BANTAO Journal 2019; 17(2): 91-96

BJ
BANTAO Journal

Original article

Importance of Vascular and Valve Calcifications in Chronic Kidney Disease

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Abstract

Introduction. Cardiovascular diseases (CVD) are a leading cause of increased mortality in patients with chronic kidney disease (CKD). Vascular and valve calcifications are a consequence of the mineral-bone disorders and one of the causes of CVD progression. We compared the calcium burden on arterial vessels and heart's aortic and mitral valves with clinical and laboratory data in patients with CKD.

Methods. The study included 47 patients (35 males, 12 females) with glomerular filtration rate below 44 ml/min/1.73 m^2. Calcium score was determined after performing abdominal laterography (individual aortic segments were analyzed at L1-L4 levels of lumbar vertebra). Pelvic and hand radiography with calcium assessment on arterial vessels and total calcium score was stated. The heart ejection fraction and the aortic/ mitral valves calcium score were determined by echocardiography.

Results. The results of the clinical study showed that higher arterial calcium score correlated with: greater aortic and mitral valve calcium load, defined a lower heart ejection fraction and increased morbidity of atrial fibrillation and ischemic heart disease. Higher calcium score from abdominal aorta was associated with upper normal level and elevated serum alkaline phosphatase values ($p<0.05$).

Conclusion. Echocardiography and X-ray allow accurate and quantitative determination of vascular and valve calcifications in patients with CKD, which compared with clinical and laboratory data can be used as a method of assessing the risk of cardiovascular morbidity and mortality in patients with CKD.

Keywords: cardiovascular disease, chronic kidney disease, valve calcifications, vascular calcifications

Introduction

Cardiovascular diseases are leading cause of increased mortality in patients with chronic kidney disease (CKD). Vascular and valve calcifications as a consequence of mineral-bone disorders are one of the potential mechanisms for the progression of cardiovascular diseases, which are observed early in the course of CKD [1-4]. Arterial calcifications (AC) are developed in the intima and media of the medium size arteries. Medial calcification is more commonly seen in patients with diabetes mellitus and CKD [5-8] and is described by Mönkeberg calcification [8-10]. Myocardial infarction from stenosis, ischemia or acute thrombosis may be a consequence of intimal calcification in atherosclerotic disease. Arterial rigidity resulting in decreased elasticity of the vessel wall and inadequate vasodilation under conditions of increased stress is caused by calcification of the media. Theoretically, these processes can develop in the coronary arteries and lead to arrhythmias and sudden death [11]. Valve calcifications (VC), although they are less common pathology, have the same risk factors and pathogenic mechanisms as AC [12]. Poor prognosis is associated with the formation of mitral and aortic valve calcifications, even in the absence of hemodynamically significant stenosis, both in the general population [13] and in patients with CKD [14]. The purpose of this study is to compare the calcium burden determined by radiography and echocardiography on arterial vessels and heart's aortic valve (AoV) and mitral valve (MV) with clinical and laboratory data in patients who have different stages of CKD.

Material and methods

We observed 47 patients (35 males, 12 females) who had different stages of CKD (glomerular filtration rate below 44 ml/min/1.73 m^2, using MDRD formula). Total vascular calcium score was determined using classical abdominal aorta laterography at the lumbar vertebrae levels (L1-L4) according to the method of L. I. Kauppila *et al*. [15] and X-ray of the radial arteries and their branching to the first finger, two internal iliac and femoral arteries-a method proposed by T. Adragao *et al*. [16]. The assessment of abdominal aorta calcium

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score was formed by the grade of involvement of each segment of the anterior and posterior wall of the vessel along the first four lumbar vertebrae. Calcification affecting less than 1/3 of the anterior wall of the aorta along the lumbar vertebral body received 1 score and calcification extending over 1/2 of the vertebral body length received 3 scores (total score-24) [9,15-17]. The method of Adragao *et al*. [16] was defined as for each artery; iliac, femoral, radial and first finger on the hands that was affected by calcifications. One point was given for single affected artery, the total maximum score being 8 points for all of the examined arteries [16]. The total vascular score is the sum of all arteries calcium load (maximum value-32). The calcium score of AoV and MV was formed by giving 1 point for each cusp, which was affected by calcifications and the total maximum score was 5 when all the cusps were affected. According to the values of calcium score from abdominal aorta laterography, the patients were divided into three groups: group I with calcium score from 0 to 7; group II from 8 to 15; and group III from 16 to 24. Depending on the total vascular calcium score values, patients were divided into three groups: total vascular calcium score from 0 to 10-group I, from 11 to 21-group II and group III - from 22 to 32. Patients were grouped also according to the sum of the total calcium score of the aortic and mitral valves, as follows: I group-from 0 to 1, II - from 2 to 3 and group III-from 4 to 5. Patients were separated into two groups according to their serum alkaline phosphatase (SAF) values: group I-with alkaline phosphatase values in the range of 30 to 120 U/L and II - with values above 120 U/L. According to the morbidity from atrial fibrillation (AF) and/or ischemic heart disease (IHD), the patients were separated into the following groups: I group with a history of AF, group II with presence of IHD without AF and group III-without data for heart disease.

The data from assessed vascular score were compared with SAF values, echocardiographic data, and the presence/absence of AF and/or IHD. The results were processed with IBM SPSS Statistics 19 software; χ^2 and linear regression were used as statistical analysis methods. The results were presented as mean values, $p < 0.05$ was considered statistically significant. Descriptive statistics (mean, percentage, degree, etc.) were used to summarize the data.

Results

Forty-seven patients with CKD (35 males and 12 females) were included in the study. The patients' summarized data; demographic characteristics, laboratory variables, diagnostic findings (mean, standard deviations, percentage) are shown in tables 1 through 5.

Table 1. Summarized patients' data. (abbrev. eGFR – estimated glomerular filtration rate)

Patients mean age in years	Average eGFR (5 - 44 ml/min/1.73 m^2)	CKD average duration in months before trial enrollment	Arterial hypertension average duration in months before trial enrollment
62.7±16	21.91±8.9	75.62±62.4	216.7±130.8

Table 2. Mean summarized patients' data. (abbrev. SAF - serum alkaline phosphatase)

SAF values (43 - 209 U/L)	Mean ejection fraction values (38-75%)	serum calcium (1.68 – 2.64 mmol/l)	serum phosphorus (0.63 – 2.40 mmol/l)	calcium phosphorus product (1.73 – 5.6 mmol/l^2)
97.6±33.8	61.8±8.1%	2.25±0.19	1.32±0.37	2.97±0.82

Table 3. Estimated average calcium score. (abbrev. AoV-aortic valve; MV-mitral valve)

Mean abdominal aorta score	Average score (hands, iliac and femoral arteries X-ray)	Mean total vascular score	MV calcifications average score	AoV calcifications average score	AoV and MV total average score
6.47±7.77	1.57±2.49	8.77±8.8	0.68±0.83	0.72±0.94	1.43±1.55

Table 4. Patient distribution according calcium score. (abbrev. AoV - aortic valve; MV - mitral valve)

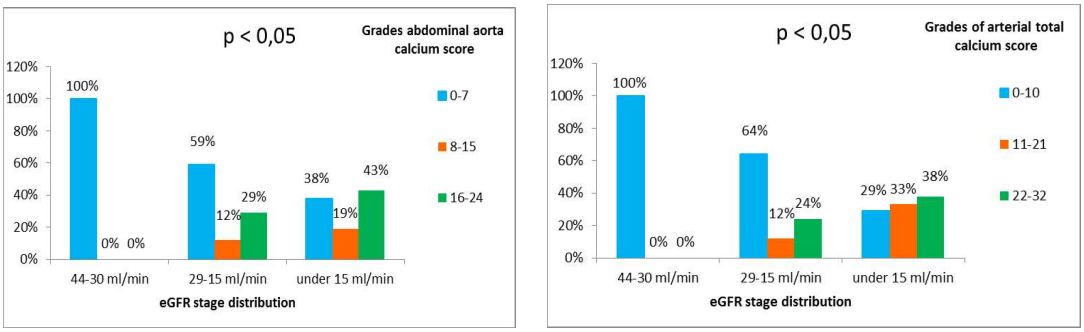
Groups according abdominal aorta calcium score			Groups according total vascular calcium score			Groups according total AoV and MV calcium score		
I Group	II group	III group	I group	II group	III Group	I group	II group	III group
30 patients (60,8%)	9 patients (19,10)	8 patients (17%)	32 patients (68,1%)	10 patients (21,3)	5 patients (10,6)	31 patients (66%)	8 patients (17%)	8 patients (17%)

Tabl.5. Patient distribution according SAF (serum alkaline phosphatase) values and heart morbidity. (abbrev. AF-atrial fibrillation; IHD-ischemic heart disease)

Patients groups according SAF values		**Patients distribution according the morbidity of AF, IHD and no history for heart disease**		
I group	**II group**	**AF**	**IHD**	**No history for heart disease**
37 patients (78,7%)	10 patients (21,3%)	11 patients (23,4%)	15 patients (31,9%)	21 patients (44,7%)

There was a clinically significant relationship between the grades of the abdominal aorta calcium score and eGFR (ml/min/1.73 m^2) according MDRD formula ($p < 0.05$). The patients with higher grades abdominal aorta calcium score had lower eGFR (Figure 1A). The same result was obtained when comparing the total calcium score grades and eGFR stage distribution ($p < 0,05$) (Figure 1B).

When comparing the grades of the abdominal aorta calcium score and serum alkaline phosphatase, it was found that there was a moderate correlation in all three patient groups (Cramer`s coefficient 0.38), $p<0.05$. Patients with serum alkaline phosphatase values equal to or greater than 120 U/L had a higher calcium score (Figure 2).



A **B**

Fig. 1. Correlation between abdominal aorta calcium score grades and eGFR (A). The connection between the grades of the total vascular calcium score and eGFR stages (B).

Clinically significant was the correlation between the grades of arterial total calcium score and the rates of aortic and mitral heart valves total calcium score ($p<0.05$), with a moderate relationship (Cramer's coefficient 0.40). With increase of the arterial total calcium score, the total valve calcium burden also increased (Figure 3).

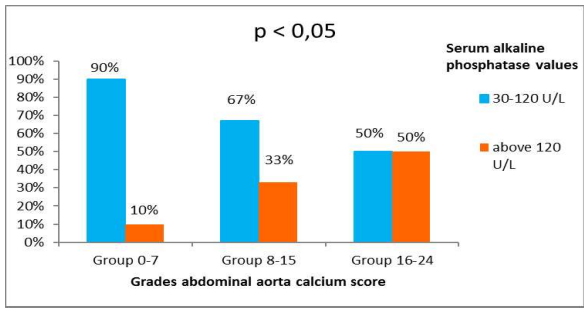


Fig. 2. Relationship between grades of abdominal aorta calcium score and serum alkaline phosphatase

There was a negative correlation [coefficient B (-0.34)] between the abdominal aorta calcium score and the heart ejection fraction (EF) ($p<0.05$). R Square was 0.105, which means that 10.5% of the EF variations were associated with abdominal aorta wall calcifications (Figure 4).

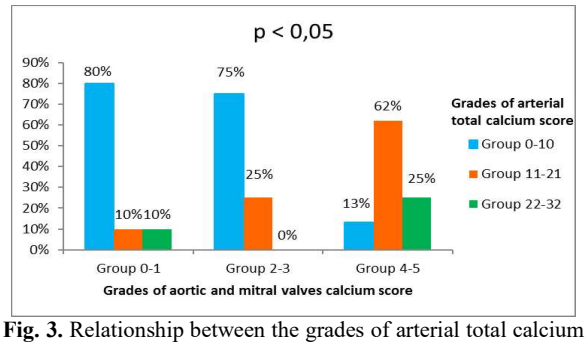


Fig. 3. Relationship between the grades of arterial total calcium score and the total aortic and mitral valve scores rates

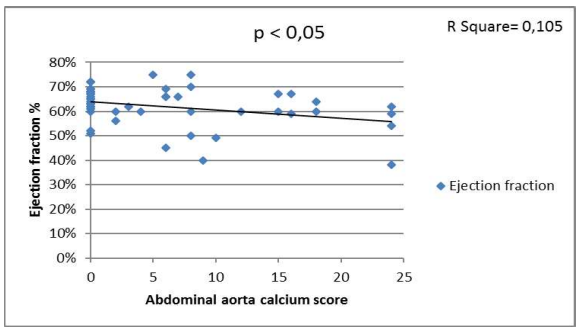


Fig. 4. Linear regression analysis between abdominal aorta calcium score and ejection fraction

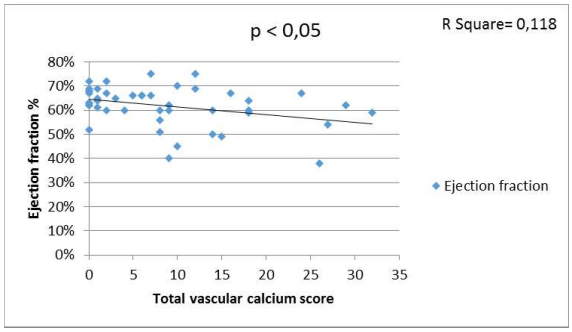


Fig. 5. Correlation between total vascular calcium score and ejection fraction

The relation [coefficient B (-0.34)] between arterial calcium score and heart EF was negative ($p<0.05$). R Square was 0.118, with 11.8% of the EF variations due to calcifications in the arterial vascular wall (Figure 5). The obtained results showed that 0.3 points increase of the artery calcium burden lead to 1% decrease in the EF, e.g. expressed in whole numbers-increase with 3 points in total vascular score lead to 10% decrease in the EF.
There was a moderate correlation (Cramer's coefficient was 0.37) between the grades of abdominal aorta calcium load and cardiac involvement from AF and/or IHD ($p <0.05$). The data showed that as the calcium score increased, the morbidity of patients with IHD and/ or AF increased also (Figure 6). A clinically significant relationship was also found ($p<0.05$) between the total calcium score from X-ray of the arteries and cardiac involvement from IHD and / or AF (Figure 7).

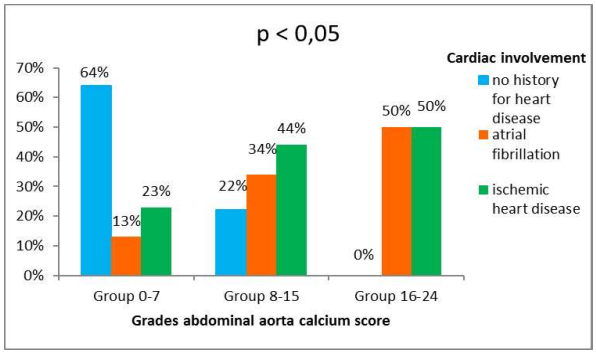


Fig. 6. Correlation between the grades of the abdominal aorta calcium load and the patients' morbidity of the ischemic heart disease and/or atrial fibrillation

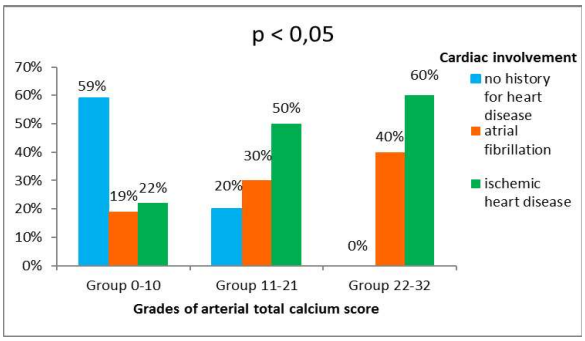


Fig. 7. Relationship between the total arterial calcium score grades and the incidence rate of ischemic heart disease and/or atrial fibrillation

Discussion

In our study, vascular calcifications were found in the walls of arterial vessels in all of the observed patients. The patients with lower glomerular filtration rate who had advanced chronic kidney disease had a higher abdominal aortic calcium score and higher total vascular calcium grade (Figure 1A and 1B). AC were found more frequently in patients with upper and higher serum alkaline phosphatase values greater than 120 U/L (Figure 2). The data support those of Ronney Shantouf *et al*. who found that serum alkaline phosphatase values above 120 U/L were a strong predictor of greater coronary artery calcification in dialysis patients [30]. Srinivasan Beddhu *et al*. showed that, independently from serum calcium and phosphorus, higher levels of serum alkaline phosphatase were associated with increased mortality in the CKD population [31]. L. Deborah *et al*. support this data in hemodialysis patients [32]. Another study by Blayney J, *et al.* found a strong relationship between increased SAF and higher risk of hospitalization and mortality, independently of serum phosphorus, calcium and parathyroid hormone levels [33]. From the obtained results, it can be concluded that higher SAF values in CKD patients are a predictor of arterial walls calcification, which may be associated with a higher risk of cardiovascular diseases.
We found that a higher vascular calcium score was associated with a higher cardio-valvular calcium burden, which corresponds to a lower EF of the heart and an increased morbidity of AF and/or IHD (Figure 3, 4, 5, 6 and 7). Phan O *et al*., Schwaiger JP *et al*., Walsh CR *et al*., Okuno S *et al*. found that vascular calcifications increase cardiovascular risk, survival and mortality, and were associated with myocardial infarction and congestive heart failure in CKD patients [15,16,18-21]. These data support the studies conducted by Blacher J *et al*., Otto CM *et al*., Wang AY *et al*., Wilson PW *et al*., Pohle K *et al*., according who the severity of vascular and valve calcifications were one of the determining factors for survival and mortality, as well as the number and severity of CKD patients' hospitalizations [13,14,22-25]. Qunibi WY *et al*., London GM *et al*., Raggi P *et al*., Panuccio V *et al*. showed that calcium deposits on different cardiovascular structures may be associated with increased morbidity and mortality. The heart valves calcifications may lead to the development of heart failure, coronary ischemia, arrhythmias, valve stenosis, increased risk of infectious endocarditis and thromboembolic events. The valves calcifications were an independent predictor, which can

induce an increased mortality, predominantly from cardiovascular diseases [6,26-29].

Conclusion

It can be summarized, that the echocardiography and X-ray allow accurate and quantitative determination of vascular and valve calcifications. Abdominal aortic laterography is proposed by a group of experts [34] as a reliable method of verifying vascular calcifications and subsequent complications and has good correlation with calcium score determined by computed tomography [35]. Other methods such as electron beam or spiral computed tomography are usually inaccessible to routine practice [17]. The safety and low cost of ultrasound imaging make the echocardiography easily achievable in daily practice and is the gold standard for heart valves morphological and function evaluation: it is not invasive, does not expose the patient to radiation, and is a moderately expensive method. Valve calcification echocardiography and/or abdominal aorta laterography with subsequent calcium burden assessment could be a surrogate marker. Each of these indicators, together with CKD stage determination by eGFR according to MDRD formula could help in clinical practice, easier to determine and predict the cardiovascular morbidity and mortality risk.

Conflict of interest statement: None declared

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