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Original Article

Diagnostic value of fibroblast growth factor 23 for abdominal aortic calcification in Indonesian hemodialysis patients

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Abstract

Objective: Homeostasis of serum phosphorus and calcitriol level is regulated mainly by fibroblast growth factor 23 (FGF23). Studies show that elevated serum FGF23 level was significantly associated with aortic calcification severity, peripheral blood vessels, and a higher score of coronary artery calcification in patients undergoing hemodialysis. We did this cross-sectional study to determine the FGF23 diagnostic value for abdominal aortic calcification in Indonesian hemodialysis patients. **Materials and Methods:** This study included seventy-five, chronic hemodialysis patients. An enzyme-linked immunosorbent assay method was used to measure serum intact FGF23 level, and abdominal aortic calcification was detected by lateral lumbar X-ray. The diagnostic value of FGF23 was analyzed using receiver operating characteristic (ROC) curves. **Results:** fifty-one (68.0%) patients had abdominal aortic calcification (AAC). Serum intact FGF23 level ranged from 217 to 950 pg/mL with a median level of 328 pg/mL. The FGF23 levels in the serum of patients with AAC were significantly higher than those without AAC ($P < 0.001$). The best cutoff point was 277 pg/mL. The calculated area under the ROC curves was 0.959 (95% confidence interval, 0.912–1.00); sensitivity was 94.0% and specificity was 84.0% ($P < 0.001$). **Conclusion:** serum intact FGF23 level may be proposed as a proper tool for abdominal aortic calcification in Indonesian hemodialysis patients.

Keywords: *Abdominal aortic calcification, Fibroblast growth factor 23, Hemodialysis*

Introduction

According to The Kidney Disease Improving Global Outcomes, one of the complications of chronic kidney disease (CKD) is CKD-mineral and bone disorder (CKD-MBD), which is defined as a clinical syndrome consisted of mineral, bone, and calcified cardiovascular diseases [1]. The variety of clinical manifestations in CKD can make this clinical syndrome and associated with mortality of end-stage kidney disease [2]. Vascular calcification is more commonly seen in hemodialysis patients compared to their age and sex-matched counterparts in the general population [3]. Research in the last decade has shown that vascular calcification is not only a passive degenerative phenomenon but a complex and active pathological process in CKD patients. Impaired mineral metabolism has been suggested as a risk factor or can be a significant cause of vascular calcification in patients with CKD [4]. One of the most important factors that govern bone and mineral metabolism are fibroblast growth factor-23 (FGF-23) [5].

FGF23, previously called a "phosphatonine," has a molecular weight of 32-kDa and contains 251 amino acid residues [6]. FGF 23 is secreted from bone osteocytes and osteoblasts [7]. Research with cross-sectional design showed that serum FGF23 level in circulation is higher in CKD patients compared to healthy individuals. This elevation will increase gradually concurrent with decreasing kidney function so that when the patient is on end-stage kidney disease, FGF-23 concentrations can reach 1000 times above the reference range [8,9].

Data show that elevated serum FGF-23 concentrations were independently associated with aortic calcification severity [10], peripheral blood vessels, and higher coronary artery calcification scores in patients undergoing hemodialysis [9,11].

Until now, there is no data in Indonesia regarding serum FGF23 concentrations as an independent predictor of vascular calcification. With this background in mind, we performed this

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study to determine the diagnostic value of FGF23 for abdominal aortic calcification in Indonesian hemodialysis patients.

Materials and methods

Ethical approval

Ethical approval for this study (324 TGL/KEPK FK USU-RSUP HAM/2018) was provided by the Health Research Ethical Committee Medical Faculty of Universitas Sumatera Utara/H. Adam Malik General Hospital, Medan, Indonesia, on May 30, 2018. Informed written consent was obtained from all patients before their enrollment in this study. This study confirmed to Good Clinical Practice and the Declaration of Helsinki.

Study design

This was single-center, cross-sectional study in the outpatient clinic at Rasyida Renal Hospital Medan, Indonesia, in February 2018.

Study subjects

Seventy-five patients who underwent regular hemodialysis for more than 30 months, with ages ≥18 years were recruited. Patients with a lack of medical records, pregnancy, as well as unattainability of imaging were exclusionary.

Clinical characteristics

Patients' general information, including clinical history and medications, were reviewed from medical charts and supplemented with data directly from patients. We measured the weight and height to calculate the body mass index (BMI). If the patients had a previous abnormal cardiac investigation or a history of myocardial infarction or angina, so we would consider them having a history of coronary artery disease. History of high blood pressure and taking or having taken antihypertensive drugs will be defined as hypertension.

Laboratory values

Serum phosphorus (mg/dL), calcium (mg/dL), and FGF-23 (pg/mL) were recorded. Blood sampling was drawn in the fasting state 5–10 min before starting of hemodialysis process. Serum intact FGF23 levels were examined using the two-site enzyme-linked immunosorbent assay technique.

Lateral lumbar X-rays

Lateral lumbar X-rays was performed to assess the presence of abdominal aortic calcification in the same day with blood sampling was drawn. By this tool, we could evaluate eight locations (anterior and posterior abdominal aortic walls at vertebral segments L1–L4) and count Framingham calcification scores (0 = no detectable calcification; 1 = small scattered calcifications over ≤1/3 of part's aortic wall; 2 = calcification of 1/3 to <2/3 of the part's aortic wall; 3 = calcification of ≥2/3 of the part's aortic wall). The eight measurements were summed for the total calcification score ranging from 0 to 24. Patients were said to have no calcification if the score was 0, mild calcification if the score was 1–4, severe calcification if the score was above 4 [12]. The interpretation was performed by a professional radiologist who did not know the patient's clinical condition.

Statistical analysis

The baseline characteristics of the study participant were analyzed with descriptive statistics. Data were expressed as mean ± standard deviation, median (range), or frequency (proportion). Spearman correlations analyzed the correlation between the score of abdominal aortic calcification and the level of FGF-23 serum. Normally distributed data were compared using unpaired *t*-tests and Mann–Whitney U-tests for nonnormally distributed data. Receiver-operating characteristic (ROC) curves assessed the predictive value of FGF23 in the diagnosis of abdominal aortic calcification. The significant result was considered if the $P < 0.05$. The statistical analysis was performed using the SPSS 22.0 software.

Results

Baseline data

Table 1 presents the clinical and demographic characteristics of the study participant. Patients were predominantly male (60.0%) with a range age of 25–78 years (median 57) and a median BMI of 23.30 kg/m^2 (range 16.73–42.67). Most patients undergo hemodialysis for 10 h a week (72.0%) with a median dialysis vintage of 67 months (range 30–331). The majority of study participants had a history of hypertension (74.7%), and only 18.7% were diabetic. A history of coronary artery disease was known in only 16.0% of patients. Twenty-four patients (32.0%) reported once or currently smoking.

Biochemical values are shown in Table 1. Participants had a median serum FGF-23 level of 328 pg/mL (range 217–950), a median serum calcium level of 9.8 mg/dL (range 8–10.9), and mean serum phosphate level of 5.47 ± 0.61 mg/dL.

Abdominal aortic calcification scores were available in all patients, with a median (range) of 5 (0–19). The prevalence of abdominal aortic calcification was 68.0%, affecting 51 of 75 evaluable patients. A total of 24 (32.0%) patients were free of abdominal aortic calcification.

Bivariate analysis was performed to determine the relationship of various factors with abdominal aortic calcification. Table 2 shows that older patients and high levels of FGF-23 serum were associated with abdominal aortic calcification. Spearman correlation coefficients showed that abdominal aortic calcification scores were positively correlated with serum FGF-23 level ($r = 0.543$, $P < 0.001$) [Figure 1].

In the current study, there was a statistically nonsignificant association between radiographic abdominal aortic calcification with gender, BMI, dialysis duration, serum calcium level, and serum phosphate level ($P > 0.05$) [Table 2].

Diagnostic value of fibroblast growth factor-23

ROC curve showed that FGF23 was associated with a higher predictive value for abdominal aortic calcification with an area under the curve was 0.959 (95% confidence interval [CI] 91.2%–100.0%, $P < 0.001$) [Figure 2]. When the detection cutoff point was 277 pg/mL, the sensitivity and specificity were 94% and 84%, respectively [Figure 3].

Table 1: Demographic and clinical characteristics of the study participant

Variables	(*n*=75), *n* (%)
Gender: Male versus female	45 (60.0) versus 30 (40.0)
Age (years), median (minimum-maximum)	57 (25-78)
BMI (kg/m^2),(minimum-maximum)	23.30 (16.73-42.67)
Dialysis vintage (months), (bulan), median (minimum-maximum)	67 (30-231)
Dialysis hours per week: 10 versus 12	54 (72.0) versus 21 (28.0)
Renal failure etiology: diabetic versus hypertension	14 (18.4) versus 56 (74.7)
History of coronary artery disease, yes	12 (16.0)
Tobacco-smokers: yes	24 (32.0)
Abdominal aortic calcification scores, median (minimum-maximum)	5 (0-19)
Abdominal aortic calcification	
No calcification	24 (32)
Calcification	51 (68)
Calcium (mg/dL), median (minimum-maximum)	9.80 (8-10.9)
Phosphate (mg/dL), mean±SD	5.47±0.61
FGF-23 (pg/mL), median (minimum-maximum)	328 (217-950)

BMI: Body mass index, SD: Standard deviation, FGF: Fibroblast growth factor

Table 2: Related factors with abdominal aortic calcification

Variables	Calcification (+) (*n*=51)	Calcification (−) (*n*=24)	*P*
Gender; male	54.2%	62.7%	0.479*
Age (years), median	45.50	58.00	0.016$^+$
BMI (kg/m^2), median	23.05	23.44	0.658$^+$
Dialysis duration (months), median	56.50	71.00	0.621$^+$
Calcium (mg/dL), median	9.70	9.90	0.502$^+$
Phosphate (mg/dL), mean±SD	5.61±0.77	5.42±0.51	0.280$^\wedge$
FGF-23 (pg/mL), median	247.50	388.00	<0.001$^+$

BMI: Body mass index, SD: Standard deviation, FGF: Fibroblast growth factor, *Chi-Square Test, $^+$Mann-Whitney Test, $^\wedge$T-Independent Test

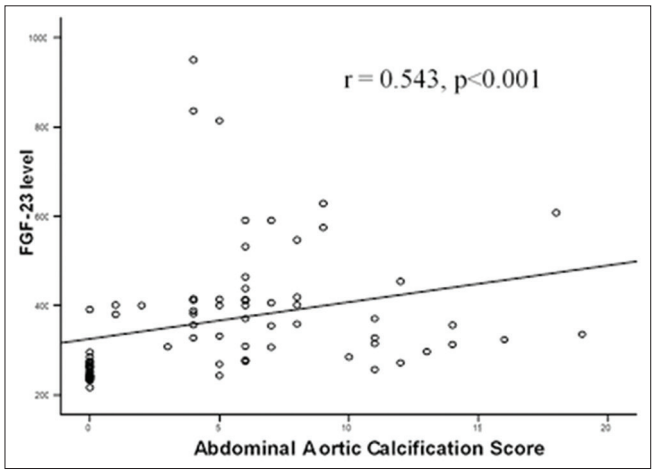

Figure 1: Scatter plot correlation of fibroblast growth factor-23 level with abdominal aortic calcification score

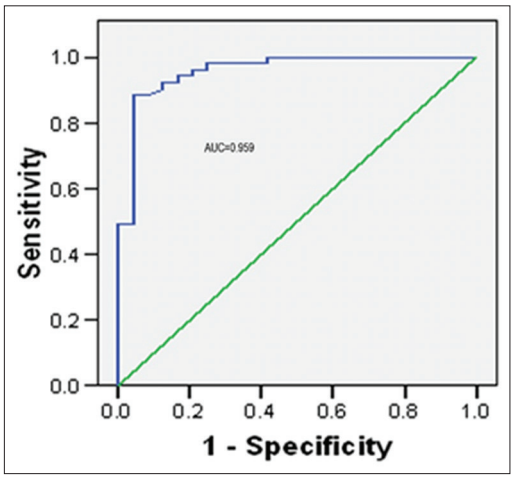

Figure 2: Receiver operating characteristic curve of fibroblast growth factor-23 levels for the prediction of abdominal aortic calcification coronary calcification. Area under receiver operating characteristic curve was 0.959 (95% confidence interval 0.912–1.00, $P < 0.001$). AUC = Area under curve; ROC = Receiver operating characteristic

Area under ROC curve was 0.959 (95% CI 0.912–1.00, $P < 0.001$). AUC = Area under curve; ROC = receiver operating characteristic.

When the detection cutoff point was 277 pg/ml, the sensitivity and specificity were 94% and 84%, respectively.

Table 3 shows the diagnostic value of the FGF-23 level for the incidence of abdominal aortic vessel calcification. The cutoff point FGF-23 ≥277 has excellent diagnostic values and accuracy.

Discussion

The CKD-MBD Working Group Guidelines recommend radiographic examination of vascular calcification, including abdominal aortic calcification, which allows assessment for the presence and semi-quantitative [1].

Vascular calcification is prevalent in chronic hemodialysis patients. Its prevalence varies significantly from 60% to 100%,

Table 3: Diagnostic value of fibroblast growth factor-23 level for abdominal aortic calcification

Cut off	Sensitivity	Specificity	PLR	NLR	PPV	NPV	Accuracy
FGF-23 (≥277) (%)	94	84	5.88	0.07	92.2	87.4	90.7

PLR: Positive Likelihood ratio (LR+), NLR: Negative Likelihood ratio (LR−), PPV: Positive predictive value, NPV: Negative predictive value

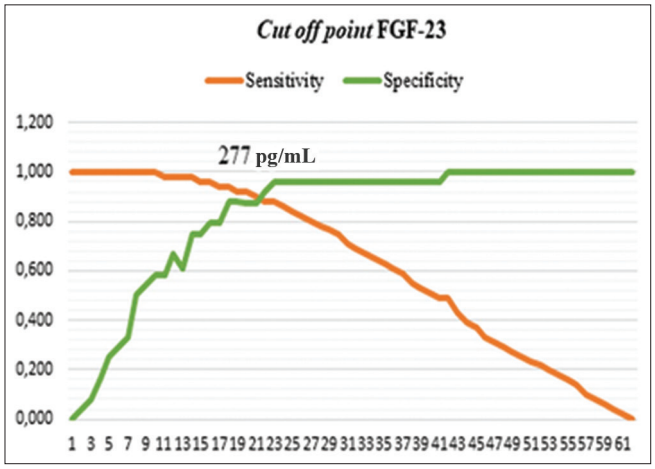

Figure 3: The cutoff point fibroblast growth factor-23 level for the prediction of abdominal aortic calcification. When the detection cutoff point was 277 pg/mL, the sensitivity and specificity were 94% and 84%, respectively

depending on the location of the examination and diagnostic method used and the area where the study was conducted [13]. This study showed that the prevalence of vascular calcification in chronic hemodialysis patients by lateral lumbar X-rays was quite high, i.e., 68% with a median (range) abdominal aortic calcification score of 5 (0–19). This result was almost the same as Woro *et al*., [14] who got the prevalence of vascular calcification in chronic hemodialysis patients, around 65%.

Most of the patients underwent dialysis 4 h for each session (3 sessions per week) in developed countries, but in Indonesia, especially in the present study, most patients received dialysis services only 5 h for each session (2 sessions per week). This difference is because the financing system strongly influences hemodialysis facilities in Indonesia, namely using national health insurance Indonesian Health care insurance (JKN), which is generally done twice a week [13,15].

In contrast with other countries, the leading cause of CKD based on the Indonesian Renal Registry data was hypertension (36%), followed by diabetes (29%) and other diseases [13]. While in the United States, the leading cause of CKD was diabetes and followed by hypertension, and another illness with a proportion reaches 44% and 29%, respectively [16]. Although the rate of hypertension was higher than internal rate of return (IRR) data, our research showed the same result with IRR data; hypertension is a major cause of CKD. This difference likely because we got information only from the history and medical records without biopsy data, so it was difficult to recognize whether hypertension occurred as a cause or as a result of kidney failure.

By comparing the results of our study with previous studies, we found that both in our research and previous studies, older patients were associated with abdominal aortic vessel calcification [17]. The atherosclerosis process has started since childhood and continues to form atheroma with various lesions that form calcification. Hence, the age is thought to be a critical determinant of the presence of calcification [18].

The risk of vascular calcification was influenced by dialysis vintage. Calcification Outcome in Renal Disease (CORD) study on multivariate analysis showed dialysis vintage independently predicted abdominal aortic calcification (per 1-year increase, odds ratio 1.110; $P < 0.001$) [12]. The same result was found by Guérin *et al*. that 27% of patients who had dialysis for a year had vascular calcification. The incidence increased to 83% in patients undergoing dialysis for more than 8 years [19]. In this study, patients' radiographic abdominal aortic calcification associated with dialysis vintage, although it did not show a statistically significant difference. It perhaps because we only involved patients, who had been on dialysis for more than 3 years, so most had experienced vascular calcification.

High serum levels of calcium and phosphate can promote calcification and contribute to increased mortality in end-stage renal disease [20]. In our study, abdominal aortic calcification did not associate significantly with serum calcium level and serum phosphate level, perhaps because almost every patient has taken calcium or noncalcium-containing phosphate binders. Unfortunately, there was no data about using calcium or noncalcium-containing phosphate binders, and it is related to serum calcium level and serum phosphate level.

FGF-23 is a polypeptide hormone, a member of the FGF family, which can regulate phosphate metabolism. The osteocytes and Gergen Bauer's cells (osteoblasts) are primarily secreting FGF-23. The main target organs of circulating FGF-23 are the kidney, bone, thyroid, and intestine [21]. Peripheral vascular calcification was detected semi-quantitatively on plain radiograph, has been independently associated with serum FGF23 levels in hemodialysis patients [22].

The previous reports have confirmed that the serum FGF23 concentrations are useful for clinical prediction of abdominal aortic calcification, and our study was consistent with it [17]. ROC curve analysis showed the value of FGF23 in the diagnosis of abdominal aortic calcification was higher than previous studies, suggesting that patients with increased FGF23 levels tended to have abdominal aortic calcification and were a high-risk population of cardiovascular complications [23].

Different from Fetuin-A, which acts as a protective factor to abdominal aortic calcification, [24] the pathogenesis of correlation between FGF23 and abdominal aortic calcification was remained unclear. Vascular smooth muscle cells' (VSMC) transdifferentiation into osteoblast-like cells was an essential mechanism of vascular calcification. The principal mechanism of vascular calcification was the transdifferentiation of VSMC into osteoblast-like cells. FGF23 accelerated phosphorus-induced VSMC transdifferentiation into osteoblast-like

cells *in vitro*. According to Jimbo *et al*., the extracellular signal-regulated protein kinases 1 and 2 pathway probably mediated the process [25]. Klotho is an essential co-factor for FGF23. Its position could explain the role of FGF23 in vascular calcification. Consequently, an increase in FGF23 concentrations with decreased of Klotho concentrations may be a result of unresolved hyperphosphatemia and impaired Vitamin D metabolism, which are also essential factors in vascular calcification [26]. Another possible explanation for the association between FGF23 and abdominal aortic calcification is that FGF23 triggers the release of inflammatory cytokines, for example, tumor necrosis factor-α, interleukin-6 (IL-6), and transforming growth factor β [27]. Mitchell *et al*., in their study of FGF23 in healthy girls' ages 9–18 years, reported that the concentration of FGF23 was inversely correlated with urinary calcium excretion, which may contribute to the accumulation of serum calcium level [28].

There were a few limitations of this study, for example, the study design was observational and cross-sectional in a single-center, single radiologist, unavailability of concomitant medication data and the need to be correlated with other markers of chronic inflammation in Hemodialysis (HD) like IL-6, and comparing these results to patients with peritoneal dialysis. As a single center with a lower prevalence of diabetes, it did not describe the condition of all hemodialysis patients in Indonesia. Although we had serum phosphorus and calcium laboratory results, data on the use of phosphate binders and other CKD-MBD drugs would have been relevant if available.

Nevertheless, for the best of our knowledge, this is the first study to show that the diagnostic value of FGF 23 for abdominal aortic calcification in Indonesian hemodialysis patients. Further prospective researches are needed to explain the mechanisms by which FGF23 may be involved in the pathogenesis of abdominal aortic calcification.

Conclusion

Abdominal aortic calcification, which is visible on lateral lumbar aorta X-ray, had a statistically significant correlation with the FGF23 level. Serum intact FGF23 level may be proposed as a promising diagnostic marker for abdominal aortic calcification in hemodialysis patients.

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Conflicts of interest

The authors declared no competing interests.

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