Abdominal aortic calcification in predialysis patients: Contribution of traditional and uremia-related risk factors

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Abstract. Cardiovascular disease is the main cause of morbidity and mortality in end-stage renal disease (ESRD) patients. Recent population based epidemiological studies demonstrated a correlation between reduced renal function and risk for all causes and cardiovascular mortality, 50% of patients dying before the commencement of renal replacement therapy. Vascular calcifications (VC) and arterial stiffness are major contributors to cardiovascular disease and are independent predictors of cardiovascular mortality in ESRD patients. Scarce information is available on the risk factors and prognosis of predialysis patients with VC. The aim of this study was to evaluate the contribution of traditional and uremia related risk factors to abdominal aortic calcification in predialysis patients. A single center, retrospective study was performed on 305 adult patients monitored at the Bucharest University Emergency Hospital for at least 6 months. Our study reports an increased incidence of VC in predialysis chronic kidney disease (CKD) patients, higher in those with advanced age, history of cardiovascular disease, osteoporosis, and declining renal function.

Introduction

The increase in the number of hypertensive and diabetic patients globally leads to an increase in the prevalence of CKD. Over time, high blood pressure and diabetes can lead to kidney damage (1-3). High blood pressure may occur as a consequence of CKD induced by another pathology (4).

Recent studies in the literature demonstrate the important role of the genetic factors in the development of diabetic nephropathy relating to the angiotensin I-converting enzyme (ACE) gene, the ceramide synthase 2 (CERS2) gene and the genetic polymorphism of vitamin D receptors. The fundamental role of glucose transporter 2, growth factor β and endothelial nitric oxide synthase has also been demonstrated in the development of diabetic nephropathy (5).

The close association between CKD and cardiovascular disease is responsible for the increased mortality rate of CKD patients. The survival is also influenced by their nutritional and inflammatory status (6).

Cardiovascular disease is the main cause of morbidity and mortality in ESRD patients (7). The presence of overt cardiovascular disease and its risk factors at the initiation of dialysis suggest a high incidence of cardiovascular disease in predialysis patients (8). Recent population based epidemiological studies demonstrated a correlation between reduced renal function and the risk for all causes and cardiovascular mortality, a high proportion of patients dying before receiving dialysis (9).

Literature indicates that a rise in VC prevalence is associated with the decline of glomerular filtration rate (GFR) (10). VC and arterial stiffness are major contributors to cardiovascular disease and are independent predictors of cardiovascular mortality in ESRD patients (11).

CKD patients develop accelerated medial as well as intimal calcification and this calcification rapidly progresses in patients on dialysis (12). VC prevalence is high in chronic hemodialysis (HD) patients. An observational multicentric study describes the presence of VC in 100% of studied patients (13).

Patients with CKD and general aging population have VC in common, which is an active process. Transdifferentiation of vascular smooth muscle cells (VSMCs) to osteoblast-like cells via upregulation of core binding factor alpha 1 (Cbfa1) is one of the first steps in arterial calcification. These differences can appear due to elevated serum phosphorus or other yet unidentified uremic toxins. Whereas, a protective role has been described for serum fetuin-A and other inhibitors of the calcification process. Deeper understanding of the pathogenesis of VC will allow the development of therapeutic strategies to arrest this process (11).

Scarce information is available on risk factors and prognosis of VC in predialysis patients (14). The aim of this study was to evaluate the contribution of traditional and uremia related risk factors to abdominal aortic calcification in predialysis patients.

This study was approved by Ethics Committee of the Emergency University Hospital of Bucharest (Romania). Written informed consent was obtained from the patients prior to publication.

Patients and methods

Study design. A single center, retrospective study was performed on 305 adult patients monitored at the Bucharest University Emergency Hospital for at least 6 months. The inclusion criteria were age >18 years and a diagnosis of CKD, defined as a GFR decline (GFR<60 ml/min/1.73 m^2) present for >6 months associated with one of the following: albuminuria (urine albumin-creatinine ratio ≥30 mg/g), urine sediment abnormalities, electrolyte and other abnormalities due to tubular disorders, histological abnormalities, structural abnormalities detected by imaging, or history of kidney transplantation (15).

Patients with neoplastic, infectious or inflammatory diseases were excluded. All the 305 patients included in the study had a lateral abdominal X-ray performed, which was employed for calculating aortic calcification score and for diagnosing osteoporosis. For all these patients, data were collected from the patient's charts at enrollment, including demographic and clinical data [age, sex, smoking habits, primary renal disease, and a history of cardiovascular disease characterized by the presence of one of the following: myocardial infarction, angina pectoris, coronary artery revascularization, stroke or positive diagnostic procedure result (stress test, coronary or peripheral angiography)] and laboratory data (see below). As these demographic, clinical, and laboratory data are routinely collected for any monitored CKD patient, there were no missing data, consequently no patient was excluded on this account.

Laboratory data. X-ray examinations were performed at the time of the study. Laboratory data were retrieved from the patient files for the previous 6 months. Blood samples were drawn in the fasting state for determination of serum levels of creatinine, urea, cholesterol, triglycerides, calcium, phosphate, albumin, fibrinogen and C reactive protein (CRP). GFR was calculated according to modification of diet in renal disease (MDRD) 4 formula. The study population was grouped according to the stages of CKD, in keeping with Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines. Time, averaged values, over the previous 6 months were used for analyses.

Abdominal aorta calcification score. A semi-quantitative scoring system assigning 1-3 points to areas of calcification identified along the anterior or posterior surface of the aorta extending from the 1st to the 4th lumbar vertebra on a lateral plain radiograph of the abdomen, as originally described by Kauppilla *et al* (16), was used. Eight locations were evaluated (anterior and posterior abdominal aortic walls of the four aortic segments corresponding to the four lumbar vertebrae L1 to L4) by lateral abdominal radiographs and assigned Framingham calcification scores (0, no detectable calcification; 1, small scattered calcifications involving 1/3 of aortic segment; 2, calcification involving 1/3 to <2/3 of the aortic segment, 3, calcification involving 2/3 of the aortic segment). With this method, the score could vary from a minimum of 0 to a maximum of 24 points. Scores were grouped into four categories: 0 (107 patients), 1-3 (47 patients), 3-10 (86 patients), >10 (65 patients). All X-rays were read by three independent reciprocally blinded investigators and a consensus was reached on the interpretation of all films. The diagnosis of osteoporosis is radiological on the same X-ray where abdominal aortic calcification score was estimated.

Statistical analysis. Data are presented as mean and standard deviation (SD) or as median and inter-quartiles range, according to distribution. Univariable and multivariable analysis, e.g. multiple linear regression (estimated as R^2) were used to investigate the correlations between aortic calcification score and several other study parameters, classified as traditional (sex, age, hypertension (HTA), smokers, triglycerides, cholesterol, glucose, cardiovascular comorbidities) and non-traditional [vascular nephropathy, phosphocalcic metabolism disorders, body mass index (BMI), CRP,

Table I. Characteristics of patients (n=305).

Parameters	Value
Age (years; median, range)	62 (53-73)
Sex (% males)	50.5
Smoking (%)	45.0
Primary renal disease (%)	
Vascular disease	44.3
Glomerular nephropathies	30.5
Interstitial nephropathies	13.8
Diabetes nephropathies	7.2
ADPKD	3.0
GFR (median; i.q.r)	28.4 (11.4-48.6)
Stage 1, 2 (%)	14.8
Stage 3 (%)	33.4
Stage 4 (%)	19.0
Stage 5 (%)	32.8
Hypertension (%)	73.4
Cardio-vascular co-morbidities (%)	
Ischemic heart disease	35.0
Cerebrovascular	7.0
Peripheral vascular disease	21.3
Cholesterol >200 mg/dl (%)	50.0
Triglycerides >150 mg/dl (%)	40.0
Glucose level (median, i.q.r)	102 (91-116)
BMI (median i.q.r)	26 (24-31)
BMI <20 (%)	8.9
BMI 20-25 (%)	26.6
BMI 25-30 (%)	36.1
BMI >30 (%)	28.5
Inflammation (CRP >3 mg/l; %)	77.0
Aortic calcification score; median (i.q.r.)	3 (0-10)
Osteoporosis (%)	50.0
Serum calcium	
Time-averaged (mg/dl per month; mean ± SD)	8.7±1.1
Serum phosphate	
Time-averaged (mg/dl per month; mean ± SD)	4.8±2.0

ADPKD, autosomal dominant polycystic kidney disease; GFR, glomerular filtration rate; BMI, body mass index; CRP, C reactive protein; SD, standard deviation.

osteoporosis] risk factors. Logistic regression was performed in the case of categorical parameters: sex, HTA, smoking, cardiovascular comorbidities, vascular nephropathy and osteoporosis. The numerical parameters (age, triglycerides, cholesterol, glucose, calcium, phosphates, calcium phosphate product, BMI, CRP) were adjusted by normalization before performing the multiple linear regression.

Comparisons among the four categories of aortic calcification score were made by means of Chi-square test (when the associations with categorical parameters were analyzed) or ANOVA and Willcoxon or Mann-Whitney test (when the associations with numerical parameters were analyzed). All analyses were performed using EPIINFO6 and GraphPad InStat 2003.

Results

There was a slight male (M) preponderance (50.5%). The median age was 62 years, and 43.3% of patients were aged >65 years. Smoking prevalence was 45% (Table I). A history of cardiovascular disease was present in 64.3% of patients. The primary renal diseases were vascular nephropathy (44.3%), followed by glomerular nephropathies (30.5%) and interstitial nephropathy (13.8%). Diabetic kidney disease was present in 7.2% of patients. The median GFR was 28.45 ml/min/1.73 m^2 (range, 11.4-48.6). 14.8% of patients was in stage 1 and 2 of CKD; 33.4% in stage 3; 19% in stage 4 and 32.8% in stage 5. HTA was present in 73.4% of the patients. Total cholesterol levels were >200 mg/dl in 50% of patients; triglycerides were >150 mg/dl in 40% of patients. Although the mean hemoglobin (Hb) value was in the normal range (112.2 g/dl), anemia (Hb<11 g/dl) was observed in 50% of patients, all of whom had stage 3, 4 or 5 CKD. The median BMI was 26 kg/m^2 (24-31) with 64.6% of patients overweight and obese. Only 8.9% of patients had BMI <20 kg/m^2. The median CRP was 12 (4-43), only 23% of patients had CRP <3 mg/l and 56% with CRP >10 mg/l. The mean albumin level was 3.7±0.4 mg/dl, with 50% of the patients with albumin <4 g/dl. Bone mineral metabolism was altered by CKD, hyperphosphatemia and hypocalcemia was present in 25.5 and 28% of patients. In the whole group, median aortic calcification score was 3 (i.q.r. 0-10) and in 35.1% the score was 0.50% of the patients with a diagnosis of osteoporosis on X-ray examination.

In univariable analysis, higher aortic calcification scores were associated with older age, smoking, HTA, glucose level, a history of cardiovascular disease, vascular nephropathy, 'macro inflammation', e.g. CRP >10 mg/l, osteoporosis and GFR (Table II).

A model of multiple linear regression including all relevant parameters resulting from univariate analysis explained 34% of aortic calcification score. In this model, age (r=3, P=0.0024), a history of cardiovascular disease (r=3.7, P=0.0002), osteoporosis (r=4.39, P<0.0001), and GFR (r=2, P=0.04) were significantly associated with aortic calcification (Table III).

Discussion

Vascular calcification (VC) is common in CKD and is associated with increased morbidity and mortality (10). In the published studies, a close link between aortic calcification, valvular calcifications and carotid plaques was observed (17). Also, studies describe a tight association between atherosclerotic plaques and retinal artery occlusion (RAO). This is why retina blood vessel anomalies are described in ESRD patients (18). A viable treatment option for RAO is Nd:Yag laser embolysis (19).

Arterial calcification is clinically detected through a number of techniques including plain radiographs, ultrasonography, tomography, scintigraphy and computed tomography (CT) scan, more recently by electron beam

Table II. Distribution of investigated parameters according to the four categories of aortic score calcification (NS, P>0.05).

Parameters Aortic calcification score	Categories according to aortic calcification score				
	0	1-3	3-10	>10	P trend
Number of patients	107	47	86	65	
Traditional risk factors					
Sex (M) (%)	50.5	44.7	58.1	44.6	NS
Age (years; mean ± SD)	51.6±13.9	62.9±10.7	66.8±11.2	72.0±10.4	0.004
HTA (%)	66.4	85.1	70.9	80.0	0.05
Smokers (%)	25.0	30.0	38.0	48.0	0.05
Triglycerides; mg/dl, median (i.q.r)	139 (98-189)	125 (105-232)	135 (102-184)	140 (101-175)	NS
Cholesterol; mg/dl, median (i.q.r)	198 (167-245)	220 (175-284)	198 (160-243)	201 (175-228)	NS
Glucose; mg/dl, median (i.q.r)	99 (89-107)	101 (89-123)	103 (93-122)	105 (97-122)	0.05
CV comorbidity (%)	31.8	74.5	75.6	95.4	0.0008
Non-traditional risk factors					
Vascular nephropathy (%)	26.2	48.9	48.8	64.6	0.05
Mean GFR (ml/min)	37.3±29.6	34.9±24.3	34.0±25.2	25.6±20.6	0.04
Calcium, time-averaged ± SD (mg/dl)	8.5±1.5	8.8±1.0	9.0±0.9	8.7±0.9	NS
Phosphates; time-averaged ± SD (mg/dl)	5.2±2.3	4.9±2.0	4.6±1.5	4.8±1.9	NS
Calcium phosphate product; time-averaged ± SD) (mg^2/dl^2)	41.7±14.5	41.6±13.2	40.3±11.4	41.2±15.5	NS
BMI (kg/m^2) (mean)	27.4±6.4	28.5±5.9	27.1±6.3	27.3±5.4	NS
CRP; (%) CRP >10 mg/l	54.2	40.4	67.4	68.0	0.05
Osteoporosis (%)	18.7	48.9	62.8	85.9	0.0001

NS, not significant; M, male; SD, standard deviation; HTA, hypertension; GFR, glomerular filtration rate; BMI, body mass index; CRP, C reactive protein.

Table III. Relationships of aortic calcification score with the investigated parameters by multiple linear regression (R^2=0.34) with aortic calcification score as dependent variable.

Independent variables	β	95% Confidence interval	P-value
Age (years)	0.08	0.02-0.13	0.0024
Smoking	1.46	-0.24-3.15	0.10
Vascular etiology	-0.04	-0.11-0.02	0.22
CV comorbidity	2.79	1.33-4.26	0.0002
HTA	-0.12	-1.51-1.26	0.85
GFR	-0.02	-0.04-0.0005	0.04
Osteoporosis	3.197	1.77-4.62	<0.0001
CRP >10 mg/l	1.36	0.8-1.5	0.55
Glucose	0.01	-0.006-0.03	0.18

GFR, glomerular filtration rate; CRP, C reactive protein.

computed tomography (EBCT) and multislice CT. The last two techniques permit reproducible quantification of coronary arteries and aorta calcification, but still do not allow differentiation between the intimal or medial site of calcification and are very expensive.

The Global Bone and Mineral Initiative (20) proposed a series of simple in-office measurements and assessments as substitutes for EBCT and multidetector CT to identify and semiquantitatively evaluate the extent of cardiovascular calcifications in ESRD patients. This group of experts suggested that a plain lateral X-ray of the lumbar spine to assess the calcification of the abdominal aorta, the measurement of pulse pressure, and an echocardiogram to visualize calcification of the cardiac valves might provide useful diagnostic and

prognostic information (21). It has been demonstrated that aortic calcification score shows a very good correlation with EBT measurements (22).

In HD patients, the presence of abdominal aorta calcifications (AAC) predicts coronary artery disease (23) and cardiovascular mortality (24). This is the first study that evaluates AAC by Kauppila score in predialysis patients and the contribution of traditional and nontraditional risk factors. Our study indicates that the prevalence of VC in predialysis patients is high. The prevalence of VC reported in predialysis population is 40-90%, depending on the site of VC evaluated, age, presence of diabetes, cardiovascular comorbidities, and degree of renal dysfunction (25,26).

In published studies the prevalence of VC was lower for younger patients, with neither diabetes, nor cardiovascular comorbidities, and higher for older diabetic patients with cardiovascular comorbidity (14,27-29). In our study, where the patients are older, obese, and with many cardiovascular comorbidities, the prevalence of VC is 65%.

In the present study, patients with AAC were older and more frequently smokers, and had HTA, a history of cardiovascular disease, and a higher fasting blood glucose level. Similarly to the studies cited above, we found a strong correlation of AAC with increasing age, and similarly to the study by Tomiyama et al (14), with HTA and a higher blood glucose. The association between AAC and an elevated level of fasting glucose suggests the contribution of insulin resistance, and in a recent study by Kobayashi et al (30) contributed to coronary artery calcification in predialysis patients. Contrary to the study by Toussaint et al (31) and Tomiyama et al (14), TG levels were not an independent determinant of VC in our study.

Among non-traditional risk factors, macroinflammation is associated in univariate analysis with VC (32). Ross (33) stated that atherosclerosis is an inflammatory disease. In CKD patients, inflammation is one of the key mediators of vessel wall calcification (34). In predialysis patients, severe coronary calcifications were associated with sFAS, a marker of inflammation, in the study of Tomiyama et al (14). In our study, high prevalence of inflammation in predialysis patients, was higher than the 30-50% reported in HD patients (35). Besides, the high burden of cardiovascular comorbidity and a high percent of patients in stage 5 CKD, the high prevalence of obesity in our patients, reported also in other studies, can be a plausible explanation. Abnormalities in calcium and phosphorus metabolism influence the development and progression of VC in CKD patients (10). Similarly to HD patients, where not all studies demonstrated an association between abnormality in mineral metabolism and VC, also in studies done on predialysis patients the results were contradictory. Our study did not find an association between AAC and the blood level of calcium or phosphorus, or calcium-phosphate product.

CKD has been individualized as an independent risk factor for CV disease, proportionally with the decline in renal function. In the studies by Fox et al (36), Kramer et al (28), Kobayashi et al (30) and Toussaint et al (31), there was an association between VC and declining renal function in the unadjusted analysis. However, in the multiple logistic regression analysis, after adjusting for age, diabetes, sex, race, HTA, and IL6, the association was lost. In our study based on an anadjusted analysis, the VC score is higher in patients with lower GFR. Bone ill-health is correlated with VC (37) particularly in patients with CKD (38,39).

There are many studies demonstrating the association between the bone quality [as evaluated by histomorphometry, radiology, ultrasonography, computerized tomography or dual-energy X-ray absorptiometry (DEXA)] and VC in HD patients (40,41). In predialysis patients there is a study by Toussaint et al (31) demonstrating an inverse correlation between femoral arterial calcifications and femoral T score (31). In our study, although the diagnosis of osteoporosis was made by X-ray, which picks up only the advanced stage, a strong correlation with VC was found, similar to the general population.

In conclusion, this study reports a high incidence of VC in predialysis CKD patients, worse with age, a history of cardiovascular disease, presence of osteoporosis and deteriorating renal function.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the author on reasonable request.

Authors' contributions

DT, DD and DI designed the study, obtained the data, and were responsible for the clinical management of the patient, the data evaluation and analysis and the writing of the manuscript. DT, AEBS and MDT analyzed and interpreted the X-rays. DT, DGB, LR, AT and OS performed the literature search and selected the studies to be included. DI and DD critically revised the manuscript. All authors read and approved the final manuscript. The contributions of all the authors on this article are greatly valued and appreciated.

Ethics approval and consent to participate

This study was approved by Ethics Committee of the Emergency University Hospital of Bucharest (Romania). Written informed consent was obtained from the patients prior to publication.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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