42 (20.9%) patients.

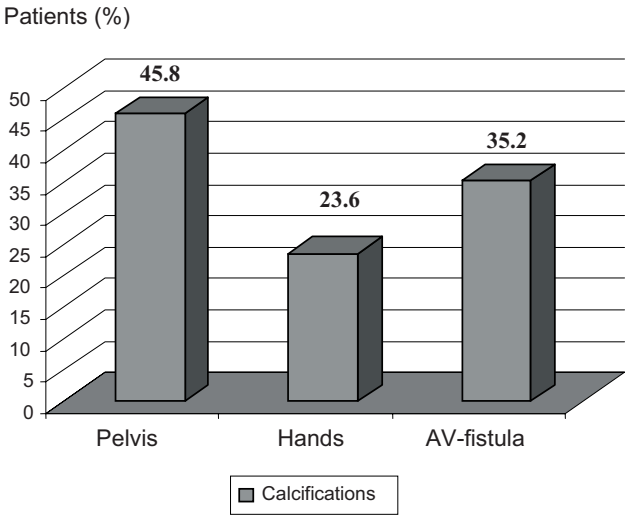

Figure 1. Distribution of VC detected by plain radiography. Calcifications of pelvis, hands and vascular access were detected in 136 (63.6%) of patients. Most of them have calcifications in two or all analyzed regions. The most frequent calcifications were in region of pelvis (45, 8%). AV, arteriovenous.

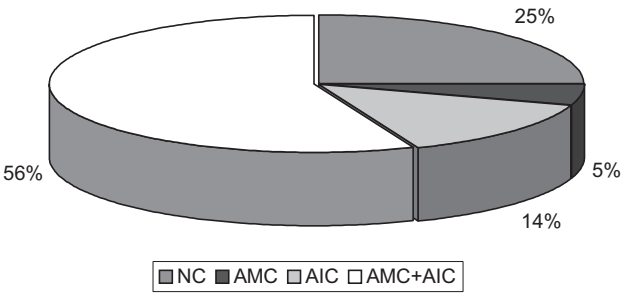

Figure 2. Distribution of different localizations of VC. There is the highest frequency of patients with mixed calcifications (isolated AMC plus AIC, 56%). NC, non-calcifying group of patients; AMC, arterial media calcifications; AIC, arterial intima calcifications

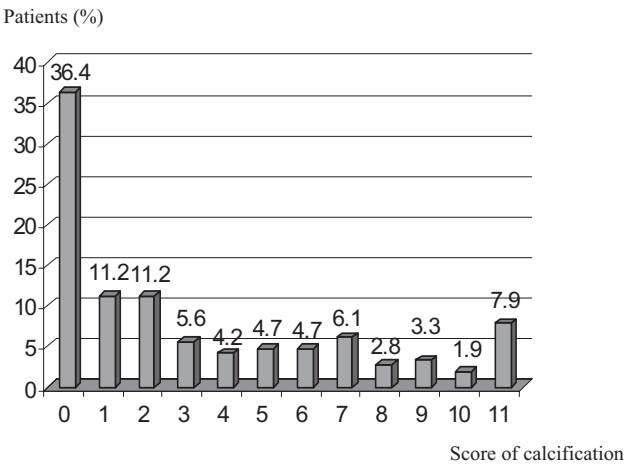

Figure 3. Frequency of patients with different overall score of calcifications detected by plain radiography. Overall score included Adragao score of blood vessels from pelvis and both hands (description in the text), plus blood vessels of arteriovenous fistula.

Extent of calcifications using owerall score is presented in Figure 3. Biochemical parameters of dialysis populations are presented in Table 1.

Risk factors for VC

Using receiver operating characteristic analysis, four out of 16 parameters tested (age, dialysis vintage, body mass index (BMI), phosphates, calcium, calcium-phosphate product, total proteins, bicarbonates, hemoglobin, total cholesterol, triglycerides, CRP, fetuin-A, ucMGP, IMT and lumen diameter of common carotid arteries), were found to be significat risk factors for VC: age (area under curve (AUC) = 0.723, p = 0.000, 95% confidence interval (CI) = 0.64–0.81, positive/negative ratio (P/N) = 54), dialysis vintage (AUC = 0.632, p = 0.020, 95% CI = 0.53–0.73, P/N = 4), IMT (AUC = 0.756, p = 0.000, 95% CI = 0.68–0.84, P/N = 0.75) and lumen diameter of common carotid arteries (AUC = 0.654, p = 0.007, 95% CI = 0.56–0.75, P/N = 6.98).

Results of the univariante analysis (Mantel-Haenszel Common Odds Ratio Estimate test) are shown in Table 2. Risk to develop VC is present in older patients (odds ratio (OR) = 2.45; relative risk (RR) = 1.6), patiens with longer dialysis vintage (OR = 5.6; RR = 2.4), thicker intima media (OR 3.94; RR 2.0), higher lumen diameter (OR 2.28; RR 1.5) and mitral valve calcifications (OR 3.7; RR = 2.7).

Multivariate multinomial logistic regression analysis reveled age, dialysis vintage, IMT, lumen diameter and valvular calcifications as an independent predictors of VC in dialysis patients (Table 3).

Table 1. Laboratory parameters in dialysis population. Data include main parameters that may be significant in the pathogenesis of VC

Variables	Values	Normal rang
Calcium (mmol/l)	2.29 ± 0.18	2.20–2.7
Phosphorous (mmol/l)	1.62 ± 0.42	0.60–1.5
iPTH (pg/ml)	363 ± 456	10–69
Ca x PO4 ($mmol^2/l^2$)	3.74 ± 1.10	<4.50
Hemoglobin (g/dl)	9.40 ± 1.50	12–18
Serum protein (g/l)	67.20 ± 4.99	64–83
Serum cholesterol (mmol/l)	5.13 ± 1.20	3.6–5.2
Serum triglycerides (mmol/l)	2.28 ± 1.28	0.4–1.7
Bicarbonates (mmol/l)	21.20 ± 2.70	21–31
CRP (mg/l)	9.46 ± 17.33	0–5
Fetuin-A (g/l)	0.55 ± 0.14	0.5–1.0
ucMGP(nmol/l)	185.4 ± 100.8	not defined

iPTH, intact parathormon; CRP, C-reactive protein; ucMGP, undercarboxylated matrix-Gla protein.

Table 2. Results of the univariante analysis (Mantel-Haenszel Common Odds Ratio Estimate test) of factors predicting VC

Parameter	OR	p	OR 95% CI	RR
Age Cutoff point – 54 years	2.45	0.028	1.1–5.5	1.6
Dialysis vintage Cutoff point – 4 years	5.62	0.000	2.4–13.0	2.4
Calcifications of mitral valve	3.70	0.020	1.2–11.1	2.7
IMT Cutoff point – 0.75 mm	3.94	0.001	1.7–8.9	2.0
Lumen diameter Cutoff point – 6.98 mm	2.28	0.039	1.05–5.0	1.5

Factors of significance are: age above 54 years, dialysis vintage longer then 4 years, calcifications of mitral valve, intima media thickness (IMT) above 0.75 mm and lumen diameter of common carotid arteries higher of 6.98 mm. OR, odds ratio; CI, confidence interval; RR, relative risk.

Table 3. Multivariate multinomial logistic regression analysis of the calcification risk in dialysis patients. Several factors were recognized to be associated with calcifications risk

Parameters	Score	p
Age	17.833	0.000
Dialysis vintage	4.994	0.025
IMT	18.555	0.000
Lumen diameter	5.289	0.021
Aortic valve calcifications	7.787	0.005
Mitral valve calcifications	6.600	0.010
Presence of valvular calcifications	11.768	0.001

Model R^2 (Nagelkerke) = 0.806. IMT, intima media thickness.

Discussion

In the present study, we found that of 214 randomly selected patients undergoing chronic HD, 86% have their arteries calcified. High prevalence of both media and intima calcifications (56 %) may be explained by similar pathogenetic mechanism proposed by some authors (Goodman 2004; Cozzolino et al. 2005) and this may also be an explanation for small percent of patient with isolated media calcifications (5%). Literature reports on this issue are not uniform. Salgeira et al. (2003) found VC in 67.5% dialysis patients using plain radiography of thorax, abdomen and pelvis. Study from Japan (Okamoto et al. 2006) included 515 patients on maintenance HD and by radiography of the left abdomen, abdominal aortic calcification was found in 56.5%. Also, London et al. (2003) found 36% of HD patients to be free of VC using plain radiography. Chertow et al. (2004) found that 17% of HD subjects had no coronary calcifications and 20% had no aortic calcifications using EBCT. Stompor et al. (2003) found that 29% of their peritoneal dialysis population remained calcium-free after 12 months. Moe et al. (2003) found 28% of HD patients had no evidence of coronary calcification using spiral CT. Oh et al. (2003) using CT scan, found coronary calcifications in 92% young adult ESRD patients with childhood-onset chronic renal failure either undergoing dialysis or after transplantation. Difference between reports may probably be explained by different methodology used and different population of patients that were included into studies.

Valvular calcifications were detected in 44% patients (mitral and aortic valve). Ix et al. (2007) detected mitral valve calcifications in 20% cardiovascular patients without renal disease. Braun et al. (1996) were detected aortic valve in 55%, and mitral valve calcifications in 59% dialysis patients using more sensitive method – EBCT.

Recently Muntner et al. (2007), revealed the importance of simple method including demographic information, dialysis vintage, abdominal aorta calcification and mitral and aortic valve calcification in predicting of coronary artery calcifications with very good accuracy. Furthermore, they concluded even simpler method warrants consideration and that omitting the echocardiogram would result in substantially reduced test cost and feasibility. It seems that every dialysis center search for the most available, feasible, less costly and, on the first place, most accurate diagnostic method for VC. Our intention was to follow the NKF-DOQI (National Kidney Foundation Disease Outcomes Quality Initiative) recommendation about screening dialysis patients for VC.

For better accuracy, standard Adragao score was strengthened by using additiononal scores (for fistula calcifications). Evaluation of media calcifications by using extended Adragao score provided us additional information about the distribution and extent of VC. We believe that follow-up data will be more conclusive about the role of scoring of calcifications in evaluation of calcifications progression.

For many years, calcifications of soft tissues and arteries were considered to passively result from calcium and phosphate precipitation due to a high calcium-phosphate ion product leading to supersaturated plasma. However, at least in the case of VC there is now strong evidence that it is an active and regulated process that may be initiated by a number of different mechanisms. Human and mouse genetic findings have determined that blood vessels normally express inhibitors of mineralization, such as pyrophosphate, MGP, fetuin/2-HS-glycoprotein and osteoprotegerin, and that lack of these molecules leads to spontaneous VC and increased mortality. The presence of bone proteins such as osteopontin, osteocalcin, and BMP2, matrix vesicles, and outright bone and cartilage formation in calcified vascular lesions, has suggested that osteogenic mechanisms may also play a role in VC. Cells derived from the vascular media undergo bone- and cartilage-like phenotypic change and calcification *in vitro* under various conditions. Bone turnover leading to release of circulating nucleation complexes (aggregates of calcium-phosphate and proteins released from remodeling bone that may initiate ectopic mineralization), and cell death can provide phospholipids rich membranous debris and apoptotic bodies that may serve to nucleate apatite, especially in diseases where necrosis and apoptosis are prevalent, such as atherosclerosis. Abnormalities in mineral metabolism that enhance the calcium-phosphate product may further exacerbate VC initiated by any of these mechanisms (Giacheli 2004; Johnson et al. 2006; Ketteler and Floege 2006).

In the present study univariate analysis indicated that risk for VC increases in older patients, patients with longer dialysis vintage, thicker intima media, higher lumen diameter and detected valvular calcifications. In multivariate regression analysis the same factors remained as independent predictors of VC.

Krasniak et al. (2007) evaluated several risk factors for coronary artery calcifications in univariate analysis (age, BMI, serum iPTH, CRP, interleukin-6, 25-OH-vitamin D3, transforming growth factor-β, plateled derived growt factor and carotid artery IMT), but in multivariate regression analysis only age and carotid artery IMT remained as independent predictors of coronary artery calcifications. Hermans et al. (2007) evaluated the relation between serum fetuin-A and arterial stiffness, as a feature of predominant VC. Fetuin-A, well known inhibitor of VC, appeared not to be an independent predictor of aortic stiffness in a dialysis population with a low level of inflammatory activity. All above suggest a great complexity of VC process and more clinical and basic research data in that field are still needed.

The current study needs to be considered in the context of its limitations. At the moment, there are no enough data

to confirm advantage or inferiority of "classic" X-ray and echosonography imaging over more modern and sophisticated (but also less available) diagnostic procedures. Unless we are provided with those data, dialysis patients should be regularly monitored according to currently accepted guidelines. The cross-sectional character of present study assessing most serum parameters at only one single time point, decreases the potential predictive power of individual serum parameters. This is, why, at least in the case of rapidly fluctuating parameters such as phosphate and calcium, we used time-averaged values for the analyses.

In summary, the data presented reveal an extremely high percentage of dialysis patients with VC and most of them exhibited both intimal and medial localizations. By multivariate analysis, significant risk factors for VC were older age, longer dialysis vintage, thicker intima media, higher lumen diameter and presence of valvular calcifications. Further studies are needed for better understanding calcification process and its consequences.

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