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Fibroblast Growth Factor-23 (FGF-23) in Patients with Regular Hemodialysis: A Risk Factor for Restless Legs Syndrome

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Abstract. Background: Restless Legs Syndrome (RLS) is one of the most common sleep disturbance problems in dialysis patients. In this study, we would like to explore some of bone and mineral marker disorder especially fibroblast growth factor-23 (FGF-23)and its correlation with RLS in regular hemodialysis patients. **Methods:** This is a cross sectional study design involving 71 respondents with chronic kidney disease that already had regular hemodialysis at Haji Adam Malik Hospital Medan. Status of RLS in this patients were being evaluated according to the International Restless Leg Syndrome Study Group (IRLSG) by interviewing and laboratory examination of FGF-23, hemoglobin (Hb), serum iron (SI), total iron binding capacity (TIBC), transferrin saturation (TSAT), serum ferritin, calcium (Ca) and phosphate (P) level. **Results:** Of all study subjects, 26 respondents (34.6%) diagnosed with RLS. Bivariate analysis result showed that there is a relationship between FGF-23, hemoglobin, phosphate, and transferrin saturation level with RLS. Logistic regression analysis used to see the most dominant factor of all. **Conclusion** This study conclude that increase in FGF-23 levels can increase the risk of RLS. However, FGF-23 is not the most dominant risk factor for RLS in regular hemodialysis patients.

Keyword: Fibroblast Growth Factor-23, Hemodialysis, Restless Legs Syndrome

Abstrak. *Latar Belakang: Restless Legs Syndrome (RLS) merupakan salah satu gangguan tidur yang paling sering dijumpai pada pasien dialysis. Pada penelitian ini, kami ingin mengeksplorasi beberapa penanda gangguan tulang dan mineral terutama fibroblast growth factor-23 (FGF-23) dan hubungannya dengan RLS pada pasien hemodialisis reguler. Metode: Penelitian cross sectional ini melibatkan 71 responden dengan penyakit ginjal kronis yang sudah menjalani hemodialisis rutin di Rumah Sakit Haji Adam Malik Medan. Status RLS pada pasien ini dievaluasi sesuai dengan International Restless Leg Syndrome Study Group (IRLSG) melalui wawancara dan pemeriksaan laboratorium FGF-23, hemoglobin (Hb), besi serum (SI), total iron binding capacity (TIBC), saturasi transferrin (TSAT), serum ferritin, kalsium (Ca) dan tingkat fosfat (P). Hasil: Dari semua subjek penelitian, 26 responden (34,6%) didiagnosis dengan RLS. Hasil analisis bivariat menunjukkan bahwa ada hubungan antara FGF-23, hemoglobin, fosfat, dan tingkat saturasi transferrin dengan RLS. Analisis regresi logistik digunakan untuk melihat faktor yang paling dominan dari semuanya. Kesimpulan: Penelitian ini menyimpulkan bahwa peningkatan*

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kadar FGF-23 dapat meningkatkan risiko RLS. Namun, FGF-23 bukan faktor risiko paling dominan untuk RLS pada pasien hemodialisis reguler.

Kata Kunci: *Fibroblast Growth Factor-23, Hemodialisis, Restless Legs Syndrome*

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1 Introduction

Hemodialysis (HD) still become the main renal replacement therapy aside from peritoneal dialysis (PD) and renal transplants in most countries in the world [1]. Hemodialysis (HD) aims to eliminate the symptoms of uremia that occur in Chronic Kidney Disease (CKD) patients. However, various complications can occur during HD [2]. Patients with regular hemodialysis can experience a variety of complaints that can directly affect the patient's quality of life and health.(3) Restless Legs Sydrome (RLS) is one of the most common sleep disturbance problems in dialysis patients with a prevalence of up to 20% in patients with CKD [3]. Patients undergoing HD who experienced RLS, had a higher mortality rate than patients without RLS (32.3% vs 14.5%; p <0.04) with Hazard Ratio of 1.39; 95% CI 1.08-1.79 [3].

Although the diagnosis of RLS can be established in a simple way by using questionnaires, this disorder is often ignored.(4) A decrease in the prevalence of RLS in patients who have received kidney transplantation (4% vs 11%; P <0.001) provides an illustration that the kidney disease itself plays a role in the occurrence of RLS [3].

There have been limited studies concerned on FGF-23, a marker of Bone and Mineral Disorder in Chronic Kidney Disease (BMD-CKD), and RLS. The connection between iron metabolism with Bone and BMD-CKD related to RLS has been previously studied by Neves et al. in [4]. Although they cannot prove the relationship between FGF-23 and the factors associated with iron metabolism, however, they found a correlation between several sign of bone and mineral disorders and iron metabolism with RLS. Patients with RLS have high phosphate levels, increased FGF-23 levels of more than > 2000 RU/mL, vitamin D deficiency, increased PTH levels and lower transferrin saturation [4]. However, the pathogensesis of anemia and phosphate in correlation with the incidence of RLS with FGF-23 remain unclear. This study aims to determine the relationship of FGF-23 with RLS in regular hemodialysis patients.

2 Research Methods

This study is an analytic observational study with cross sectional design. Patients who had hemodialysis at Haji Adam Malik Hospital Medan in May - July 2019 and met the inclusion criteria; patients with CKD who had undergone hemodialysis for more than 3 months and were 18 years old, were included in the study. Hospitalized patients, or patients with infections (chronic and severe), had malignancy, had drug or alcohol abuse, patients with neurological disorders (eg stroke), patients with myalgia, venous static, arthritis, leg cramps, or foot discomfort due to

position and stomping habits, patiens with NYHA IV congestive heart disease and having incomplete data, they are all excluded from the study.

Sampling was done by using consecutive sampling technique, in this technique all subjects who came in sequence and met the selection criteria were included in the study until the required number of samples met. This study involved 71 respondents.

Patients who were willing to participate in this study were asked to give their written consent (informed consent) to take part in research. This research had been approved by the Ethics Commission of The Faculty of Medicine, Universitas Sumatera Utara (No: 442/TGL/KEPK FK USU-RSUP HAM/2019). Data of age, sex, and duration of hemodialysis were obtained from medical records. History of blood transfusions and use of drugs such as erythropoietin, iron supplementation, phosphate binders and gabapentin were noted. RLS was diagnosed by interviewing the patients according to the IRLSSG (International Restless Legs Syndrome Study Group) criteria. If the patient meets the four diagnostic criteria, the interview will continue to assess the RLS degree according to the International Restless Legs Syndrome Scale (IRLS) which has been validated in English and translated into Indonesian by the University of North Sumatra Language Center. Subsequent to interview, a biochemical examination consisting of FGF-23, hemoglobin, serum iron, total iron binding capacity (TIBC), ferritin serum, calcium, and phosphate from the taken blood samples was conducted. FGF-23 examination was conducted using the enzyme linked immunosorbent assay (ELISA) double-sandwich from Qayee Biochemicals with a limit of 15.6-2000 pg/ml. Other biochemical tests were conducted according to the recommended inspection standards.

Data were analyzed using the SPSS-21 application. Univariate data was analyzed to determine the frequency distribution. Categorical variables were presented with the number or frequency (n) and percentage (%) and numerical variables were presented with the mean and standard deviation for normally distributed data, whereas numerical data that were not normally distributed were presented with the median. The independent variables studied were FGF-23, hemoglobin (Hb), serum iron (SI), total iron binding capacity (TIBC), transferin saturation (TSAT), ferritin, calcium (Ca) and phosphate (P) with RLS as the dependent variable.

Statistical analysis were performed by using *t*-test for independent and dependent variables with normally distributed numeric and categorical data types, and *the Mann-Whitney U test* for data that is not normally distributed. Chi square test is used to compare the independent variable and the dependent variable both of which have categorical data types. If there were some requirements that were not fulfilled in *the Chi-Square test*, *the Fisher Exact Test* will be conducted. A value of $p < 0.05$ was considered statistically significant.

3 Results

This study was conducted at the Haji Adam Malik Hospital Medan involving 71 respondents who had regular HD. The mean age of respondents was 53.0 ± 11.04 years dominated by male by 42 people (59.2%). Comorbid diseases mostly found were DM by 13 people (18.3%) and hypertension by 51 people (71.8%). Complications observed in this study were Restless Leg Syndrome (RLS), experienced by 26 people (36.6%) with the majority of patients having moderate degrees by 21 people (80.8%) followed by severe degrees by 3 people (11.5%) and mild degrees by 2 people (7.7%). Respondents with RLS had a higher mean age than respondents without RLS (57.27 ± 11.130 vs. 53.02 ± 11.042). The age distribution of < 40 years old experienced less RLS but did not show statistically significant results (p=0.492). Based on sex, women experienced more RLS than men (55.2% vs. 31.0%), but were also not statistically significant (p=0.233). Neither DM nor hypertension showed a statistically significant difference in RLS status (p=0.879 vs. p=0.359) (Table 1).

Table 1 Characteristics Distribution of Patients Based on Status of RLS in Regularly HD Patients

Variables	**Status of RLS**		P-Value	OR (95%CI)
	Yes n =26	**No n= 45**		
Age (Years)	57.27 ± 11.130	53.02 ± 11.042	0.492	1.5 (0.27 - 8.34)
< 40	2 (28.6 %)	5 (71.4 %)		
≥ 40	24 (37.5 %)	40 (62.5 %)		
Sex			0.233	1.8 (0.68 - 4.84)
Male	13 (31.0 %)	29 (69.0 %)		
Female	13 (44.8 %)	16 (55.2 %)		
Comorbid Disease				
DM			0.879	0.9 (0.26 - 3.14)
Yes	5 (38.5 %)	8 (61.5 %)		
No	21 (36.2 %)	37 (63.8 %)		
Hypertension			0.359	1.6 (0.57 - 4.70)
Yes	17 (33.3 %)	34 (66.7 %)		
No	9 (45.0 %)	11 (55.0 %)		

Notes : DM: *Diabetes Mellitus*; HD: *Hemodialysis*; Hb = *Hemoglobin*; Ca = *Calcium*; P = *Phosphate*; FGF-23 = *Fibroblast Growth Factors*; SF = *ferritin serum*; SI = *Serum Iron*; ST = *Tranferin Saturation*; TIBC = *Total Iron Binding Capacity* RLS: *Restless Leg Syndroms.*

Most of the respondents with RLS have Hb levels of>10 (48.6%) (p=0.028). Respondents with Hb levels of <10 have 3.079 times risk for experiencing RLS [OR 95% CI (1.109 – 8.852)]. Respondents with Ca levels of > 9.5 suffering RLS were found more in numbers compared to respondents with Ca levels of ≤ 9.5 (41.9% vs. 28.6%) but it did not show statistically significant (p = 0.286). Respondents with phosphate levels > 5.5 suffering RLS higher compared to respondents with phosphate levels ≤5.5 (47.4% vs. 24.2%) which was statistically significant (p = 0.044). Respondents who had a phosphate levels of > 5.5 had 2.813 times risk for experiencing RLS [OR 95% CI = 2.813 (1.0-7.8)]. This study found that respondents with RLS having FGF-

23 levels > 319.5 are more than respondents with FGF-23 levels of ≤ 319.5 (48.6% vs. 25.0%) which showed statistically significant results (p = 0.039). Respondents who have a FGF-23 levels of > 319.5 have 2.883 times risk for experiencing RLS [OR 95% CI = 2.883 (1.0 - 7.7)]. This study also found that most respondents with RLS have higher Serum Feritin levels, which is ≥ 200, compared with respondent with SF <200 (37.5% vs. 33.3%) but was not statistically significant (p = 0.766). Respondents with RLS having ST levels of > 39.3 were more in number than respondent with ST levels of ≤ 39.3 (48.7% vs. 21.9%) which showed statistically significant results (p = 0.039). Respondents who have an ST levels of > 39.3 have 3,393 times risk for experiencing RLS [OR 95% CI = 3.3993 (1.2 - 9.7)] (Table 2).

Table 2 Characteristics Distribution of Patients Based on Status of RLS in Regularly HD Patients

Variables	**Status of RLS**		**p**	**OR 95%(CI)**
	Yes n=26	**No n=45**		
Hb (g/dL)			0.028*	3.079 (1.109 – 8.852)
< 10	18 (48.6%)	19 (51.4%)		
≥ 10	8 (23.5%)	26 (76.5%)		
Ca (mg/dL)			0.256	1.80 (0.6 – 4.9)
≤ 9.5	8 (28.6%)	20 (71.4%)		
> 9.5	18 (41.9%)	25 (58.1%)		
P (mg/dL)			0.044*	2.813 (1.0-7.8)
≤ 5,5	8 (24.2%)	25 (75.8%)		
> 5,5	18 (47.4%)	20 (69.2%)		
FGF-23 (RU/mL)			0.039*	2.883 (1.0 – 7.7)
≤ 319.5	9 (25.0%)	27 (75.0%)		
> 319.5	17 (48.6%)	18 (51.4%)		
SF (ng/mL)			0.766	1.20 (0.4 – 3.9)
< 200	5 (33.3%)	10 (66.7%)		
≥ 200	21 (37.5%)	35 (62.5%)		
TSAT (%)			0.019*	3.393 (1.2-9.7)
≤ 39.3	7 (21.9%)	20 (78.1%)		
> 39.3	19 (48.7%)	25 (51.3%)		

Notes : *(p < 0,05); Mean ± SD (Standard of Deviation); Hb = *Hemoglobin*; Ca = *Calcium*; P = *Phosphate*; FGF-23 = *Fibrolast Growth Factors*; SF = *ferritin serum;* TSAT = *Tranferin Saturation*

From the bivariate analysis, more than one statistically significant variable was found in the respondent's RLS status, which was FGF-23, transferrin saturation, phosphate and hemoglobin level. To get the most dominant risk factor affecting RLS status in regular HD patients, these variables were included in the multiple logistic regression test analysis. This analysis showed that FGF-23 was not a dominant risk factor for RLS status, but Hb levels was. Hb levels of <10 have a 3.613 risk for having RLS [OR = 3.613, 95% CI (1.172 – 11.138)] which was statistically significant with p value of = 0.025(Table 3).

Table 3 Logistic Regression Test Analysis As Risk Factor Towards Status Of RLS

Variables	OR	95% *Confident Interval*		*P-Value*
		Lower	**Upper**	
P > 5.5	3.056	0.106	1.010	0.052
ST≤ 39.32	3.069	1.001	9.407	0.050
Hb < 10	3.613	1.172	11.138	0.025*

Notes : Hb = *Hemoglobin*; Ca = *Calcium*; P = *Phosphate*; FGF-23 = *Fibrolast Growth Factors*; SF = *Ferritin Serum*; TSAT = *Tranferin Saturation;* p < 0.05*; OR = *Odds Ratio*.

4 Discussion

In this study, of 71 people who were on regular hemodialysis twice a week, 26 of them (36.6%) experienced RLS. Based on RLS data in America, RLS was found in 2.5-15% of the American population and around 2-5% in India and other Asian countries [7]. The quite varied prevalence in various regions may be caused by differences in race, culture, socioeconomic status and availability of health facilities [8]. Restless Leg syndrome or also known as Wills Ekbom Disease (WEB) is a neurological disease with various complaints and degrees of morbidity. The last few years, various studies have been carried out to study factors related to RLS. In Indonesia alone there is not much data about RLS.

In the general population, the RLS ratio is 2:1 in women compared to men [7]. In this study, the percentage of RLS in females was higher than males (55.2% vs. 31.0%) but did not show statistically significant results (p = 0.233). This is consistent with studies by Wali et al in [6] in Saudi and Neves et al in [4] who did not find any difference in the prevalence of RLS between male and female hemodialysis patients.

In this study, the age of respondents with RLS was older than non-RLS but was not statistically significant. RLS can be divided into primary and secondary RLS. The primary RLS has unknown cause while the secondary RLS is generally associated with neurological disorders, iron deficiency and kidney disorders. The prevalence and severity of the degree of RLS that increases with age leads to the degeneration process playing a role in the occurrence of RLS [6,9].

Diabetes mellitus and hypertension were the main etiology of CKD in all developed countries and in many developing countries [10]. Data from the Indonesian Renal Registry (2017) shows that hypertension is still the most common comorbid disease in CKD patients undergoing hemodialysis in Indonesia with (36%) and followed by diabetes (29%) [11]. This study is also consistent with study conducted by Muzasti et al in 2018 in Medan, Indonesia, where the majority of subjects who experienced CKD were men as many as 61.8% and also suffering from comorbid hypertension by 75% [12]. In line with this study, hypertension is the most common disease suffered by 51 respondents (71.8%) and DM in 13 respondents (18.3%). This study found that patients with RLS having more hypertension than DM as comorbid disease (38.5% vs. 33.3%). Neither DM nor hypertension showed a statistically significant difference in RLS status (p = 0.879

vs. p = 0.359). This is in line with the study of Kim et al that did not find any difference in RLS status in patients with DM and patients with hypertension [9]. Both can cause kidney damage and anemia which is one of the risk factors of RLS but pathophysiologically, both DM and hypertension were not related to RLS [13].

Most of respondents with RLS have Hb levels of <10 compared with Hb levels of >10 (48.6% vs. 23.5%), which showed statistically significant results (p = 0.028). In the bivariate analysis it can also be seen that Hb levels <10 g/dL increase the risk for RLS by 3.079 times [OR 95% CI = 3.079 (1.09 - 8.552)]. Based on logistic regression analysis it was found that Hb level was the most dominant risk factor for RLS status, where Hb levels of <10 had a 3.613 times risk for having RLS [OR = 3.613, 95% CI (1.172 – 11.138)] which was statistically significant with a p value of = 0.025. Molnar et al in [14] observation of 992 kidney transplant patients showed lower hemoglobin levels and iron deficiency in RLS patients were found in renal dialysis patients (p <0.05) compared to controls. Araujo et al in [15] study showed lower hemoglobin levels in RLS patients (p <0.05).

In renal anemia, in addition to erythropoietin deficiency as the main cause, other contributing factors were iron deficiency. Therefore, before administering therapy (erythropoiesis stimulating agent / ESA), assessment of iron status in patients with chronic kidney disease must be done first [16]. The relationship between iron metabolism and dopamine transmission has been demonstrated, where iron deficiency causes a decrease in dopamine D2 receptor density in the striatum and nucleus accumbens accompanied by a decrease in the density of dopamine transporters [4]. This mechanism is similar to that which occurs in dialysis patients, because iron deficiency is commonly associated with RLS [6]. According to Filho et al in [17], the condition of uremia with its wide-ranging effects on cell physiology affects iron uptake in the brain barrier and causes iron deficiency in tissues cerebral as found in primary RLS. Iron deficiency in the brain causes a decrease in dopaminergic function which then encourages hyperexcitability and causes sensory stimulation and spontaneous motor movements in RLS [6].

At present, treatment of RLS include iron supplementation and administration of dopaminergic agonist [4]. Serum iron was higher in respondents without RLS compared to respondents with RLS (86.22 ± 19.676 vs. 79.77 ± 16.834) whereas TIBC levels were higher in respondents with RLS compared to respondents without RLS (217.42 ± 15.214 vs. 213 , 54 ± 14.058), but the SI and TIBC levels did not show statistically significant results with RLS status (p = 0.166 vs. p = 0.291). Transferrin saturation, which is the result from division of serum iron and TIBC, has a higher mean in patients without RLS compared to respondents with RLS (39.74 ± 8.76 vs. 36.92 ± 7.52). This is in line with serum ferritin levels where respondents with RLS have a higher value than respondents without RLS (477.94 ± 326.704 vs. 453.99 ± 309.875), where respondents with RLS have more percentages with SF ≥ 200 levels compared to SF value <200 (37.5% vs. 33.3%) but did not show statistically significant results (p = 0.766). However, in general the

characteristics of all respondents had relatively sufficient iron status with serum iron levels of more than 65 µg / dL, transferrin saturation of more than 30%, and ferritin levels with a median of 340 ng / mL. Even so, there were 34.6% of respondents who suffering from RLS.

Bone and mineral disorders in BMD-CKD patients were now being put forward as one of the new factors since there is an association of hyperphosphatemia and vitamin D deficiency with RLS in uremic patients and in the general population [4]. Dopamine mediates phosphate excretion in the kidneys. In theory, any dopaminergic nerve disorder can cause hyperphosphatemia [8]. However, the relationship between the two is still uncertain. In this study, the mean phosphate levels in RLS respondents was higher than respondents without RLS (5.49 ± 0.655 vs. 5.41 ± 0.582). Respondents who had a phosphate level of > 5.5 had a 2.813 times risk for experiencing RLS [OR 95% CI = 2.813 (1.0-7.8)].

FGF-23 is increased in dialysis patients and is associated with hyperphosphatemia [18]. FGF-23 is a marker of impaired phosphate metabolism [4]. Therefore, FGF-23 is associated with RLS. The mean value of FGF-23 in RLS respondents was higher compared to respondents without RLS (499.85 ± 470.650 vs. 312.9 ± 76.180) where there are more respondents with RLS who had FGF-23 levels of > 319.5 compared to patients with FGF- levels of ≤319.5 (48.6% vs. 25.0%) which showed statistically significant results (p = 0.039). The same conditions were found in this study population. Respondents who have FGF-23 levels> 319.5 have a 2.883 times risk to experience RLS [OR 95% CI = 2.883 (1.0 - 7.7)].

In individuals with normal kidney function, iron deficiency can stimulate production and clearance of intact FGF-23 which results in terminal FGF-23 fraction. In CKD patients, there is a disruption to the clearance, so that almost all FGF-23 is intact [4]. In multivariate analysis of this study, FGF-23 was ultimately not a dominant risk factor for RLS. This may be due to the fact that respondents have relatively sufficient iron content and so is the mean phosphate value which almost hit the target value according to KDIGO guidelines given the iron and phosphate status is closely related to FGF-23. On the other hand, the direct effect of FGF-23 on RLS cannot be ruled out. Increased FGF-23 is associated with hematopoiesis [18]. FGF-23 is proven to be one of the causes of renal anemia [19]. The inhibition of the FGF-23 activity will stimulate erythropoiesis, overcome anemia and iron deficiency in rats with CKD [19]. In a previous study by Neves et al. in [4], FGF-23 was associated with RLS where with an increase in FGF-23 levels cause a 3.16 times risk of experiencing RLS (95% CI 3.16 (2.13-4.18) which was statistically significant (p < 0.0001).

Another marker of BMD-CKD is calcium. In this study, mean calcium levels were not too different between patient with and without RLS (9.77 ± 0.78 vs. 9.61 ± 0.76). There are more patients with RLS who had calcium levels of > 9.5 than respondents with calcium levels of <9.5 mg / dL (41.9% vs. 28.6%), but there were no statistically significant differences. Neither in the study of Wali et al. in [6] nor by Araujo et al. in [15] found a significant difference in calcium

levels and RLS in hemodialysis patients. The role of calcium cannot be concluded and with a larger sample, it is expected to answer the existing problem.

Limitation of this study is that this study was only conducted in one place (single-center). Hemodialysis patients with decreased kidney function result in the emergence of various complications can cause bias in the study. In addition, lack of data on drug use such as benzodiazepines, gabapentin, tricyclic antidepressants, calcium channel blockers whose role cannot be separated from RLS. Finally, this study uses a cross-sectional design, therefore a causal relationship cannot be proven. Research into factors related to RLS in hemodialysis patients is still needed and it is recommended to use samples from various hemodialysis (multi-center) centers.

5 Conclusion

From the research that has been done, it can be concluded that there is a correlation between FGF-23 levels with RLS in regular hemodialysis patients where an increase in FGF-23 levels is 2.883 times risk for having RLS. Based on bivariate analysis, besides FGF-23, hemoglobin, phosphate and transferrin saturation levels have a relationship with Restless Legs Syndrome (RLS). Based on multivariate analysis, hemoglobin (Hb <10) is the dominant risk factor of RLS.

RLS is increased and is often found in patients with regular hemodialysis, but often undiagnosed. There is no data on the prevalence of hemodialysis in Indonesia. Therefore, screening of health facilities that provide renal replacement therapy needs to be done, especially hemodialysis.

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