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The Correlation between Fibroblast Growth Factor 23 (FGF23) and Iron Profile in Chronic Kidney Disease Patients on Dialysis with Anemia

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ABSTRACT

Patients with chronic kidney disease on dialysis (CKD-5D) often develop various complications, one of them is iron deficiency anemia. Iron is needed as a raw material for the formation of red blood cells. Iron deficiency increases levels of Fibroblast Growth Factor 23 (FGF23). In CKD-5D patients, the functional iron deficiency often occurs and FGF23 levels increase. FGF23 levels can be a poor prognosis in CKD-5D. This study aims to find out the correlation between FGF23 with hemoglobin level, serum iron, total iron-binding capacity, and ferritin level in CKD-5D patients with anemia. This study was cross-sectional. Subjects were CKD patients undergoing routine hemodialysis (HD) twice a week at least 3 months, aged >18 years, anemia (hemoglobin levels <13 g/dL (men) and <12gr/dL (women)) and were willing to participate in the study by signing an informed consent letter in the Hemodialysis Unit of Hasan Sadikin General Hospital, Bandung. The statistical test used was Pearson correlation if the data were normally distributed and Spearman Rank Analysis if the data were not normally distributed. There were 181 patients with CKD-5D, 137 patients had complete data and met 97 inclusion and exclusion criteria. Seventy-five patients were taken randomly from 97 patients to become subjects of the study. The results showed there were significant correlations between levels of Total Iron-Binding Capacity (TIBC) with FGF23 (r = 0.249, p = 0.015) and levels of Transferrin Saturation with FGF23 (r = -0.259, p = 0.012). There were no statistical correlation between hemoglobin levels with FGF23 (r = 0.025, p = 0.417) and levels of Serum Iron (SI) with FGF23 (r = -0.060, p = 0.306). There were correlations between FGF23 with TIBC and Transferrin Saturation levels, and there were no significant correlations between FGF23 with hemoglobin and SI levels in CKD-5D patients with anemia.

Keywords: CKD-5D, Anemia, Iron deficiency, Hemoglobin, FGF23

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INTRODUCTION

Chronic kidney disease (CKD) is a chronic disease with a high prevalence of about 5-10% in the world. Also, the disease occupies rank 12 causes of death and the 17th cause of disability.[1] Based on data from the Indonesian Renal Registry (IRR) in 2015, there were 21,050 patients diagnosed with end-stage renal disease (ESRD) who underwent routine hemodialysis. This number has quadrupled compared to 2007 with 4,977 patients with the most leading cause of death 44% due to cardiovascular disease.[2]

One of the complications that occur in CKD patients is iron deficiency anemia.[3] A study conducted by Obrador, et al. showed that among the patients predialysis, 68% of patients with CKD advanced stage who require renal replacement therapy had a hematocrit of less than 30 mg/dL; of these, 51% of patients have hematocrit less than 28 mg/dL.[4] Although anemia is not commonly found in the early stage of CKD, the prevalence of recurrent anemia is 5.2% in patients with stage III disease and increased to 44.1% in the group with stage IV disease.[5]

Anemia prevalence in CKD is higher in patients aged over 60 years than ages 46 to 60 years. This is a secondary cause related to higher CKD levels in old age, where the glomerular filtration rate is related to age.[5] Iron is needed as a raw material for the formation of red blood cells. Iron deficiency increases levels of Fibroblast Growth Factor 23 (FGF23).[6] In CKD-5D patients, the functional iron deficiency often occurs and FGF23 levels increase.

FGF23 is a phosphorus-regulating hormone, which act by increasing the rate of phosphate urinary excretion and prevent renal production of 1,25-dihydroxyvitamin D.[7,8] In patients with kidney disease, this action may mitigate hyperphosphatemia. CKD patients have higher FGF23 than normal one. Some studies revealed that the FGF23 level increase is an independent risk factor for CKD progression, cardiovascular event, and mortality.[7,9] FGF23 levels can be a poor prognosis in CKD-5D.[10]

The correlation between FGF23 with hemoglobin levels and iron profile on chronic kidney disease is available but until now there has been no such study in Indonesia. This study aims to find out the correlation between hemoglobin levels and FGF23 in CKD-5D patients.

METHODS

This study used a cross-sectional method to determine the correlation between FGF23 and iron profile in CKD-5D patients with anemia. The study population was all CKD-5D patients at the Hemodialysis Installation, Dr. Hasan Sadikin Hospital, Bandung, West Java, Indonesia in June 2017. The selection of subjects based on consecutive sampling during the study period who had met the inclusion criteria.

The inclusion criteria of this study are CKD-5D patients on routine hemodialysis twice a week for at least 3 months, aged >18 years, anemia (hemoglobin level of <13 g/dL (men) and <12 gr/dL (women) and were willing to participate in the study by signing an informed consent letter in the Hemodialysis Unit of Hasan Sadikin General Hospital, Bandung, Indonesia.

Exclusion criteria from this study were patients who met the inclusion criteria but there were other severe comorbidities such as sepsis, malignancy, hospitalization, iron therapy, transfusion <1 month, severe hypoalbuminemia (albumin <2.5 g/dL) and patients who quit during the study. This study was approved by the ethics committee of Dr. Hasan Sadikin General Hospital, Bandung, Indonesia (ethical approval No: LB.04.01/A05/EC/161/V/201).

To analyze the correlation between FGF23 with hemoglobin, iron serum (SI), total iron-binding capacity (TIBC), and transferrin saturation (TSat) level in CKD-5D patients using the Pearson Correlation Test if the data were normally distributed and Spearman Rank Analysis if the data were not normally distributed for continuous data. The Chi-Square test was applied for categorical data. Newman-Keuls Student T-test was applied to compare two normally distributed data or the Mann-Whitney U test if the data were not normally distributed. The correlation was considered significant if $p < 0.05$ with a 95% confidence interval.

RESULTS

In this study, there were 40 men (53.3%) and 35 women (46.7%) patients, with an average age of 46.67 ± 11.73 years. The old median of HD in this study was 36 (12-168) months. Baseline characteristic of this study was provided in figure 1, table 1, and 2.

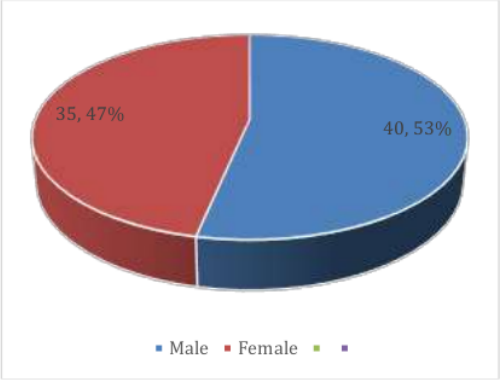

Figure 1: Characteristic of Subjects Based on Gender (n=75)

Table 1: Baseline Characteristic of CKD-5D patients (n=75)

Variable	Median (range) or Average ± SD
Age (years)	46.67 ± 11.73
Duration of Hemodialysis (month)	36 (12-168)
Hemoglobin level (mg/dL)	9.1 (7.0-12.7)
Iron level (SI, µg/dL)	51 (14-166)
TIBC (µg/dL)	235 (137-429)
Transferrin Saturation (%)	21.4 (10.2-75.1)
FGF23 level (ru/mL)	6737 (958-10723)

Note: SD = Standard Deviation , CKD = chronic kidney disease, SI = serum iron , TIBC = total iron-binding capacity , FGF23 = fibroblast growth factor 23.

Anemia parameters were median hemoglobin level 9.1 (7.0-12.7) gr/dL, serum iron (SI) levels median 51 (14-166) µg/dL, TIBC level 235 (137-429) µg/dL and Transferrin Saturation (TSat) level of 21.4% (10.2-75.1). The median FGF23 level was 6737 (958-10723) ru/mL (Table 1).

Table 2: Baseline Characteristics of Study Subjects by Sex of CKD-5D (n = 75)

Variable	Sex		p*
	Male	Female	
	n = 40	n = 35	
Hemoglobin (gr/dL)	9.1 (7-12.7)	9.1 (7-11.5)	0.706
SI (µg/dL)	51 (14-166)	53 (22-165)	0.975
TIBC	248.58 (137-429)	245.86 (162-370)	0.815
Transferrin Saturation (%)	21.65 (10.2-75.1)	20.3 (10.4-72.4)	0.996

Note: SI = serum iron; TIBC = total iron binding capacity

* Statistical tests using unpaired t test (normally distributed) and Mann-Whitney U test (not normally distributed), with significance if p <0.05.

A comparative test was performed, there were no differences between men and women in terms of hemoglobin (p=0.706), SI (p=0.975), TIBC (p=0.815) and TSat (p=0.996) (Table 2). The correlation between FGF23 levels with several variables was shown in table 3. The variables include the duration of HD, hemoglobin, SI, TIBC, and TSat levels were performed using the Rank-Spearman Analysis test because they were not normally distributed.

Table 3: The Correlations between FGF23 and Several Variables in CKD Patients Undergoing Routine HD (n = 75)

Variable	FGF23 (n = 75)	
	Correlation Coefficient (r)	p*
Duration of HD (month)	-0.066	0.287
Hemoglobin (gr/dL)	0.025	0.417
SI (µg/dL)	-0.060	0.306
TIBC (µg/dL)	**0.249**	**0.015** *
Transferrin Saturation (%)	**-0.259**	**0.012** *

Note: HD = hemodialysis, SI = serum iron, TIBC = total iron-binding capacity, FGF23 = fibroblast growth factor 23.

*Statistical tests using Rank-Spearman Analysis (because all data were not normally distributed); with significance if p <0.05.

The correlation between FGF23 levels with several variables: duration of HD (p=0.287), hemoglobin levels (p=0.417), and SI (p=0.306) were not significant (Table 3). But the correlation between FGF23 with TIBC and TSat levels were significant (p=0.015 and p=0.012).

DISCUSSION

The basic characteristics of this study include gender, age, duration of HD, hemoglobin levels, SI, TIBC, TSat, and FGF23. The sex in the subjects of this study was proportional to 40 male patients (53.3%) and 35 female patients (46.7%). The mean age of patients of the study subjects in this study was 47±12 years. These results were not much different from those reported from the IRR data, which showed the average age group of CKD-5D was 45-64 years.[2]

Hemoglobin levels in this study were low because subjects included were required to be anemia according to the KDIGO 2012 criteria for anemia in CKD.[1] This study was to determine the status of iron in anemic patients thus the hemoglobin level for men <13 gr/dL and women <12 gr/dL. The mean hemoglobin level in this study was 9.47±1.35 gr/dL, and statistical analysis using Kolmogorov Smirnov revealed the data was not normally distributed so the median and range used for statistical calculations are 9.1 (7.0-12.7) gr/dL.

This hemoglobin level was higher than the KDIGO standard (9.0 gr/dL) as a limit for the administration of erythropoietin (EPO) for CKD-5D patients (Ahemi K, 2012). This demonstrated that the average hemoglobin levels of study subjects were categorized as good as the initiation of EPO. Hemoglobin level is a parameter of anemia condition and has an influence on the general condition that low hemoglobin increases morbidity and mortality especially in CKD-5D patients.[3,11] Anemia suffered in patients with CKD-5D is iron deficiency anemia.[3] In this study, serum iron with a median level of 51 (14-166) µg/dL. This level was still within normal limits, but the clinical importance of patients with CKD-5D is lack. Because the functional iron score is needed. For the determination of functional iron anemia, TIBC examination is needed which in this study obtained median TIBC levels of 235 (137-429) µg/dL. Calculation of SI divided by TIBC produces Transferrin Saturation (TSat) as one of the parameters of iron deficiency anemia.[1,11,12]

The TSat results in this study were 21.4% (10.4-102) which were above the threshold for determining iron deficiency anemia (20%).[1,11] It indicates the possibility of CKD-5D patients in this study being in a condition, not functional iron deficiency. But it needed to be understood that transferrin was an acute negative phase reactant, which plays a role in the calculation of transferrin saturation and was not reliable in chronic conditions.[13,14,15] Thus, the determination of functional iron deficiency anemia using TSat is less valid.

The correlations between FGF23 levels with several variables were performed in this study are duration of HD, hemoglobin levels, SI, TIBC, TSat. The data were not normally distributed thus they were performed using the Rank-Spearman Analysis test. In this study there was a significant correlation between FGF23 with TIBC (r=0.249; p=0.015) and Transferrin Saturation levels (r=-0.259; p=0.012). But, there were no significant correlation between

FGF23 with hemoglobin (r=0.025; p=0.417) and SI levels (r=-0.06; p=0.306).

Iron is a regulator of FGF23 production. Some studies in animals and humans have shown that iron deficiency stimulates transcription of FGF 23, which is offset by an increase in fragment synthesis of FGF23 in healthy osteocyte. This results in a high concentration of circulating FGF23 fragments.[16] In hemodialysis patients, administration of intravenous saccharated ferric oxide induces an increase of FGF23 levels. This increase does not induce hypophosphatemia and inappropriately low 1,25-dihydroxy vitamin D levels in the absence of a functioning kidney but may induce temporary PTH suppression. This condition may be caused by directly acting on the parathyroid.[17] Parenteral iron may suppress renal tubular phosphate reabsorption and 1α-hydroxylation of vitamin D resulting in hypophosphatemia.[18]

FGF23 levels increase are related to increased mortality, which is independent level of the serum phosphate level but related to vascular calcification. The main factor associated with high serum FGF23 levels is still phosphataemia, which may appear paradoxical. FGF23 may be used as a marker of mortality risk in ESRD patients that demonstrate phosphate overload, which is only partially reversed by long hemodialysis.[19]

Lack of functional iron without inflammation increases the production of FGF23. Hepcidin is an important molecular mediator in functional iron deficiency. Hepcidin is produced by the liver in response to inflammation, and increases iron absorption and

decreases gastrointestinal iron absorption.[16] FGF23 levels elevation are associated with higher levels of inflammatory markers in patients with CKD and increase adverse outcomes in CKD.[20]

Besides, one of mechanisms of iron deficiency that increases the expression of FGF23 is to stabilize hypoxia-inducible factor 1 (HIF1). HIF is a basic heterodimeric member of the helix-loop-helix family of transcription factors. HIF heterodimers regulate gene expression by binding to hypoxia response elements in the target gene promoter. Degradation and activation of HIF1 depend on iron. Iron decrease and iron chelators may stabilize HIF1 . Stabilization HIF1 has been implicated as the mechanism of the increase in the production of FGF23 in iron deficiency.[16]

In the study of David V, *et al* (2016) it was found that iron deficiency caused a significant increase in serum cFGF23 levels.[16,21,22,23] In the study of Clinkenbeard EL, *et al* (2014), in young rats it was found that iron deficiency also significantly increased iFGF23.[21,24,25,26]

In this study, it was found that hemoglobin and SI levels did not affect FGF23 levels. It can be caused by heterogeneous subject; not all of the subjects were included as iron deficiency anemia. Further research in a particular group of iron deficiency anemia is required.

CONCLUSION

The conclusions of this study were:

1. In CKD-5D patients, FGF23 levels were very high (6737 ru/mL (958-10723)).
2. There was a significant correlation between FGF23 and TIBC levels (p=0.015).
3. There was a significant correlation between FGF23 and transferrin saturation levels (p=0.012).
4. There was no significant correlation between FGF23 and hemoglobin levels in CKD-5D (p=0.417).
5. There was no significant correlation between FGF23 and SI levels in CKD-5D (p=0.306).

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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