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The correlation between serum fibroblast growth factor-23 with urinary fractional excretion of phosphate in predialysis chronic kidney disease

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ABSTRACT

Purpose: To investigate the correlation of serum fibroblast growth factor-23 (FGF-23) with urinary fractional excretion of phosphate (FEPi) in predialysis chronic kidney disease (CKD).

Methods: This cross-sectional study involved 75 patients with CKD stage 2-4. Blood and 24-hour urine samples were taken from eligible participants to measure key variables using standard commercial assays. FGF-23 concentration was measured using enzyme-linked immunosorbent assay (ELISA). The correlation between FGF-23 serum level and urinary FEPi was analyzed using

the Spearman correlation test.

Results: Of 75 eligible subjects, the majority had the characteristics of male gender, CKD stage 3, with mean age and body mass index of 50 ± 10.8 and 23.51 ± 3.3 , respectively. The median FGF-23 level was 108.7 (13.6-1226.2) RU/ml, while the median urinary FEPi was 24.3% (4.04%-65.9%). There was a moderate positive correlation between FGF-23 and FEPi ($r = 0.44$, $p < 0.001$).

Conclusion: The result confirmed the correlation between serum FGF-23 level with urinary FEPi in predialysis CKD.

Keywords: FGF-23, fractional excretion of phosphate, chronic kidney diseases, predialysis

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INTRODUCTION

Mineral and metabolism disorder as one of the chronic kidney disease (CKD) complications consisted of disorder of calcium, phosphate, and parathyroid homeostases.¹ Disorder of phosphate metabolism has been detected earlier in CKD.² Renal phosphate handling, or the excretion of phosphate filtrated by kidney, is expressed as fractional excretion of phosphate (FEPi). Recent clinical studies demonstrated a high FEPi value despite the presence of normophosphatemia in early CKD.³

Fibroblast growth factor-23 (FGF-23) is known to stimulate phosphaturia as a response to phosphate overload. It exerts its action at renal tubules by increasing urinary phosphate excretion and decreasing serum calcitriol level, thus maintaining the normal level of phosphate in serum.³⁻⁵ FGF-23 serum level rises progressively as estimated glomerular filtration rate (eGFR) declines in the beginning in CKD stage 2, and significantly elevated level of FGF-23 can be detected in most stage 3 and 4 of CKD.^{3,6}

Early detection and intervention play an important role in decreasing mortality in CKD.¹ Currently, there is no evidence of the correlation

between FGF-23 serum level and FEPi urine in the Indonesian population. This study aimed to investigate the correlation between FGF-23 serum level and urinary FEPi in predialysis CKD.

METHODS

The analytical cross-sectional study recruited out and inpatient in Sanglah General Hospital from October 2014 through March 2015. Participants were deemed eligible if they aged 18-65 years old with eGFR of 15-89 ml/minute or clinically stable patients with CKD stage 2-4. The exclusion was done with any evidence of the following: current treatment with activated vitamin D analogs, oral phosphate binders or supplements, treatment with calcimimetic, and history or laboratory evidence of malabsorption syndrome and malignancy.

Baseline data were retrieved from the medical record registry. Blood and 24-hour urine samples were taken from eligible participants to measure baseline characteristics. The samples were immediately sent to an independent out-of-hospital laboratory and processed using standard commercial assays. FGF-23 concentration was measured using Immunotopics enzyme-linked immunosorbent assay (ELISA). The value of FEPi

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was derived from the formula: $FEPi = (\text{urinary phosphate} \times \text{serum creatinine}) / (\text{serum phosphate} \times \text{urinary creatinine}) \times 100\%$.⁷ The eGFR was calculated from Cockcroft-Gault formula. This study was approved by the Ethical Committee of Medical Faculty of Udayana University/Sanglah

General Hospital, and all subjects provided written and informed consent.

Statistical analyses were performed using Statistics Program for Social Science version 15.0. (SPSS Inc, USA). The results were expressed in suitable central tendency and dispersion based on the normality test. Spearman's correlation test was used to analyze the correlation between FGF-23 and FEPi. A *P*-value of less than 0.05 was considered statistically significant.

Table 1. Subject characteristics

Variable	Mean ± SD or median (min-max)
Gender	
Male	54 (72%)
Female	21 (28%)
Age (year)	50±10.8
BMI (kg/m ²)	23.51±3.3
Hypertension	37 (49.3%)
Diabetes	30 (40%)
Serum phosphate (mg/dL)	3.48±0.86
Urinary phosphate (mg/dL)	500 (100-1300)
Serum creatinine (mg/dL)	1.52 (0.58-4.13)
Urinary creatinine (mg/dL)	922.7±410.2
eGFR (ml/minute)	50.1±20
FGF-23 (RU/ml)	108.7 (13.6-1226.2)
FEPi (%)	24.3 (4.04-65.9)
Serum calcium (mg/dL)	9.23±0.7
CKD stage	
Stage 2	19 (25.3%)
Stage 3	43 (57.3%)
Stage 4	13 (17.3%)

BMI, body mass index; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; FEPi, fractional excretion of phosphate; FGF-23, fibroblast growth factor-23.

RESULTS

The subject characteristics were listed in Table 1. Study subjects were mostly male (72%) with CKD stage 3 (57.3%). The mean age and body mass index were 50±10.8 and 23.51±3.3, respectively. Hypertension (49.3%) and diabetes (40%) comorbidities were found in less than half of the subjects. The result in Figure 1 showed moderate positive correlation between FGF-23 and FEPi urine ($r = 0.44$; $p < 0.001$).

DISCUSSION

Fibroblast growth factor-23 is released by multiple organs including bone, spleen, and brain, and additionally from kidney under pathophysiological circumstance. Pathophysiological circumstances closely related to CKD are well-known as FGF-23 production determinants. Together with its co-receptor, Klotho, FGF-23 plays an important role in regulating calcium and phosphate metabolism.⁸ Predialysis CKD cases may exhibit normal level of serum phosphate, while the increase in FGF-23 and urinary FEPi have occurred. The secondary excess of serum FGF-23 has been proposed as a compensatory mechanism for phosphate retention due to impaired renal excretion or reduced renal expression of Klotho that induces FGF-23 resistance. FGF-23 promotes renal phosphate wasting by internalizing the sodium phosphate cotransporter IIa and IIc at the proximal tubular apical membrane.⁹⁻¹²

FEPi levels below 20% are considered normal in subjects with preserved renal function. In this study, the median FEPi value (24.3%) exceeded the upper limit, with the maximum value reaching 65.9%. Although the normal range and clinical significance of FEPi are not well-established, an incremental risk of progression into end-stage renal disease (ESRD) with increasing FEPi value was observed. FEPi level greater than 55% corresponded with 12.3 fold increase in the risk of dialysis initiation.¹³

The upper limit of serum FGF-23 level normal value in previous studies was determined either by median or adverse outcomes risk. FGF-23 level

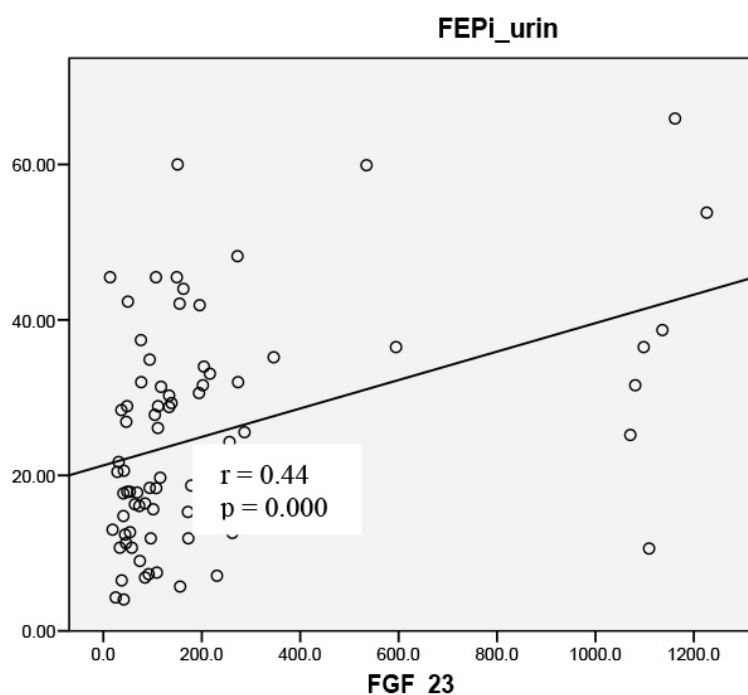


Figure 1. Scatter plot diagram showing correlation between serum FGF-23 and urinary FEPi in predialysis CKD

equals to or greater than 100 pg/ml was chosen in one study¹⁴ based on the finding of increased risk of mortality and ESRD in another study.¹⁵ The median value in a study by Tsai et al. was double the value (200 pg/ml) despite similarity in subject's stage of CKD.¹⁶ The wide range of FGF-23 level in this study was supported by Chathoth et al. who reported mean levels of 61.20±14.10, 118.50±63.20, and 1,526.40±1,456.00 in CKD stage 3 through 5 consecutively.¹⁷ Of note, a multinational study by Yuen et al. involving non-CKD subjects reported different median values for United States (57.41 RU/mL), Seychelles (42.49 RU/mL), and Ghana (33.32 RU/mL).¹⁸ It was noteworthy that the greatest median value in non-CKD subjects of the latter was within the mean level of CKD stage 3 in the study by Chathoth et al.

Serum FGF-23 and urinary FEPi levels are elevated early in most CKD stage 2-4 and both parameters are inversely correlated with decreasing GFR.^{11,12,19-21} Our study showed that serum level of FGF-23 had positive correlation with urinary FEPi urine in predialysis CKD ($r=0.44$, $p=0.000$), which was consistent with study by Sakan et al. ($r=0.401$, $p<0.0001$), Bech et al. ($r=0.36$, $p<0.001$), Isakova et al. ($r=0.25$, $p<0.0001$), and Dominguez et al. ($r=0.21$, $p<0.05$).^{9,11,12,22}

There were some limitations in the current study. Current study design did not allow for causality assessment as no analysis on CKD progression was intended. Despite multiorgan clinical effects the FGF-23 inflicted, we only focus on one particular function of the kidney. Other biochemical parameters not addressed here may also represent potential confounders.

CONCLUSION

FGF-23 serum level had a positive correlation with urinary FEPi in predialysis CKD. Future efforts are required to validate their role in predialysis CKD management.

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AUTHOR CONTRIBUTIONS

Research design, Y.K., V.W., and W.D.L.; clinical data and material collection, Y.K., V.W., and W.D.L.; data analysis, Y.K.; writing—review and editing, Y.K. and V.W.

CONFLICT OF INTEREST

The authors declare no conflict of interest for this issue.

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Nil.

ETHICAL CONSIDERATIONS

Written ethical clearance was obtained from the Ethical Committee of Medical Faculty of Udayana University/Sanglah General Hospital.

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