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CORRESPONDENCE

Serum inorganic phosphate level is associated with fibroblast growth factor 23 among cardiac patients with preserved renal function

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We have read, with great interest, the paper recently published by Imazu *et al.*,[1] in which the authors showed that serum levels of fibroblast growth factor 23 (FGF23) were predominantly correlated with the clinical outcomes of heart failure patients, and that serum FGF23 levels may provide different clinical information than plasma B-type natriuretic peptide (BNP) levels.

Recent studies have shown that, exerting a phosphaturic effect via FGFR-1c in the presence of α-Klotho,[2] FGF23 may promote cardiac hypertrophy via a different FGF receptor, FGFR4.[3] Serum FGF23 levels are higher in subjects with renal dysfunction, in whom circulating phosphate levels are increased due to decreased urinary phosphate excretion. In the above-mentioned study by Imazu *et al.*,[1] FGF23 was significantly correlated with eGFR. Thus, FGF23 may mediate the observed increase in cardiovascular events among subjects with renal dysfunction. Of note, Isakova *et al.*[4] showed that, among subjects with relatively preserved renal function ($eGFR \geqslant 50\ ml\ min^{-1}$ per $1.73\ m^2$), serum FGF23 levels start to increase among subjects with early phase chronic kidney disease (CKD) before their serum phosphate starts to increase.

We have recently shown that serum FGF23 levels are associated with left ventricular hypertrophy among cardiac patients with $eGFR \geqslant 60\ ml\ min^{-1}$ per $1.73\ m^2$ as well as among those with $eGFR < 60\ ml\ min^{-1}$ per $1.73\ m^2$.[5] Serum FGF23 levels were shown to serve as a biomarker for heart failure in the study by Imazu *et al.*,[1] although more than one-fourth of the enrolled patients had CKD (i.e., $eGFR < 60\ ml\ min^{-1}$ per $1.73\ m^2$) in their study; therefore, it seems to be important to question what condition would be responsible, if present at all, for the elevation of FGF23 levels among non-CKD patients. To this end, we set out to examine what parameters are associated with serum FGF23 levels among patients with preserved renal function. We analyzed total of 298 cardiac patients with $eGFR \geqslant 60\ ml\ min^{-1}$ per $1.73\ m^2$ who were admitted to the cardiology department between January 2012 and July 2016. In the current study, considering that cystatin C may better approximate GFR than creatinine, especially among patients with preserved renal function and elderly,[6] we calculated the cystatin C-based eGFR ($eGFR_{Cys}$) in addition to the creatinine-based eGFR ($eGFR_{Cr}$) using the equations proposed by the Japanese Society of Nephrology that have been described elsewhere.[7] The study was approved by the Ethics Committee of Osaka Medical College, and all participants gave written informed consent.

The mean age of the study population was 64.9 ± 13.2 years and included 208 (70.0%) male patients. The mean body mass index in the study population was $23.4 \pm 3.5\ kg\ m^{-2}$, and worsening heart failure was the main reason for admission in 10 patients (3.4%). Serum levels of intact FGF23 were measured using a two-step FGF23 enzyme-linked immunosorbent assay kit (Kainos Laboratories, Tokyo, Japan). All patients had an $eGFR_{Cr}$ of $\geqslant 60\ ml\ min^{-1}$ per $1.73\ m^2$; however, 15 patients (4 female and 11 male) were found to have $eGFR_{Cys}$ of $< 60\ ml\ min^{-1}$ per $1.73\ m^2$. By Spearman's correlation test, serum FGF23 was significantly correlated with $eGFR_{Cys}$ ($R = -0.18$, $P = 0.002$), inorganic phosphate (iP) ($R = -0.18$, $P = 0.001$) (Figure 1), and BNP ($R = 0.15$, $P = 0.012$, $n = 289$), but not with age, $eGFR_{Cr}$ ($R = -0.07$, $P = 0.258$), corrected calcium ($n = 297$), C-reactive protein, or intact parathyroid hormone ($n = 205$). Multivariate logistic regression analysis showed that both $eGFR_{Cys}$ and iP are significantly associated with the highest FGF23 tertile ($> 56\ pg\ ml^{-1}$) after adjustment for age and sex (model 1, Table 1). After further adjustment for diuretic use (model 2), iP remained associated with the highest FGF23 tertile among the overall study population or subgroup who had $eGFR_{Cys}$ of $\geqslant 60\ ml\ min^{-1}$ per $1.73\ m^2$. On the other hand, in model 2, $eGFR_{Cys}$ lost significant association with the highest FGF23 tertile. By further adjustment for log(BNP) (model 3), iP lost the significant relationship with the high FGF23 levels, although it still tended to be related with high FGF23 among overall population and those with $eGFR_{Cys}$ of $\geqslant 60\ ml\ min^{-1}$ per $1.73\ m^2$.

In contrast to the results of the current study, we previously reported that iP was significantly correlated with FGF23 levels among patients with CKD but not among those without CKD.[8] The discrepancy may, at least in part, be attributed to the difference in the sample size; only 44 non-CKD patients were enrolled in the previous study. In the current study, we also found that $eGFR_{Cys}$, but not $eGFR_{Cr}$, was correlated with FGF23 levels among non-CKD patients; therefore, $eGFR_{Cys}$ may be superior to $eGFR_{Cr}$ not only in terms of accuracy, prediction of cardiac outcome but also in association with FGF23 levels among cardiac patients without renal dysfunction. Thus, it is possible that FGF23 may represent a novel biomarker for predicting cardiac prognosis among subjects with preserved renal function, as in the case of BNP.[9]

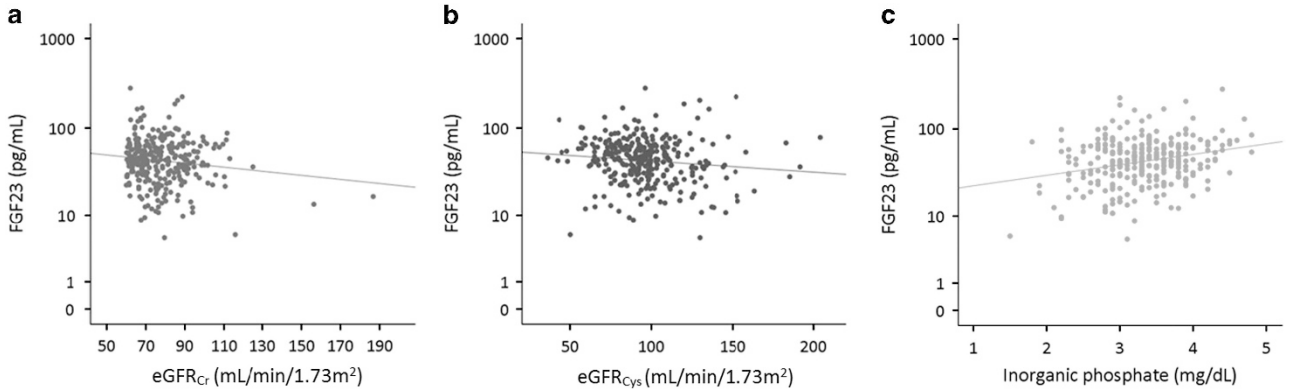

Figure 1 Correlation between FGF23 levels, $eGFR_{Cr}$, $eGFR_{Cys}$, and inorganic phosphate levels. (**a**) Correlation between FGF23 levels and $eGFR_{Cr}$. (**b**) Correlation between FGF23 levels and $eGFR_{Cys}$. (**c**) FGF23 and inorganic phosphate levels. Note that the Y axis (FGF23) is logarithmic scale. A full color version of this figure is available at *Hypertension Research* online.

Table 1 Multivariate logistic regression analysis

	Overall study population		*$eGFR_{Cys} \geqslant 60$ ml min^{-1} per 1.73 m^2*	
	Odds ratio 95% confidence interval	P-*value*	*Odds ratio 95% confidence interval*	P-*value*
Model 1				
$eGFR_{Cys}$, per 10 ml min^{-1} per 1.73 m^2	0.88 (0.78–0.98)	0.025	0.89 (0.78–1.01)	0.066
Inorganic phosphate, per 1 mg dl^{-1}	1.72 (1.07–2.75)	0.024	1.75 (1.07–2.86)	0.027
Model 2				
$eGFR_{Cys}$, per 10 ml min^{-1} per 1.73 m^2	0.90 (0.80–1.01)	0.065	0.90 (0.79–1.03)	0.116
Inorganic phosphate, per 1 mg dl^{-1}	1.72 (1.07–2.76)	0.025	1.75 (1.07–2.86)	0.027
Model 3				
$eGFR_{Cys}$, per 10 ml min^{-1} per 1.73 m^2	0.91 (0.80–1.02)	0.105	0.91 (0.80–1.04)	0.185
Inorganic phosphate, per 1 mg dl^{-1}	1.58 (0.98–2.56)	0.061	1.58 (0.95–2.61)	0.076

The highest FGF23 tertile (>56 pg ml^{-1}) was used as the dependent variable. Model 1, adjusted for sex, and age; model 2, adjusted for variables used in model 1 plus diuretic (loop or thiazide) use; model 3, adjusted for the variables used in model 2 plus log(BNP). In model 3, 289 patients were analyzed, because BNP value was not available in 9 patients. $eGFR_{Cys}$ indicates cystatin C-based eGFR.

Together with the findings of the study by Imazu *et al.*,[1] our findings suggest that physicians need to become more aware of the serum iP levels for patients with cardiac disease. Long-term consumption of excessive phosphate-containing food and drinks may affect the serum and urinary phosphate levels, although the risk of which often remains under-recognized.[10] Although in the study by Isakova *et al.*,[4] the estimated daily dietary phosphorus intake did not significantly correlate with serum phosphate, we should examine whether excessive phosphate intake in non-CKD subjects leads to the elevation of serum phosphate that potently induces the elevation of FGF23 in cardiac patients. Furthermore, we may have to pursue investigation of what parameters, other than iP, can potently influence the serum FGF23 levels. Such information may be important for predicting the cardiovascular prognosis according to the intriguing report by Imazu *et al.*[1]

CONFLICT OF INTEREST

The authors declare no conflict of interest.

Hideaki Morita, Tomohiro Fujisaka, Shu-ichi Fujita and Nobukazu Ishizaka

Departments of Cardiology, Osaka Medical College, Osaka, Japan
E-mail: ishizaka@osaka-med.ac.jp

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