Original Article

Gender Specific Association between Serum Fibroblast Growth Factor 23/ α -Klotho and Coronary Artery and Aortic Valve Calcification

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Aim: Fibroblast growth factor 23 (FGF23) and α -Klotho have been recently identified to play a crucial role in calcium/phosphate metabolism. We herein investigated the possible relation between serum FGF23/ α -Klotho levels and coronary artery calcification (CAC) and aortic valve calcification (AVC).

Methods: Among subjects with diagnosed or suspected coronary artery disease (CAD), CAC and AVC were estimated via the Agatston score of 320-detector computed tomography images, and serum FGF23 and α -Klotho levels were measured.

Results: In total, 157 subjects were enrolled (75 women and 82 men). We performed logistic regression using CAC as a dependent variable; the highest FGF23 tertile (>52.5 pg/mL) was significantly positively associated with CAC with an odds ratio of 6.61 versus the lowest FGF23 tertile (<35.3 pg/mL) in women after the adjustment for potential confounding variables including age, renal function, hypertension, statin use, diuretic use, and calcium/phosphate metabolism related factors. In addition, the highest α -Klotho tertile (>561 pg/mL) was significantly associated with AVC with an odds ratio of 6.31 versus the lowest α -Klotho tertile (<306 pg/mL) in men after adjusting for the same variables. On the other hand, the association between FGF23 and CAC/AVC in men or that between α -Klotho and CAC/AVC in women was nonsignificant.

Conclusion: Among subjects with diagnosed or suspected CAD, serum FGF23 was positively associated with CAC in women and serum α -Klotho was positively associated with AVC in men independent of the confounding variables, including the renal function and calcium/phosphate metabolism-related factors.

J Atheroscler Thromb, 2015; 22: 1338-1346.

Key words: Coronary artery, Aortic valve, Calcification, FGF23, α -Klotho

Introduction

Fibroblast growth factor 23 (FGF23), a recently identified bone-derived hormone, regulates the 1,25-dihydroxyvitamin D ($1,25(\text{OH})_2\text{D}$) levels and exerts phosphaturic effects in the presence of α -Klotho, and

therefore, plays a crucial role in the regulation of systemic phosphate homeostasis¹⁻³. FGF23 levels are found to be increased in the early stages of chronic kidney disease (CKD)^{4, 5}. The finding that FGF23 levels are associated with cardiac hypertrophy and dysfunction^{6, 7} suggests that FGF23 represents an independent risk factor for global or cardiac morbidity/mortality^{8, 9}.

It has been reported that coronary artery calcification (CAC) can be used as a surrogate marker of the total burden of coronary atherosclerosis and that the presence of CAC is associated with peripheral isch-

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Received: March 30, 2015

Accepted for publication: July 12, 2015

emia¹⁰) and with coronary artery disease-related events even in the asymptomatic subjects^{11, 12}). In addition, aortic valve calcification (AVC) was reported to predict coronary event risk and all-cause mortality independent of traditional risk factors^{13, 14}). Several previous histological studies support the role of FGF23 in vascular calcification¹⁵); serum FGF-23 concentrations were significantly associated with the degree of atherosclerosis calcification¹⁶), and calcium deposition was correlated with FGF23 immunoreactivity in the coronary artery of the explanted heart¹⁷). Using multidetector computed tomography (MDCT), the potential association between FGF23 and CAC and/or AVC has also been clinically examined¹⁸⁻²⁰), albeit with inconsistent results. However, the possibility remains that hyperphosphatemia rather than the FGF-23 level is the major factor driving vascular calcification²¹), which may also be indicated by the finding that FGF23 was not associated with arterial calcification and does not promote calcification²²).

To evaluate the clinical utility of serum FGF23/ α -Klotho for the detection or management of CAC/AVC, various confounders, including calcium, phosphate, parathyroid hormone (PTH), and 1,25(OH)₂D, should be considered, as observed in several recent studies^{20, 23}). To this end, in the current study, we investigated whether FGF23/ α -Klotho levels are independently related with CAC/AVC calculated from image data obtained by 320-row MDCT.

Methods

Study Population

In the current study, patients who underwent electrocardiogram (ECG)-triggered MDCT under the diagnosis/suspicion of coronary artery disease who gave written informed consent between August 2012 and December 2012 were enrolled. The current study was approved by the Ethics Committee of the Osaka Medical College.

Clinical Data and Laboratory Analysis

After excluding one patient who was undergoing chronic hemodialysis, 157 patients were enrolled in the study. Diagnosis of hypertension was derived from the clinical records, because some patients administered beta blockers and/or renin-angiotensin-aldosterone system blockers for the treatment of heart failure. Blood samples were collected in the morning after an overnight fast. Aliquots of serum was obtained and stored at -80 degrees immediately until use. When serum albumin was ≤ 4 mg/dL, the serum calcium levels were corrected by using the formula: calcium + (4 -

“serum albumin”), and designated as corrected calcium (cCa). The measurement of FGF23 and α -Klotho was performed using enzyme immunoassay kits as described elsewhere^{7, 24}). The eGFR was calculated by the following Modification of Diet in Renal Disease equation modified for Japanese subjects: $eGFR = 194 \times (\text{serum creatinine})^{-1.094} \times (\text{age})^{-0.287}$ ²⁵). The serum levels of intact PTH (iPTH), 25-hydroxyvitamin D (25(OH)D), and 1,25(OH)₂D were measured by the immunochemical detection method using electrochemiluminescence, competitive protein binding assay, and radioimmunoassay, respectively (LSI Medience, Tokyo, Japan).

Assessment of Calcification of the Coronary Artery and Aortic Valve

CT images were acquired by ECG-triggered CT scanning using a 320-row CT scanner (Aquilion® ONE, Toshiba Medical Systems, Tochigi, Japan). The extent of calcification of the coronary arteries and aortic valve, which was measured at the aortic valve leaflets and below the origins of the coronary arteries including the attachment points of the leaflets, was quantified via the Agatston method^{26, 27}). Calcification with a density of >130 Housefield units was measured using an Aquarius workstation (Tera Reconn, Inc, San Mateo, CA). CAC was defined when Agatston coronary artery calcium score (AgatCACs) was >10 , and AVC was defined when Agatston aortic valve calcium score (AgatAVCs) was >0 .

Statistical Analysis

Baseline characteristics were assessed with standard descriptive statistics. Data were expressed as either mean $\pm$ standard deviation, or median and interquartile range (IQR). For the correlation analysis, Pearson's correlation test was used unless stated otherwise. Linear regression analysis and logistic regression analysis was used for the assessment of the association with various parameters with coronary/aortic valve calcium. Data analysis was performed by using IBM SPSS statistics version 22.0 (IBM, Chicago, IL).

Results

Patient Characteristics

Among the 157 subjects enrolled, 75 were women and 82 were men. The clinical characteristics and laboratory data of the enrolled subjects according to gender are described in **Table 1**. CAC was more frequently found in men (56 patients, 68.3%) than in women (38 patients, 50.7%, $p=0.034$ by χ^2 test). On the other hand, the prevalence of AVC did not signifi-

Table 1. Baseline characteristics and laboratory data

Variables	Women (n=75)	Men (n=82)	P value
Age, years	68.5 ± 11.5	67.0 ± 11.6	0.399
Body mass index, kg/m ²	22.7 ± 3.4	24.0 ± 3.4	0.012
Systolic blood pressure, mmHg	133 ± 17	134 ± 19	0.907
Diastolic blood pressure, mmHg	76 ± 10	79 ± 13	0.090
Smoking history	5 (6.7)	41 (50.0)	<0.001
Hypertension	50 (66.7)	57 (69.5)	0.702
Current medication			
ACE inhibitors/ARB, n (%)	26 (34.7)	41 (50.0)	0.052
Beta blockers, n (%)	5 (6.7)	14 (17.1)	0.046
Calcium channel blockers, n (%)	34 (45.3)	33 (40.2)	0.520
Insulin, n (%)	6 (8.0)	2 (2.4)	0.113
Sulfonyl urea, n (%)	2 (2.7)	10 (12.2)	0.025
DPP-4 inhibitors, n (%)	5 (6.7)	9 (11.0)	0.344
Statin, n (%)	27 (36.0)	16 (19.5)	0.021
Fibrate, n (%)	1 (1.3)	5 (6.1)	0.120
Loop diuretics, n (%)	9 (12.0)	5 (4.9)	0.106
Thiazide diuretics, n (%)	3 (4.0)	6 (7.3)	0.372
Laboratory data			
White blood cell count, ×10 ³ /μL	5.3 (4.4–6.8)	5.7 (4.9–7.1)	0.118
Hemoglobin, g/dL	13.3 (12.4–13.7)	14.5 (13.4–15.3)	<0.001
Platelet count, ×10 ³ /μL	227 (172–270)	222 (189–253)	0.965
Total cholesterol, mg/dL	195 (175–225)	188 (174–211)	0.133
HDL cholesterol, mg/dL	65 (50–81)	57 (43–68)	0.043
Triglycerides, mg/dL	99 (73–147)	123 (92–173)	0.004
eGFR, mL/min/1.73 m ²	67.7 (54.6–83.1)	68.6 (57.5–77.7)	0.668
Corrected calcium, mg/dL	9.4 (9.2–9.6)	9.3 (9–9.5)	0.080
Inorganic phosphate, mg/dL	3.8 (3.4–4.1)	3.4 (3.1–3.8)	0.001
Intact parathyroid hormone, pg/mL	32.0 (17.0–49.0)	24.5 (14.8–37.3)	0.108
25(OH) Vitamin D, pg/mL	21.6 (17.3–26.4)	25.7 (22.0–30.6)	<0.001
1,25(OH) ₂ Vitamin D, pg/mL	1.8 (1.7–1.9)	1.8 (1.7–1.9)	0.410
FGF23, pg/mL	40.7 (31.0–56.4)	45.1 (33.7–54.1)	0.758
α-Klotho, pg/mL	427 (299–679)	384 (251–640)	0.228
Computer tomographic data			
Agatston coronary artery calcium score	11 (0–218)	52 (0–364)	0.107
Agatston aortic valve calcium score	0 (0–65)	0 (0–72)	0.758

DPP-4, dipeptidyl Peptidase-4.

cantly differ between women (35 patients, 46.7%) and men (32 patients, 39.0%, $p=0.419$). The correlation coefficient between $\log(\text{Agat}_{\text{CACS}} + 1)$ and $\log(\text{Agat}_{\text{AVCS}} + 1)$ was 0.42 ($p<0.001$) in men, and 0.59 ($p<0.001$) in women. Neither FGF23 nor α -Klotho differed significantly by gender. FGF23 level was higher in subjects who were using diuretics (loop or thiazide) (median 62.2, IQR 43.6–75.1 pg/mL) than in those who were not using diuretics (median 40.5, IQR 31.5–53.5 pg/mL, $p=0.001$). On the other hand, the α -Klotho level did not differ significantly according to

the use or non-use of diuretics ($p=0.114$).

Among calcium/phosphate metabolism-related factors, FGF23 was significantly negatively correlated with 1,25(OH)₂D in both genders (**Table 2**). FGF23 was positively correlated with calcium in men, but not in women. α -Klotho was negatively correlated with intact PTH and positively correlated with calcium and 1,25(OH)₂D in women but not in men.

Table 2. Correlation with FGF23/ α -Klotho

	FGF23	α -Klotho
	R	R
Overall		
Age	0.09	-0.14
Systolic blood pressure	0.13	-0.08
Diastolic blood pressure	-0.04	0.00
Corrected calcium	0.09	0.19*
Inorganic phosphate	0.08	0.13
Intact parathyroid hormone	0.05	-0.26 [†]
25(OH) Vitamin D	-0.12	0.11
1,25(OH) ₂ Vitamin D	-0.32 [†]	0.22 [†]
Women		
Age	0.06	-0.19
Systolic blood pressure	-0.03	0.00
Diastolic blood pressure	-0.13	-0.01
Corrected calcium	-0.09	0.34 [†]
Inorganic phosphate	0.00	0.10
Intact parathyroid hormone	-0.05	-0.32 [†]
25(OH) Vitamin D	-0.29*	0.07
1,25(OH) ₂ Vitamin D	-0.26*	0.33 [†]
Men		
Age	0.11	-0.13
Systolic blood pressure	0.24*	-0.17
Diastolic blood pressure	0.04	0.02
Corrected calcium	0.26*	0.04
Inorganic phosphate	0.15	0.09
Intact parathyroid hormone	0.17	-0.21
25(OH) Vitamin D	-0.01	0.18
1,25(OH) ₂ Vitamin D	-0.39 [†]	0.11

*indicates $p < 0.05$, and [†] indicates $p < 0.01$. Spearman's correlation test was used.

Relationship between FGF23/ α -Klotho and Prevalence of CAC and AVC

Log(FGF23) was significantly correlated with log(Agat_{CACS} + 1) ($R = 0.244$, $p = 0.035$) and log(Agat_{AVCS} + 1) ($R = 0.270$, $p = 0.019$) in women, but these associations were not significant in men. When the data were assessed in the tertiles of FGF23 separately for each gender, the prevalence of CAC increased significantly ($p = 0.038$ by χ^2 test) in women (**Fig. 1**). Although the prevalence of AVC also increased with increasing FGF23, the relationship did not reach statistical significance ($p = 0.336$). On the other hand, when the data were assessed in the tertiles of α -Klotho in a gender-separate manner each, the prevalence of CAC tended to decrease ($p = 0.067$) in men but no apparent association was observed in women (**Fig. 2**). Log(α -Klotho) was not significantly correlated with log(Agat_{CACS} + 1) ($R = -0.058$, $p = 0.621$) or log(Agat_{AVCS} +

1) ($R = 0.030$, $p = 0.797$) in women. Correlation between log(α -Klotho) and log(Agat_{CACS} + 1) ($R = -0.097$, $p = 0.384$) or that between log(α -Klotho) and log(Agat_{AVCS} + 1) ($R = 0.076$, $p = 0.496$) was not significant also in men.

Logistic Regression Analysis for the Association between FGF23 and CAC/AVC

In women, in model 1 [adjusted for age and chronic kidney disease (CKD) stage], log(FGF23) was found to be associated significantly with CAC (**Table 3**). In a model with further adjustment for hypertension, and statin and diuretic medication (model 2), and further adjustment for calcium/phosphate metabolism-related factors including cCa, log(iP), log(iPTH), 25(OH)D, and log(1,25(OH)₂D) (model 3), essentially the same statistical significance was observed. In men, on the other hand, neither log(FGF23) nor

Fig. 1. Prevalence of coronary artery calcification (CAC) and aortic valve calcification (AVC) according to FGF23 tertile and gender. A. Prevalence of CAC according to FGF23 tertile. B. Prevalence of AVC according to FGF23 tertile.

Fig. 2. Prevalence of coronary artery calcification (CAC) and aortic valve calcification (AVC) according to α -Klotho tertile and gender. A. Prevalence of CAC according to α -Klotho tertile. B. Prevalence of AVC according to α -Klotho tertile.

higher FGF23 tertiles was associated with CAC or AVC in any statistical model. When “smoking history” was added as an additional covariate in model 2 in **Table 3**, the odds ratio of the highest FGF23 tertile for CAC became 5.31 (95% CI, 1.05–26.9) in women and 0.43 (95% CI, 0.08–2.22) in men.

Logistic Regression Analysis for the Association between α -Klotho and CAC/AVC

In men, in model 1, the highest α -Klotho tertile was borderline significantly *negatively* associated with CAC; however, the association did not retain significance ($p > 0.1$) in models 2 and 3. On the other hand, the highest α -Klotho tertile was *positively* associated with AVC with an odds ratio of 6.31 (model 3) as compared with the lowest α -Klotho tertile. In women, the highest α -Klotho tertile was not associated with either CAC or AVC in any statistical model. When

“smoking history” was added as an additional covariate in model 2 in **Table 4**, the odds ratio of the highest α -Klotho tertile for AVC became 2.56 (95% CI, 0.45–14.75) in women and 5.47 (95% CI, 1.11–26.9) in men. Therefore, the addition of smoking history to the independent variables did not greatly change the relationship between FGF23/ α -Klotho and CAC/AVC in both genders.

Discussion

In the current study, we examined the relationship between FGF23 and α -Klotho calcium in the coronary artery and aortic valve as measured using ECG-gated 320-detector CT images. There seemed to exist a gender-difference in the association among these variables; FGF23 levels were significantly positively associated with both CAC and AVC in only

Table 3. Logistic regression analysis for the association between FGF23 value and coronary artery/aortic valve calcium

Dependent Variables			FGF23 tertiles					
			t1 (13.2–35.2 pg/mL)		t2 (35.4–52.5 pg/mL)		t3 (52.5–180.3 pg/mL)	
			OR		OR		OR	
CAC	Overall	model 1	1	(referent)	0.79	(0.31–1.97)	1.98	(0.73–5.38)
		model 2	1	(referent)	0.86	(0.32–2.32)	1.60	(0.55–4.70)
		model 3	1	(referent)	0.99	(0.34–2.88)	2.39	(0.73–7.88)
	Women	model 1	1	(referent)	1.19	(0.32–4.46)	5.10*	(1.19–21.8)
		model 2	1	(referent)	1.72	(0.38–7.70)	5.31*	(1.05–26.9)
		model 3	1	(referent)	1.17	(0.21–6.45)	6.61*	(1.09–39.9)
	Men	model 1	1	(referent)	0.51	(0.13–1.99)	0.74	(0.17–3.30)
		model 2	1	(referent)	0.42	(0.09–1.89)	0.43	(0.08–2.22)
		model 3	1	(referent)	0.57	(0.09–3.67)	0.45	(0.05–3.70)
AVC	Overall	model 1	1	(referent)	1.48	(0.59–3.70)	1.60	(0.61–4.19)
		model 2	1	(referent)	1.96	(0.72–5.31)	1.68	(0.58–4.82)
		model 3	1	(referent)	1.78	(0.63–5.02)	1.73	(0.57–5.20)
	Women	model 1	1	(referent)	2.26	(0.57–8.89)	2.31	(0.57–9.28)
		model 2	1	(referent)	4.14	(0.85–20.1)	3.29	(0.67–16.2)
		model 3	1	(referent)	3.42	(0.59–20.0)	3.35	(0.58–19.2)
	Men	model 1	1	(referent)	0.97	(0.27–3.44)	1.31	(0.32–5.32)
		model 2	1	(referent)	1.19	(0.30–4.64)	1.08	(0.24–4.93)
		model 3	1	(referent)	0.87	(0.20–3.86)	0.95	(0.18–4.90)

Model 1, adjusted for age and CKD stage; model 2, adjusted for variables in model 1 plus hypertension, statin, diuretic medication; model 3, adjusted for variables used in model 2 plus cCa, log(iP), log(iPTH), 25(OH)D, and log(1,25(OH)₂D). * indicates $p < 0.05$ and OR indicates odds ratio. t1, t2, and t3 indicate the lowest, middle, and highest tertile, respectively.

women, whereas the association of α -Klotho with CAC and AVC was significant in only men.

The mechanism underlying the observed gender difference in the association between FGF23/ α -Klotho and CAC/AVC remains unclear. CAC was significantly more prevalent in men; therefore, it is possible that gender difference in the relationship between FGF23/ α -Klotho and CAC/AVC was in part attributed to the gender difference in the prevalence of atherosclerosis. Smoking history was more prevalent in men; however, the addition of smoking history to independent variables did not greatly change the results. Nevertheless, considering that majority (93%) of the female subjects enrolled in the current study did not have smoking history, we may have to perform the investigation targeting only male and female never smokers in future studies. We previously reported that FGF23 and α -Klotho had, respectively, positive and negative association with E/e' ratio, an echocardiographic parameter of cardiac diastolic function, among patients with preserved left ventricular ejection fraction⁵. Osawa *et al.* recently reported that higher coro-

nary artery calcification was associated with diastolic dysfunction among elderly patients without a history of CAD²⁸, which suggests the possibility that FGF23/ α -Klotho activity resides in the close link between diastolic dysfunction and coronary artery calcification. Although diastolic function was not assessed in the current study, diastolic dysfunction is reported to be more common in female subjects²⁹. Whether the prevalence of diastolic dysfunction between women and men affected the relationship between FGF23/ α -Klotho and arterial/valvular calcification awaits further investigation.

Pronounced arterial wall calcification has been reported in a mouse model of defective klotho gene expression³⁰. Similarly, ectopic calcification in the kidney cardiovascular system can be observed in FGF23 deficient mice³¹. These findings suggest a possible relation between FGF23/ α -Klotho and ectopic (including arteries) calcification. Kitagawa *et al.* demonstrated that serum α -Klotho was lower in CKD patients with aortic calcification than in those without³². Furthermore, Kiu Weber *et al.* reported that higher FGF23

Table 4. Logistic regression analysis for the association between α -Klotho value and coronary artery/aortic valve calcium

Dependent Variables			α -Klotho tertiles					
			t1 (33–305 pg/mL)		t2 (306–560 pg/mL)		t3 (561–4859 pg/mL)	
			OR	95% CI	OR	95% CI	OR	95% CI
CAC	Overall	model 1	1	(referent)	1.00	(0.39–2.57)	0.67	(0.26–1.77)
		model 2	1	(referent)	1.28	(0.45–3.60)	0.71	(0.25–2.02)
		model 3	1	(referent)	1.00	(0.31–3.15)	0.50	(0.16–1.60)
	Women	model 1	1	(referent)	1.76	(0.46–6.76)	1.83	(0.44–7.70)
		model 2	1	(referent)	2.71	(0.55–13.3)	1.96	(0.35–10.8)
		model 3	1	(referent)	2.69	(0.47–15.5)	1.61	(0.22–11.5)
	Men	model 1	1	(referent)	0.55	(0.13–2.34)	0.27	(0.07–1.08)
		model 2	1	(referent)	0.95	(0.17–5.28)	0.36	(0.08–1.62)
		model 3	1	(referent)	0.50	(0.05–5.02)	0.27	(0.04–1.69)
AVC	Overall	model 1	1	(referent)	1.91	(0.74–4.88)	2.57	(0.96–6.91)
		model 2	1	(referent)	2.12	(0.76–5.93)	2.83	(0.99–8.14)
		model 3	1	(referent)	2.49	(0.83–7.46)	2.94	(0.98–8.85)
	Women	model 1	1	(referent)	1.90	(0.48–7.59)	2.41	(0.53–11.0)
		model 2	1	(referent)	2.21	(0.46–10.6)	2.31	(0.42–12.7)
		model 3	1	(referent)	1.43	(0.21–9.81)	1.06	(0.12–9.16)
	Men	model 1	1	(referent)	1.87	(0.48–7.27)	3.09	(0.81–11.8)
		model 2	1	(referent)	2.09	(0.36–12.0)	5.46*	(1.11–26.9)
		model 3	1	(referent)	3.22	(0.46–22.7)	6.31*	(1.05–38.0)

Model 1, adjusted for age and CKD stage; model 2, adjusted for variables in model 1 plus hypertension, statin, diuretic medication; model 3, adjusted for variables used in model 2 plus cCa, log(iP), log(iPTH), 25(OH)D, and log(1,25(OH)₂D). * indicates $p < 0.05$ and OR indicates odds ratio. t1, t2, and t3 indicate the lowest, middle, and highest tertile, respectively

was associated with greater coronary artery calcium volume among patients with CKD stages 3 and 4³³. However, in several studies, including that of Kiu Weber *et al.*, whether the observed association was independent of calcium/phosphate metabolism-related parameters was not assessed^{22, 33, 34}. Such adjustment should be performed to assess the statistical independence of the association, particularly because in the mice model of the genetic deletion of FGF23 and α -Klotho, further deletion of vitamin D 1 α -hydroxylase, leading to a decrease in serum 1,25(OH)₂D, suppressed the ectopic arterial calcification observed^{31, 35}. In addition, in the study by Kitagawa *et al.*, the relation between α -Klotho and aortic calcification lost statistical significance after other covariates, including calcium/phosphate metabolism-related parameters (calcium, phosphate, intact PTH, and 1,25(OH)₂D), were considered³².

The possible association between FGF23 and CAC has been examined also in a few previous studies^{23, 36}; for example, Masai *et al.* found a significant association between FGF23 and coronary calcifica-

tion²³. In contrast, Buiten found that the association between FGF23 or α -Klotho and coronary calcification was insignificant³⁶; however, they did not assess the relationship in each gender separately. Whether FGF23/ α -Klotho might be a therapeutic target for modulating vascular calcification ultimately awaits studies investigating the alteration of FGF23/ α -Klotho can reduce the extent of arteriosclerosis.

The extent of coronary calcium [$\log(\text{Agat}_{\text{CACs}} + 1)$] and that of aortic valve calcium [$\log(\text{Agat}_{\text{AVCS}} + 1)$] were significantly correlated in both women in men. On the other hand, in men, the highest α -Klotho tertile was borderline significantly *negatively* associated with CAC (model 1), and on the other hand, the highest α -Klotho tertile was *positively* associated with AVC (models 2 and 3). This suggested that the risk factors for CAC and AVC are different, although coronary artery calcium and aortic valve calcium are, in general, positively correlated²⁷. This notion might be supported by the findings in previous reports that lipoprotein(a) levels were associated with aortic valve calcification but not with coronary calcification³⁷,

and that female subjects who had high bone mineral density had higher coronary artery calcium score but not aortic valve calcium score³⁸⁾. We cannot conclude whether α -Klotho has really opposite effects, if at all, on the coronary artery and aortic valve calcification because the association between the highest α -Klotho tertile and CAC did not reach statistical significance. This point should be re-evaluated in future studies.

The fact that we considered calcium/phosphate-related parameters in the statistical analysis is a strength of the current study. On the other hand, the study has a few limitations. First, the study sample was relatively small. Second, it has been reported that FGF23 level may be higher among subjects with incident myocardial infarction³⁹⁾ and patients with significant CAD present lower soluble concentrations of Klotho⁴⁰⁾. The current study population underwent chest MDCT under the clinical diagnosis or suspicion of coronary artery disease; therefore, our findings may not be applicable to the general population.

In summary, by analyzing data from ECG-gated 320-detector CT images, we investigated the relationship between FGF23/ α -Klotho and calcification of the coronary artery and aortic valve. It was found that FGF23 was significantly positively associated with CAC in women, but not in men. In contrast, α -Klotho was associated with AVC in men but not in women. The possible mechanism underlying the observed gender difference awaits further investigation.

Acknowledgements

We are highly appreciative of Chieko Ohta, Yumiko Ohgami, and Megumi Hashimoto for their excellent technical assistance.

Disclosure Statement

No potential conflicts of interest were disclosed.

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