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ORIGINAL ARTICLE

Fibroblast growth factor 23 and parathyroid hormone predict extent of aortic valve calcifications in patients with mild to moderate chronic kidney disease

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Abstract

Background: Cardiac valve calcifications are present in dialysis patients and regarded as dependent on a deranged mineral metabolism. Few data are available for patients with chronic kidney disease (CKD) not on dialysis. This study evaluates the potential association between the extent of cardiac valve calcification and levels of intact parathyroid hormone (i-PTH), phosphorus, calcium, 25-OH vitamin D, fibroblast growth factor 23 (FGF-23), Klotho and C-reactive protein (CRP) simultaneously measured in patients with mild to moderate CKD.

Methods: Consecutive non-hospitalized patients referring to five nephrology units were evaluated. Inclusion criteria were age >18 years, CKD Stages 3–4, and the presence of aortic and/or mitral valve calcification assessed by echocardiography as routinely clinical evaluation. Patients underwent clinical examination and routine biochemistry. Baseline i-PTH, phosphorus, calcium, 25-OH vitamin D, FGF-23, Klotho and CRP were simultaneously ascertained.

Results: Extent of aortic valve calcification (n = 100 patients) was moderate in 68 patients and mild in the remaining patients. Mitral valve calcification (n = 96 patients) score was 1, 2 and 3 in 61, 34 and 1 patients, respectively. In univariate analysis, no association was found between extent of mitral valve calcification and markers of mineral metabolism and CRP; aortic valve extent of calcification was positively associated with i-PTH ($r^2 = 0.212$; P = 0.03) and FGF-23 ($r^2 = 0.272$; P = 0.01), and negatively with Klotho ($r^2 = -0.208$; P = 0.04). In multivariable analysis, extent of aortic valve calcification was associated with FGF-23 (P = 0.01) and PTH (P = 0.01) levels.

Conclusions: Extent of aortic valve calcification is associated to FGF-23 and PTH in naïve CKD patients with mild to moderate CKD. Further studies should examine whether FGF-23 assay should be included in routine clinical evaluation of CKD as part of cardiovascular risk stratification.

Key words: aortic valve calcification, FGF-23, Klotho, mitral valve calcification, PTH

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Introduction

Cardiovascular mortality is high in incident and prevalent patients on dialysis [end-stage renal disease (ESRD)] as well as in patients with chronic kidney disease not requiring dialysis (CKD-ND) [1, 2]. Interestingly, factors that are dependent on CKD are stronger predictors of cardiovascular events than traditional risk factors [3–8].

The presence of cardiac valve calcification is frequently observed in CKD patients, and is associated with an increased risk for cardiovascular events [9–12].

The clinical relevance of cardiac valve calcification has been highlighted by Kidney Disease Improving Global Outcomes guidelines [13]; indeed, the detection of cardiac valve calcification has been suggested for risk stratification of CKD patients.

Derangement of mineral metabolism is regarded as the leading factor responsible for cardiac valve calcification. The association between mineral metabolism and cardiac valve calcification has been extensively evaluated in ESRD patients but seldom in patients with CKD-ND [14–19].

The present study aimed to assess the best predictor(s) of extent of cardiac valve calcification among several markers of mineral metabolism in naïve CKD-ND patients.

To our knowledge, this issue has never been addressed before by simultaneously measuring serum concentration of intact parathyroid hormone (i-PTH), phosphorus, calcium, 25-OH vitamin D, fibroblast growth factor 23 (FGF-23), Klotho and C-reactive protein (CRP).

Methods

This is a multicentre study carried out in 125 consecutive naïve out-patients admitted to five nephrology units for clinical assessment.

Inclusion criteria were age >18 years, CKD Stages 3–4 and the presence of either aortic or mitral valve calcification ascertained by echocardiography as routine clinical evaluation. Exclusion criteria were age >75 years, therapy with phosphate binders or vitamin D, previously diagnosed cardiovascular disease (heart attack, angina, stroke, transient ischaemic attack, heart failure, atrial fibrillation, coronary angioplasty or artery bypass graft, valve replacement), past neoplasia, chronic inflammatory diseases and inability to sign written informed consent.

Local ethic boards approved the protocol. The study was performed in accordance with the Declaration of Helsinki guidelines regarding ethical principles for medical research involving human subjects. All participants gave informed consent in writing prior to inclusion in the study.

Patients underwent clinical examination and routine biochemistry measurements. Blood specimens were collected in the morning in overnight fasting state. Levels of 25-OH vitamin D, Klotho, FGF-23, calcium, phosphorus, i-PTH, CRP and 24-h urinary phosphate excretion were simultaneously measured at baseline. Glomerular filtration rate was assessed by chronic kidney disease epidemiology collaboration (EPI) formula (eGFR).

Extent of mitral and aortic valve calcification was evaluated and scored by 2D echocardiography using a 3.3-mHz multiphase array probe. Patients were kept lying in left decubitus position. Images were analysed at each nephrology centre by an experienced cardiologist. The extent of mitral valve calcification was measured with the Wilkins calcification score and graded from 0 to 4 [20]. Grade 1 and 2 calcification indicates single or scattered areas of increased echo brightness located at cusps margins, respectively; Grade 3 indicates brightness extending into the mid-portion of the cusps, while Grade 4 indicates extensive brightness throughout much of the leaflet tissue. Semi-quantitative method was used for assessing the extent of aortic valve calcification. The following empirical scoring was used: score 1 = partial calcification on single cusp; score 2 = partial calcification on two cusps; score 3 = extended calcification on two cusps and score 4 = extended calcification on all three cusps. Scores 1 + 2 and 3 + 4 were regarded as mild and moderate extent of aortic valve calcification, respectively.

Serum levels ranging from 8.9 to 10.0 mg/dL for calcium, 3.0 to 4.5 mg/dL for phosphorus and 30 to 75 pg/mL for i-PTH were regarded as normal. Levels of 25-OH vitamin D <10 ng/mL and ≥10 but <30 ng/mL indicated deficiency and insufficiency, respectively.

FGF-23 (COOH terminal) was assayed with ELISA Kit, Klotho with ELISA Kit (Biocompare Laboratories), vitamin D with Solid Phase Sandwich ELISA Kit (R&D Systems) and i-PTH with chemiluminescent immunometric method (RADIM). Assay of Klotho and FGF-23 was performed in 50 normal subjects to establish normal values for our laboratory; normal values for FGF-23 and Klotho were 3–10 ng/mL and 380–1050 pg/mL, respectively.

Normal distribution of variable was evaluated with Shapiro–Wilk tests. Univariate analysis was used to assess the association between valve calcification score and variables of interest. Variables significantly associated with the extent of cardiac valve calcification at univariate analysis were used in a multivariate linear regression model. Continuous data are reported as median and interquartile range. Frequency data are given as numbers and percentages.

Data were analysed with Statistical Package for the Social Sciences (SPSS) version 19 (Chicago, IL, USA); P value <0.05 was considered as significant.

Results

From the initial cohort of 125 patients, 100 met the inclusion criteria. One hundred patients had aortic and 96 mitral valve calcification.

Clinical characteristics and biochemistry of the whole population are shown in Table 1.

Population was represented by middle-aged patients with not far advanced stages of CKD.

The extent of aortic valve calcification was moderate in 68 patients; the remaining patients had mild calcification extent. The score of mitral valve calcification was 1, 2 and 3 in 61, 34 and 1 patients, respectively.

Biochemistry of patients according to score of aortic and mitral valve calcification is reported in Tables 2 and 3, respectively.

Inverse association was found between FGF-23 and PTH (r^2 = −0.252; P = 0.01) and 25-OH vitamin D (r^2 = −0.605; P = 0.01); a positive association was found between FGF-23 and serum phosphorus (r^2 = 0.248; P = 0.01), 24-h urinary phosphorus excretion (r^2 = 0.513; P = 0.01) and CRP (r^2 = 0.398; P = 0.01).

In univariate analysis, mitral valve calcification score was associated with serum calcium (r^2 = 0.565; P = 0.01); no association was found between mitral valve calcification score and eGFR (r^2 = −0.146), serum phosphorus (r^2 = −0.08), PTH (r^2 = 0.17), FGF-23 (r^2 = 0.052), Klotho (r^2 = 0.098), 25-OH vitamin D (r^2 = 0.020), 24-h urinary phosphorus excretion (r^2 = 0.099) and CRP (r^2 = 0.030). Aortic valve calcification score was positively associated with PTH (r^2 = 0.212; P = 0.03) and FGF-23 (r^2 = 0.272; P = 0.01), and negatively with Klotho (r^2 = −0.208; P = 0.03); no association was found between aortic valve calcification score and eGFR (r^2 = −0.029), serum phosphorus (r^2 = 0.094), serum calcium (r^2 = −0.057),

25-OH vitamin D ($r^2 = -0.122$), 24-h urinary phosphorus excretion ($r^2 = 0.108$) and CRP ($r^2 = 0.054$).

Results of multivariable analysis are shown in Table 4.

FGF-23 and PTH were significantly associated with aortic valve calcification score.

Discussion

The aim of the present study was to assess the potential association between the extent of cardiac valve calcification and some markers of mineral metabolism and inflammation such as serum phosphorus, calcium, i-PTH, FGF-23, Klotho, 25-OH vitamin D and CRP.

The assessment was done in a population of naïve CKD-ND patients that is commonly referred to nephrology units.

Interesting and clinically relevant findings were attained.

FGF-23 and PTH were significantly associated with the extent of aortic valve calcification. No association was found with eGFR, serum phosphorus, calcium, Klotho, 24-h phosphaturia, vitamin D and CRP.

An association between FGF-23 and aortic valve calcification has never been reported before in CKD-ND patients, to our knowledge.

FGF-23 has been recognized as being responsible for cardiovascular mortality in dialysis patients [21, 22]. In a CKD-ND population, levels of FGF-23 were associated with cardiovascular mortality in community-dwelling adult men, and the predictive power of FGR-23 was more evident in patients with mild reduction of renal function [18]. In patients with advanced CKD, FGF-23 but no other markers of mineral metabolism was strongly associated with all-cause mortality, cardiovascular events and initiation of dialysis [23]. In patients participating in a community study, those with eGFR<60 mL/min and higher FGF-23 tertile presented a nearly 6-fold increased risk for having high total body atherosclerosis measured in many vascular territories such as neck, aorta, kidney, upper leg and lower leg [24]. In patients on CKD Stages 3–4, elevated FGF-23 plasma levels predicted first occurrence of myocardial infarction, coronary artery angioplasty/stenting/bypass surgery and stroke [25]. However, in none of the above studies was assessment of cardiac valve calcification performed.

Although the association between FGF-23 and mortality is well ascertained in the CKD population, underlining mechanisms remain not well known yet. Indeed, several mechanisms have been proposed for FGF-23 other than those linked to mineral metabolism [26–29]. For instance, FGF-23 has been associated with increased inflammation, direct activation of renin angiotensin system (RAAS), reduced endothelial-dependent relaxation and inhibition of vitamin D synthesis. The latter action further potentiates the negative effects of FGF-23, because vitamin D regulates endothelial function, reduces inflammation processes and hampers the activity of RAAS [24–33].

Taken together, the proposed mechanisms indicate that FGF-23 acts as a strong promoter of the atherosclerotic process. In this regard, extent of cardiac valve calcification has been considered a marker of systemic atherosclerotic process [34].

In the present study, a different association was found between patients with aortic and mitral valve calcification. This finding has also been observed in patients on dialysis. Variables

Table 1. Clinical characteristics and biochemistry of whole cohort (N = 100)

Male gender	60
Age (years)	51 (46–56)
Aortic valve calcification (%)	100
Mild aortic valve calcification (%)	32
Moderate aortic valve calcification (%)	68
Mitral valve calcification (%)	96
Wilkins score = 0 (N)	4
Wilkins score = 1 (N)	61
Wilkins score = 2 (N)	34
Wilkins score = 3 (N)	1
Hypertension (%)	88
Diabetes (%)	10
eGFR (ml/min)	28.8 (27.8–30.0)
Stage 3 CKD (%)	33
Stage 4 CKD (%)	67
Serum phosphorus (mg/dL)	4.3 (4.2–4.4)
Serum phosphorus within normal range (%)	81
Low serum phosphorus (%)	19
Serum calcium (mg/dL)	9.2 (8.9–9.4)
Serum calcium within normal range (%)	100
i-PTH (pg/mL)	59 (54.0–65.9)
Low PTH (%)	1
High PTH (%)	4
Serum vitamin D (ng/mL)	32.0 (23.0–48.0)
Vitamin D insufficiency (%)	47
Vitamin D deficiency (%)	1
Klotho (pg/mL)	895.0 (811.0–985.0)
FGF-23 (ng/mL)	10.3 (9.1–11.0)
Phosphaturia (mg/24H)	980 (870–1250)
CRP (mg/L)	8.0 (7.0–10.7)
Calcium channel blockers (%)	31
Calcium channel blockers plus beta blockers (%)	7
Doxazosin (%)	5
Calcium channel blockers plus doxazosin (%)	43

Numbers are median and (interquartile range).
i-PTH, intact parathyroid hormone; FGF-23, fibroblast growth factor 23.

Table 2. Biochemistry of patients with aortic valve calcification

	Score 0	Score 1	Score 2	Score 3	Score 4
Number	0	32	58	9	1
eGFR (ml/min)		29.0 (28.1–30.0)	28.5 (270–29.8)	29.5 (28.4–30.3)	30.5
Klotho (pg/ml)		876 (788–894)	975 (890–990)	640 (627–773)	576
FGF-23 (ng/ml)		10.8 (10.3–11.1)	9.5 (8.9–10.4)	13.1 (12.4–14.9)	17.5
Phosphaturia (mg/24 h)		1000 (946–133)	965 (790–1117)	1250 (840–1450)	1600
Serum calcium (mg/dl)		9.0 (8.8–9.4)	9.2 (8.9–9.4)	9.3 (8.5–9.5)	8.5
Serum phosphorus (mg/dl)		4.3 (4.2–4.5)	4.2 (4.2–4.2)	4.7 (4.3–4.75)	4.6
i-PTH (pg/dl)		55.1 (47.4–59.0)	61.7 (55.4–66.1)	60.0 (49.0–65.0)	59.0
CRP (mg/L)		9.0 (7.0–10.7)	8.0 (6.0–10.0)	13.0 (10.5–14.5)	11.0
Vitamin D (ng/ml)		31.5 (24.0–44.0)	41.5 (24.7–49.0)	17.0 (11.0–25.0)	22.0

Table 3. Biochemistry of patients with mitral valve calcification

	Score 0	Score 1	Score 2	Score 3
Number	4	61	34	1
eGFR (ml/min)	28.9 (26.7–30.2)	29.0 (28.0–30.1)	28.4 (27.0–29.4)	29.2
Klotho (pg/ml)	786 (628–958)	890 (870–977)	927 (834–989)	1015
FGF-23 (ng/ml)	10.6 (8.9–15.9)	10.4 (9.2–11.0)	10.2 (9.2–11.0)	7.9
Phosphaturia (mg/24 h)	920 (715–1462)	970 (870–1100)	995 (890–1315)	870
Serum calcium (mg/dl)	8.5 (8.5–8.8)	9.1 (8.8–9.3)	9.4 (9.2–10.1)	10.1
Serum phosphorus (mg/dl)	4.4 (4.3–4.7)	4.3 (4.2–4.4)	4.3 (4.2–4.4)	4.2
i-PTH (pg/ml)	57.0 (54.8–58.7)	58.4 (51.5–64.3)	61.9 (54.8–67.4)	66
CRP (mg/L)	8.5 (5.0–10.5)	8.0 (7.0–10.0)	8.0 (5.7–11.2)	8.0
Vitamin D (ng/ml)	36.5 (22.5–52.0)	32.0 (23.0–45.0)	39.0 (22.0–48.0)	48

Table 4. Multivariable linear regression analysis with aortic valve calcification score as dependent variable

Variable	Unstandardized coefficients beta	Standard error	t	P	Lower interval for beta	Upper interval for beta
FGR-23	0.116	0.034	3.389	0.001	0.048	0.183
PTH	0.020	0.007	2.867	0.005	0.006	0.034

significantly associated with aortic valve calcification were different from those predicting mitral valve calcification and vice versa [35, 36]; cinacalcet therapy attenuated only aortic valve but not mitral valve calcification progression [17]. It is unknown whether the contrasting correlation between mitral or aortic valve calcification and markers of mineral metabolism may depend on different pathogenetic mechanisms.

Another interesting finding of the present study is that no association was found between extent of cardiac valve calcification and serum phosphorus, which is the foremost studied marker of mineral metabolism and the main pathogenetic factor of vascular calcification in CKD. The lack of association appears in contrast with other data. In CKD-ND patients of the Multi-Ethnic Study of Atherosclerosis (MESA), serum phosphorus levels within the normal ranges were significantly associated with cardiac valve calcification. For each 1 mg/dL increase in serum phosphate, the prevalence of aortic valve and mitral valve calcification increased by 25 and 62%, respectively; mitral valve but not aortic valve calcification was dependent on the levels of phosphorus; PTH and vitamin D had no predictive role of cardiac valve calcification; but FGF-23 was not assayed [37]. The role of phosphorus on cardiac valve calcification has been confirmed in a recent study; aortic valve calcification extent was reduced after 12-month treatment with phosphate binder in Stage 3–4 CKD patients; however, in that study, levels of PTH, calcium, phosphorus and FGF-23 were not evaluated as predictors of the extent of cardiac valve calcification [38].

Limitations

This study is an observational one, and its design only allows the assessment of association. Clinical and biochemical data as well as echocardiography evaluation were recorded at one study time. Finally, it would have been interesting to have a control group of patients with normal renal function. Nonetheless, the study has some strengths. The study population was represented by naïve CKD patients who are most frequently admitted to nephrology units. Clinically relevant markers of mineral metabolism and inflammation were simultaneously evaluated as potential predictors of the extent of cardiac valve calcification.

Conclusions

In naïve patients with not far advanced stages of CKD, no association has been found between extent of mitral valve calcification and serum levels of i-PTH, phosphorus, calcium, Klotho, vitamin D and CRP. Extent of aortic valve calcification is associated to the levels of FGF-23 and i-PTH. The latter result may suggest that FGF-23 and PTH play a direct action on the process leading to aortic valve calcification.

Further larger studies should examine whether FGF-23 assay should be included in routine clinical evaluation of CKD-ND patients as part of cardiovascular risk stratification.

Conflict of interest statement

The results presented in this paper have not been published previously in whole or part. The authors have no conflict of interest to declare.

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