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Research article

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Relationship between fibroblast growth factor 23 level and vitamin D status in chronic kidney disease: A cross-sectional study

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Abstract. *Complications stemming from chronic kidney disease (CKD) significantly contribute to increased morbidity and mortality rates. During the early stages of CKD, a delicate balance in homeostasis and mineral regulation is maintained largely due to fibroblast growth factor 23 (FGF-23). However, as kidney function declines, there is a detrimental effect on vitamin D synthesis. Understanding the dynamics of FGF-23 levels in relation to vitamin D status is crucial for assessing kidney function and its implications on hormonal regulation, calcium homeostasis, and cardiovascular health. Therefore, this study aimed to scrutinize and comprehend the correlation between FGF-23 levels and vitamin D status in patients afflicted with CKD.*

Methods. A cross-sectional study was undertaken at Dr. Wahidin Sudirohusodo Hospital in Makassar, South Sulawesi, Indonesia, involving 58 patients diagnosed with stage 3-5 non-dialysis CKD. Relationships between FGF-23 level with vitamin D level status and CKD stage were analyzed by chi-square and Kruskal-Wallis test.

Results. The FGF-23 levels, with a median of 100 pg/mL as the designated cut-off, exhibit significance concerning the levels of vitamin D (p=0.003). The average values of FGF-23 in cases of deficiency and insufficiency are markedly elevated when compared to patients with sufficient vitamin D levels (p=0.016). The significance of FGF-23 levels becomes more prominent with advancing CKD stages (p=0.06).

Conclusions. FGF-23 is a related marker with vitamin D deficiency in patients with CKD but is inconsistent in stage development and not an independent factor.

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Взаємозв'язок між концентрацією фактора росту фібробластів 23 і статусом вітаміну D у хворих на хронічну хворобу нирок: перехресне дослідження

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Резюме. *Ускладнення хронічної хвороби нирок (ХХН) значною мірою сприяють підвищенню захворюваності та смертності. На ранніх стадіях ХХН баланс у мінеральній регуляції підтримується в основному завдяки фактору росту фібробластів 23 (ФРФ-23). Однак, зі зниженням функції нирок відбувається значні зміни синтезу вітаміну D. Розуміння динаміки рівня ФРФ-23 у зв'язку зі статусом вітаміну D має вирішальне значення для оцінки функції нирок та її наслідків для гормональної регуляції, гомеостазу кальцію та серцево-судинної системи. Таким чином, це дослідження мало на меті визначити зв язок між концентрацією ФРФ-23 та статусом вітаміну D у пацієнтів з ХХН.*

Методи. Перехресне дослідження було проведено в лікарні доктора Вахідіна Судірохусодо в Макассарі, Південний Сулавесі, Індонезія, за участю 58 пацієнтів з ХХН III-V стадій, які не отримували ниркову замісну терапію. Взаємозв'язки між концентраціями ФРФ-23 та вітаміну D залежно від стадії ХХН аналізували за допомогою хі-квадрат і тесту Краскела-Уолліса.

Результати. Концентрація ФРФ-23 із середнім значенням 100 пг/мл, як визначеним пороговим значенням демонструє статистично зна щодо рівнів вітаміну D (p=0,003). Середні значення FGF-23 у випадках дефіциту та недостатності помітно підвищені порівняно з пацієнтами з достатнім рівнем вітаміну D (p=0,016). Значущість рівня FGF-23 стає більш помітною з прогресуючими стадіями ХХН (p=0,06).

Висновки. ФРФ-23 є спорідненим маркером з дефіцитом вітаміну D у пацієнтів з ХХН, але не залежить від стадії ХХН та не є незалежним фактором.

Ключові слова: *фактор росту фібробластів 23, вітамін D, хронічна хвороба нирок.*

Introduction. Complications arising from chronic kidney disease (CKD) contribute to heightened morbidity and mortality among affected individuals, stemming from the systemic dysfunction of the kidneys [1] culminating in end stage renal disease (ESRD. The regulation of key minerals, notably potassium and sodium, is intricately linked to the management of blood pressure. Simultaneously, the control of minerals, particularly calcium and phosphate, plays a pivotal role in the regulation of ionic compartments [2]. Notably, in the initial stages of kidney damage, homeostasis and mineral balance remain undisturbed owing to the presence of the hormone phosphatonin, exemplified by fibroblast growth factor 23 (FGF-23), which is synthesized in osteocytes [3, 4].

Furthermore, diminished kidney function adversely impacts the synthesis of vitamin D, a process facilitated by various organs including the skin, intestines, and kidneys. This impairment arises from a reduction in the synthesis of 1-α hydroxylase, responsible for converting calcidiol to calcitriol [5, 6]. The utilization of FGF-23 as a parameter for renal function can provide insights into hormonal vitamin D-calcium homeostasis activity and cardiovascular risk [7-9].

The decrement in kidney function precipitates concurrent disruptions in mineral regulation and vitamin D synthesis. However, current research on the alterations in vitamin D levels attributable to FGF-23 regulation remains somewhat limited [10, 11]. Due to this background, we aim to scrutinize and comprehend the correlation between FGF-23 and vitamin D levels in patients afflicted with CKD.

Material and methods. ***Subjects and data collection.*** A cross-sectional study was conducted at Dr. Wahidin Sudirohusodo Hospital in Makassar, South Sulawesi, Indonesia, from August to December 2023. The study was approved by the Research Ethics Commission of the Faculty of Medicine, Hasanuddin University (No: 596/UN4.6.4.5.31/PP36/2023). The study involved 58 patients diagnosed with stage 3-5 non-dialysis CKD. Demographic (age, sex) and clinical data (body mass index or BMI, estimated glomerular filtration rate (eGFR) stage, diabetes mellitus type 2 status, hypertension status, FGF-23 level, vitamin D level, phosphate level, and calcium level) were collected by collecting medical record data from patients who were examined in Clini-

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cal Laboratory of Dr. Wahidin Sudirohusodo Hospital Laboratory. FGF-23 level is measured by enzyme-linked immunosorbent assay (ELISA) kit by Immutopics® on the same day as another laboratory test with a total of 15 ml of vein blood in ethylenediamine tube.

Statistical analysis. Baseline data (age, sex, body mass index or BMI, estimated glomerular filtration rate (eGFR) stage, diabetes mellitus type 2 status, hypertension status, FGF-23, vitamin D, phosphate, and calcium levels) were descriptively summarized. The cut-off value of FGF-23 was analyzed by the median value of FGF-23 and vitamin D level was categorized by reference in Kidney Disease Outcome Quality Initiative (KDOQI) (vitamin D deficiency: less than 20 ng/mL; an insufficiency: 21-29 ng/mL; sufficiency: more than 30 ng/mL) [12]. The cut-off of FGF-23 is 100 pg/mL due to kidney function to reabsorb phosphate [13]. The differences between the studied groups were analyzed by chi-square or Kruskal-Wallis test, as appropriate. Factors associated with vitamin D status were assessed utilizing multiple regression analysis. Significant values were determined at $p<0.05$. All statistical analyses were performed using the Statistical Program for Social Sciences (IBM SPSS 24, IL, USA).

Results. The findings of this study reveal that the predominant age group comprised individuals younger than 60 years, demonstrating an average age of 49.5 ± 12.7 years. The distribution between males and females was equitable, and the majority of participants exhibited a non-obese profile, characterized by an average BMI of 22.9 ± 3.9 kg/m^2. In terms of FGF-23 levels among CKD patients in this investigation, a range spanning from 12.3 to 2013.2 pg/mL was observed, with an average value of 262.2 ± 374.9 pg/mL. Concurrently, the vitamin D levels in the CKD patient cohort exhibited a distribution ranging from 4.8 to 46.5 ng/mL, with an average concentration of 20.2 ± 9.7 ng/mL, as detailed in Table 1.

Table 1

Characteristics of the study cohort

Variable	N (%)	Min	Max	Mean (SD)
Age (years)		18	65	49.5 (12.7)
<60 years	44 (75.9)			
≥60 years	14 (24.1)			
Sex				
Female	29 (50.0)			
Male	29 (50.0)			
BMI		15	35	22.9 (3.9)
Obese	18 (31.0)			
Non-obese	40 (69.0)			
CKD				
Stage 3	19 (32.8)			
Stage 4	19 (32.8)			
Stage 5 non-HD	20 (34.5)			
Diabetes mellitus				
Yes	23 (39.7)			
No	35 (60.3)			
Hypertension				
Yes	28 (48.3)			
No	30 (51.7)			
Phosphate		2.2	13.5	4.8 (2.3)
Increase	21 (36.2)			
Normal	37 (63.8)			
Calcium		5.4	9.8	7.9 (0.9)
Decrease	49 (84.5)			
Normal	9 (15.5)			
FGF-23 (pg/ml)		12.3	2013.2	262.2 (374.9)
<100 pg/mL	29 (50.0)			
≥100 pg/mL	29 (50.0)			
Vitamin D level/status		4.8	46.5	20.2 (9.7)

Continuation of Table 1

Variable	N (%)	Min	Max	Mean (SD)
Deficiency	30 (51.7)			
Insufficiency	19 (32.8)			
Sufficiency	9 (15.5)			

Abbreviations: N, subjects; SD, standard of deviation; BMI, body mass index; CKD, chronic kidney disease; ND, non-dialysis; FGF-23, fibroblast growth factor 23.

Notably, the average values of FGF-23 in cases of deficiency and insufficiency are markedly elevated when compared to patients with sufficient vitamin D levels, as delineated in Table 2.

Table 2

Vitamin D and FGF-23 levels

Vitamin D	n	FGF-23		p-value
		Mean	SD	
Deficiency	30	237.1	330.1	0.016*
Insufficiency	19	396.9	478.3	
Sufficiency	9	61.5	29.3	

Kruskall-Wallis Test, *significant

CKD stage, FGF-23 level, sex, and diabetes mellitus status were associated with vitamin D levels (Table 3).

Table 3

Variable associated with vitamin D level

Variable	Vitamin D level			p-value
	Deficiency	Insufficiency	Sufficiency	
CKD Stage				
Stage 3	6 (31.6)	9 (47.4)	4 (21.1)	0.038*
Stage 4	11 (57.9)	3 (15.8)	5 (26.3)	
ND Stage 5	13 (65.0)	7 (35.0)	0 (0.0)	
FGF-23 level				
<100 pg/mL	14 (48.3)	6 (20.7)	9 (31.0)	0.003*
≥100 pg/mL	16 (55.2)	13 (44.8)	0 (0.0)	
Sex				
Female	22 (75.9)	6 (20.7)	1 (3.4)	0.001*
Male	8 (27.6)	13 (44.8)	8 (27.8)	
Age				
<60 years-old	25 (56.8)	14 (31.8)	5 (11.4)	0.224
≥60 years-old	5 (35.7)	5 (35.7)	4 (28.6)	
BMI				
Obese	9 (50.0)	6 (33.3)	3 (16.7)	0.980
Non-obese	21 (52.5)	13 (32.5)	6 (15.0)	
Diabetes mellitus				
Yes	18 (78.3)	3 (13.0)	2 (8.7)	0.004*
No	12 (34.3)	16 (45.7)	7 (20.0)	

Chi-square test *significant.

Abbreviations: BMI, body mass index; CKD, chronic kidney disease; ND, non-dialysis; FGF-23, fibroblast growth factor 23.

Male sex without diabetes mellitus was associated with vitamin D levels (Table 4).

Table 4

Adjusted FGF-23 level in variable associated with vitamin D level

Variable	FGF-23 Level	Vitamin D level			p-value
		Deficiency	Insufficiency	Sufficiency	
CKD Stage					
Stage 3	<100 pg/mL	6 (40.0)	5 (33.3)	4 (26.7)	0.060
	≥100 pg/mL	0 (0.0)	4 (100.)	0 (0.0)	
Stage 4	<100 pg/mL	6 (50.0)	1 (8.3)	5 (41.7)	0.110
	≥100 pg/mL	5 (71.4)	2 (28.6)	0 (0.0)	
ND Stage 5	<100 pg/mL	2 (100.0)	0 (0.0)	0 (0.0)	#
	≥100 pg/mL	11 (61.1)	7 (38.9)	1 (0.0)	
Sex					
Female	<100 pg/mL	10 (76.9)	2 (15.4)	1 (7.7)	0.460
	≥100 pg/mL	12 (75.0)	4 (25.0)	0 (0.0)	
Male	<100 pg/mL	4 (25.0)	4 (25.0)	8 (50.0)	0.008*
	≥100 pg/mL	4 (30.8)	9 (69.2)	0 (0.0)	
Diabetes mellitus					
Yes	<100 pg/mL	8 (80.0)	0 (0.0)	2 (20.0)	0.086
	≥100 pg/mL	10 (76.9)	3 (23.1)	0 (0.0)	
No	<100 pg/mL	6 (31.6)	6 (31.6)	7 (36.8)	0.020*
	≥100 pg/mL	6 (37.5)	10 (62.5)	0 (0.0)	

*significant; #can not be analyzed;

Abbreviations: ND, non-dialysis; FGF-23, fibroblast growth factor 23.

According to the results of multiple regression analysis, the variables that exert influence on vitamin D levels in CKD patients include sex, the presence of diabetes mellitus, and calcium levels (Table 5).

Table 5

Multiple regression analysis

Variable	p-value
FGF-23	0.61
Age	0.18
Sex	0.00*
BMI	0.58
CKD stage	0.98
Diabetes mellitus status	0.01*
Hypertension	0.88
Phosphate	0.85
Calcium	0.00*

*Significant.

Discussion. Patients in this study generally fall below the age of 60, and the gender distribution is evenly balanced. This observation suggests a relatively rapid progression of CKD [**14, 15**]. Diabetes mellitus and hypertension emerge as the predominant comorbidities among the majority of patients. The primary focus of this investigation points to the factors influencing vitamin D levels in CKD patients. Notably, the levels of vitamin D, phosphate, and FGF-23 exhibit variations across different groups, indicating the intricate interplay between FGF-23 levels and other factors in the regulation of vitamin D homeostasis.

FGF-23 levels, as per research findings, exhibit variability in CKD patients. Broadly, an elevation in FGF-23 accompanies a decline in kidney function due to the regulation of phosphate and the intake of vitamin D (1.25-dihydrocholecalciferol). The research outcomes reveal generally low vitamin D levels, particularly in groups with higher FGF-23 levels within the insufficiency category. However, an overall increase is observed in CKD patients with both deficiency and insufficiency. This phenomenon stems from the body's adaptive response to maintain blood phosphate levels. During the compensation phase, patients with CKD cannot tolerate phosphate deficiency, leading to increased production of FGF-23 alongside vitamin D analogs. Additionally, dietary factors can impact FGF-23 levels. The deterioration of kidney conditions causes a subsequent decrease in FGF-23 production after the compensation phase due to a negative feedback mechanism [**10, 16, 17**].

Despite its significance with a median value of 100 pg/mL, FGF-23 does not independently influence vitamin D levels. Analysis reveals that FGF-23 lacks independent effects, a condition influenced by factors such as deficiency tolerance, CKD severity, comorbidities, and the impact of FGF-23 inhibition on vitamin D metabolism. Consequently, FGF-23 cannot be singularly employed as a determining factor for assessing vitamin D levels [**18-21**].

Prior research underscores the inconsistent indication of worsening kidney function by FGF-23, rendering it influential as a parameter for vitamin D levels [**22**]. Some results indicate an inverse relationship, with higher FGF-23 levels correlating with an overall deterioration in kidney function, impacting erythropoiesis, hormonal regulation, and mineral homeostasis [**23, 24**].

According to research findings, the stage of CKD does not exhibit a significant correlation with vitamin D levels. This observation is intricately linked to vitamin D homeostasis, which is influenced by various factors such as malnutrition, gastrointestinal disorders, dietary restrictions, and proteinuria. It is noteworthy that while some previous studies have demonstrated a noteworthy increase in this association, those investigations were conducted on larger and more homogeneous populations [**24-27**].

In contrast, the results diverge concerning FGF-23 levels, which exhibit a significant increase in CKD patients as the disease stage progresses. This phenomenon is attributed to a diminished ability of the kidneys to respond to FGF-23 signals, leading to the accumulation of FGF-23 in the serum. Although the escalation in FGF-23 levels is noticeable at each stage, the increment is not uniform, thus failing to reflect specific kidney function. It's worth noting that non-renal mechanisms may also contribute to an increase in FGF-23 levels [**28, 29**].

The age of patients with CKD does not exert a significant influence on vitamin D levels. This circumstance is shaped by factors such as cutaneous vitamin D production, urinary loss of vitamin D, and a diet deficient in vitamin D [**30, 31**]. Prior research has indicated a connection between age and vitamin D levels, although this association is often mediated by the synthesis and response of parathyroid hormone. Notably, the impact of age on vitamin D levels may vary depending on the study design, particularly when examining specific groups with a baseline vitamin D deficiency [**24, 32, 33**].

Gender significantly influences vitamin D levels, with a direct correlation observed in males exposed to sunlight [**34**]. This phenomenon is linked to the regulation of vitamin D, which is affected by decreased menopausal status. Consequently, gender exerts an independent effect on vitamin D levels in CKD patients, albeit the precise mechanism remains unclear [**35-37**].

Body mass index (BMI) does not exhibit a significant impact on vitamin D levels in CKD patients. This outcome is influenced by the greater synthesis of parathyroid hormone in individuals with higher body fat composition, inversely proportional to lean mass, as adipose tissue serves as a storage site for vitamin D [**38, 39**]. The variability in BMI effects may stem from challenges in estimating the true BMI in CKD patients due to water retention.

The CKD stage does not yield a significant effect on vitamin D levels in CKD patients. This circumstance is tied to the kidney's diminished ability to hydroxylase secondary vitamin D into its active form, a process that also experiences decline. Dietary vitamin D intake affects plasma vitamin D levels and imposes negative feedback on the parathyroid hormone, yet other factors can still influence vitamin D levels in CKD patients [**40-42**].

In contrast, diabetes mellitus status has a notable effect on vitamin D levels in CKD patients, driven by a cycle of podocyte damage. Vitamin D deficiency is associated with podocyte damage, disrupting phosphate and calcium homeostasis, and triggering negative feedback on parathyroid hormone production. The ongoing decline in kidney function further diminishes the effect of vitamin D synthesis, perpetuating the cycle of damage [**43-46**]. Diabetes mellitus emerges as an independent factor linked to vitamin D deficiency in CKD patients.

Hypertension, however, does not significantly impact vitamin D levels in CKD patients. While previous studies have suggested a relationship between hypertension and vitamin D levels, potentially mediated by the regulation of the renin-angiotensin-aldosterone system (RAAS), variations in outcomes may result from antihypertensive consumption, tolerance mechanisms in longstanding CKD, or the presence of other comorbidities such as diabetes [**47-49**].

Phosphate levels do not exert a significant effect on vitamin D levels in CKD patients. This is attributed to vitamin D homeostasis being influenced by parathyroid hormone, which also regulates phosphate and calcium. Additionally, phosphate retention is influ-

enced by klotho, apart from FGF-23 [**40-51**]. Variability in phosphate data may be influenced by population-specific factors, limiting its ability to describe the pattern of association between phosphate levels and vitamin D.

In contrast, calcium demonstrates a significant effect on vitamin D levels in CKD patients. This underscores the regulatory role of calcium, influenced by vitamin D intake and feedback from the kidneys to retain calcium through parathyroid hormone. Vitamin D also functions in an autocrine manner in the RAAS and contributes to calcium retention [**25, 26, 52, 53**].

There is a lot of study limitations. This study employs a cross-sectional design, thereby precluding the depiction of a causal relationship between FGF-23 and vitamin D based on CKD biology. Measurements of other factors such as calcium and parathyroid hormone were not conducted quantitatively but rather semi-quantitatively. Additionally, this study does not provide insight into the duration of CKD, which may impact FGF-23 levels.

Conclusions. FGF23 is a related marker with vitamin D deficiency in patients with CKD but is inconsistent in stage development and not an independent factor. Instead, indicators such as gender, diabetes mellitus status, and calcium level are more reliable markers for identifying vitamin D deficiency in this patient population. These factors can serve as valuable indicators when assessing and monitoring vitamin D levels in patients with CKD.

Ethics statement. This study was approved by the Research Ethics Commission of the Faculty of Medicine, Hasanuddin University (No: 596/UN4.6.4.5.31/PP36/2023). All patients provided informed consent before participating in the study.

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Data availability statement. The data that support the findings of this study are not openly available due to reasons of sensitivity and are available from the corresponding author upon reasonable request. Data are located in controlled access data storage at the Department of Internal Medicine, Faculty of Medicine, Hasanuddin University.

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