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CORRELATION BETWEEN GLOMERULAR FILTRATION RATE AND CALCIUM AND PHOSPHATE LEVELS IN PREDIALYSIS CHRONIC KIDNEY DISEASE PATIENTS AT PROF. DR. I.G.N.G. NGOERAH GENERAL HOSPITAL

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ABSTRACT

Background: Chronic Kidney Disease (CKD) is a disease that occurs due to structural and functional alterations in the kidney for more than 3 months. Glomerular Filtration Rate (GFR) is the best parameter used to measure kidney function. The decline in kidney function leads to changes in mineral levels, particularly calcium and phosphate.

Objectives: To determine the correlation between GFR and calcium and phosphate levels in pre-dialysis CKD patients at Prof. dr. IGNG Ngoerah General Hospital Denpasar.

Methods: Analytical observational design with a cross-sectional study on 50 pre-dialysis CKD patients who were treated at Prof. dr. IGNG Ngoerah General Hospital Denpasar in 2021-2022, fulfilling inclusion and exclusion criteria. The correlation between GFR and calcium and phosphate levels was analyzed using Spearman correlation test.

Results: The patients were mostly males (64%), with a median age of 59.5 (21-70) years, and the majority in stage 5 (70%). The median GFR value was 6.57 (1.78-56.86) mL/minute/1.73m², the mean calcium level was 8.22 ± 0.83 mg/dL, and the median phosphate level was 4.94 (2.85-12.07) mg/dL. The Spearman correlation result between GFR and calcium levels was not significant (r = 0.131, p = 0.365) and between GFR and phosphate was significant (r = -0.527, p = 0.000).

Conclusions: There was no significant correlation between GFR and calcium levels, but there was a significant moderate correlation between GFR and phosphate levels in pre-dialysis CKD patients in this study.

Keywords : Glomerular Filtration Rate., Calcium., Phosphate

INTRODUCTION

Chronic kidney disease is a worldwide public health concern that requires high treatment costs.[1] Chronic kidney disease is defined as an irreversible disease in the structure or function of the kidneys that lasts for more than three months.[2] Hypertension and Diabetes Mellitus are two of several major risk factors for CKD.[3] The disease is often asymptomatic, so undetected by patients and clinicians in the early stages.[2]

Between 8-16% of people worldwide are affected by CKD and the prevalence continues to increase.[2] According to the Global Burden of Disease (GBD) data from 1990 to 2016, CKD patients globally 86.95% increase in prevalence and 98.02% increase in mortality.[4] The prevalence of CKD varies across Europe, from 3.3% to 17.3% in Norway and Germany.[5] In Asia, the prevalence of CKD also varies significantly, ranging from 7.0% to 34.3% in South Korea and Singapore.[6] However, the characteristic data of CKD in low- and middle-income countries (LMICs) is inadequate due to the paucity of community-based studies, uneven assessments for kidney function, and less standardized methodologies.[7] According to the Basic Health Research (*Riset Kesehatan Dasar*) data from 2018, the prevalence of CKD in Indonesia among people aged 15 and above was 713,783 individuals, with a percentage of 0.38%, while the prevalence of CKD in Bali was 12,092 individuals, with a percentage of 0.44%.[8]

According to the Kidney Disease: Improving Global Outcomes (KDIGO) 2020 guidelines, classification of CKD based on GFR divided into 5 stages: stage 1 with GFR ≥90 mL/minute/1.73m^2, stage 2 with GFR 60-89 mL/minute/1.73m^2, stage 3a with GFR 45-59 mL/minute/1.73m^2, stage 3b with GFR 30-44 mL/minute/1.73m^2, stage 4 with GFR 15-29 mL/minute/1.73m^2, and stage 5 with GFR <15 mL/minute/1.73m^2.[9] Decline in kidney function marked by a decrease of GFR leads to alteration of mineral metabolism, Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD), that is estimated to occur in 86% of CKD patients.[10] Minerals affected by CKD-MBD include calcium and phosphate. Calcium has functions in muscle contraction, blood clotting, nerve signal transmission, hormone secretion, and cell adhesion, while phosphate is involved in energy metabolism, bone development, signaling pathways, and serves as component in phospholipids and nucleic acids.[11]

In early-stage CKD with GFR >60 mL/minute/1.73m², reduced phosphate excretion and decreased calcitriol synthesis lead to a condition of hyperphosphatemia and hypocalcemia. However, parathyroid hormone (PTH), which stimulates calcitriol synthesis and fibroblast growth factor-23 (FGF-23), has a role in increasing phosphate excretion to restore calcium and phosphate to normal levels. As GFR decreases, these compensatory mechanisms fail to maintain calcium and phosphate at normal levels.[12]A study indicates that an increase in phosphate levels begins when GFR is <60 mL/minute/1.73m². Another study shows that at GFR <30 mL/minute/1.73m², most patients exhibit hyperphosphatemia, followed by calcitriol deficiency resulting in hypocalcemia.[13] However, another study suggests that calcium and phosphate levels remain normal at GFR 60 mL/minute/1.73m² due to compensatory mechanisms involving PTH.[14] Therefore, patients diagnosed with CKD require regular screening of calcium and phosphate levels to take appropriate intervention measures.[2]

The purpose of this study is to determine the correlation between GFR and calcium and phosphate levels in pre-dialysis CKD patients, so that expected to be used for further research development, provide education on the importance of evaluating calcium and phosphate levels, and maintaining patient mineral levels in a normal range to prevent and minimize complications associated with CKD.

METHODS

Analytical observational design with a cross-sectional study was conducted and has been ethically approved [2023.01.1.0066] by the Research Ethics Commission Unit, Faculty of Medicine, Udayana University. The research sample was taken from medical records of pre-dialysis CKD patients undergoing treatment at Prof. dr. IGNG Ngoerah General Hospital in Denpasar from 2021 to 2022, that fulfill the inclusion and exclusion criteria. The inclusion criteria included patients who had been diagnosed with CKD, had not yet undergone dialysis, and were between 18 and 70 years old. The exclusion criteria included patients with insufficient medical records. The sample was collected from eligible patients using consecutive sampling, where patients who met the criteria were included sequentially with a total of 50 patients involved in this study. Data taken from medical records included GFR, calcium levels, phosphate levels, age, and gender of the patients. All collected data were analyzed descriptively, with the results presented in the form of mean ± Standard Deviation (SD) if the data is normally distributed and in median (minimum-maximum) if the data is not normally distributed. The normality of the data was assessed using the Shapiro-Wilk test, where it is considered to follow a normal distribution if the p-value is >0.05. The correlation analysis between GFR and calcium and phosphate levels was conducted using the Spearman correlation test (with a significance level of $\alpha = 0.05$).

RESULTS

The characteristics of pre-dialysis CKD patients in this study are presented in **Table 1**. Of the 50 participants, the median age was 59.5 years, with a range of 21-70 years old, and the majority were male (n = 32; 64%). According to the CKD stages defined by KDIGO 2020, the majority of the patients were in stage 5 CKD (n = 35 patients; 70%).

Table 1. Characteristics of Pre-Dialysis CKD Patients

Characteristics	n (%)	Median (min-max)
Age (years)		59,5 (21-70)
Sex		
Male	32 (64)	
Female	18 (36)	
Staging of CKD		
Stage 3a (45-59)	1 (2)	
Stage 3b (30-44)	1 (2)	
Stage 4 (15-29)	13 (26)	
Stage 5 (<15)	35 (70)	

Note: CKD= chronic kidney disease

The characteristics of GFR value, calcium levels, and phosphate levels are presented in **Table 2**. The median value of GFR (CKD-EPI) is 6.57 mL/minute/1.73m², with the lowest value being 1.78 mL/minute/1.73m² and the highest value being 56.96 mL/minute/1.73m². The calcium levels had a mean ± Standard Deviation (SD) of 8.22 ± 0.83 mg/dL. The distribution of calcium levels in the 50 patients was 11 patients categorized having normal calcium levels and 39 patients categorized having low calcium levels. There were no high calcium levels observed in this study. The median phosphate level was 4.94 mg/dL, with the lowest value being 2.85 mg/dL and the highest value being 12.07 mg/dL. The distribution of phosphate levels in the 50 patients was 15 patients categorized having normal phosphate levels and 35 patients categorized having high phosphate levels. There were no low phosphate levels observed in this study.

Table 2. GFR Value, Calcium Levels, and Phosphate Levels of Pre-Dialysis CKD Patients

Parameter	Mean ± SD	Median (min-max)	Normality test (p-value)*
GFR (mL/minute/ 1.73m²)		6,57 (1,78-56,96)	<0.05
Calcium levels (mg/dL)	8,22 ± 0,83		>0.05
Phosphate levels (mg/dL)		4,94 (2,85-12,07)	<0.05

Note: *Based on Shapiro-Wilk test, GFR= glomerular filtration rate

The correlation between GFR value and calcium and phosphate levels are presented in **Table 3**. The correlation analysis results using the Spearman correlation test indicated a very weak and non-significant positive correlation between GFR value and calcium levels, with a correlation coefficient of r = 0.131 (p = 0.365). The interpretation of the strength of the correlation (r) is as follows: very weak with a range of 0.0 to <0.2, weak with a range of 0.2 - <0.4, moderate with a range of 0.4 - <0.6, strong with a range of 0.6 - <0.8, and very strong with a range of 0.80-1.00.[15] The correlation analysis results using the Spearman correlation test showed a moderate and significant negative correlation between GFR value and phosphate levels, with a correlation coefficient of r = -0.527 (p = 0.000). This means that as GFR values decrease, phosphate levels tend to increase.

Tabel 3. Correlation Between GFR Value and Calcium and Phosphate Levels of Pre-Dialysis CKD Patients

Correlation	Correlation coefficient (r)	p-value
GFR with calcium	0.131	0.365
GFR with phosphate	**-0.527****	**0.000****

Note: **Significant, GFR= glomerular filtration rate

DISCUSSION

Our study consisted of 50 pre-dialysis CKD patients who met the inclusion and exclusion criteria. A study by Anthoni et al. had 100 samples, while Kovesdy et al. and Levin et al. used 1,243 and 1,814 samples. In our study, the age of the subjects ranged from 21 to 70 years, with the median age of the subjects being 59.5 years, and the majority in the 60-70 years age group. These results are consistent with the findings of Anthoni et al., Kovesdy et al., and Levin et al.[16–18] Data from the Ministry of Health (*Kementerian Kesehatan*) (2018) also reveals that CKD patients in Indonesia with age category 65-74 years are the highest group, accounting for approximately 0.82% of the total Indonesian population.[8] The decline in kidney function begins around the ages of 30-40 years and accelerates after the age of 50-60 years, with an average decline in GFR of about 1% per year, influenced by conditions such as hypertension, obesity, and diabetes.[19–21]

The majority of the subjects in our study were male (64%). Similar results were also found in the studies by Lim et al. and Anthoni et al., where the proportion of male patients was higher than females.[16,22] Data from the Ministry of Health (2018) also indicate a higher proportion of male CKD patients compared to females, with a ratio of 6:5.[8] However, a different result was obtained in the study by Levin et al., where the proportion of females was larger, at around 52%.[18] There is no clear understanding of the relationship between gender and the occurrence of CKD due to the influence of various complex factors. A study by Carrero et al. explains that the difference in CKD incidence is suspected to be due to biological factors, with women having a protective effect from estrogen, while men have a pro-inflammatory and pro-apoptotic effect from testosterone on the kidneys.[23] Health factors such as poor lifestyle and comorbidities also contribute to an individual's risk of developing CKD. A study by García et al. states that the occurrence of CKD is also influenced by economic conditions, occupation, residential location, educational level, access to healthcare services, and environmental sanitation.[24]

In our study, the distribution of patients according to CKD stages based on KDIGO 2020 was uneven, with the majority of patients being in stage 5, which is GFR <15 mL/minute/1.73m². The GFR value calculated using the CKD-EPI formula had a median of 6.57 mL/minute/1.73m², ranging from 1.78 to 56.96 mL/minute/1.73m². The fact that our study location, Prof. dr. IGNG Ngoerah Central Hospital Denpasar, serves as a referral center for CKD patients from across Denpasar. Therefore, the number of end-stage CKD patients was higher compared to other CKD stages.

Of our 50 subjects, 11 subjects (22%) had normal calcium levels (8.8-10.4 mg/dL), while 39 subjects (78%) had calcium levels below the normal range (<8.8 mg/dL). The mean ± Standard Deviation (SD) calcium level in this study was 8.22 ± 0.83 mg/dL. A study by Anthoni et al. reported a similar median calcium value of 8.6 mg/dL, while studies by Lim et al. and Kovesdy et al. found higher average calcium levels of 9.2 mg/dL and 9.4 mg/dL, respectively.[16,17,22] On the other hand, 15 subjects (30%) had normal phosphate levels (2.5-4.5 mg/dL), while 35 subjects (70%) had phosphate levels above the normal range (>4.5 mg/dL). The phosphate levels in this study had a median of 4.94 mg/dL, ranging from 2.85 to 12.07 mg/dL. However, the studies by Kovesdy, Anderson, et al. and Lim et al. reported lower average phosphate levels of 3.9 mg/dL.[22,25]

Based on CKD stage grouping, the distribution of mean calcium levels shows a decreasing trend with the decline in GFR value. Specifically, from 9.3 mg/dL in stage G3a, 9.0 mg/dL in G3b, 8.44 ± 0.60 mg/dL in G4, to 8.08 ± 0.89 mg/dL in G5. However, our study indicates a very weak and non-significant positive correlation between GFR value and calcium levels, with a correlation coefficient of r = 0.131 (p = 0.365). Our finding differs from a previous study by Janmaat et al., which divided the correlation between GFR and calcium levels in each CKD stage. That study showed a significant positive correlation between GFR value and calcium levels in stages 3b-5, but no significant correlation between GFR value and calcium levels in stage 3a CKD patients.[26] However, research by Levin et al. stated that calcium levels remain relatively stable until GFR drops below <20 mL/minute/1.73m².[18] The decrease in kidney function leads to a reduction in calcium levels in the body. As GFR decreases, there is an increase in the production of FGF-23, which reduces the synthesis of 1α-hydroxylase and calcitriol, thereby decreasing calcium absorption in the intestines.[27] A limitation of our study was did not consider other factors that influence calcium levels such as calcium and vitamin D supplementation intake. Research by Levin et al. explained that 25% of their research subjects consumed calcium supplements and 40% consumed multivitamins.[18] Therefore, the results in our study are suspected to be due to supplementation and diet that were not controlled and may also be due to differences in the number of research subjects and the uneven distribution of subjects. Our study included 50 pre-dialysis CKD patients with an uneven distribution of subjects, with the majority in stage 5, which is GFR <15 mL/minute/1.73m² (70%).

Our study found a moderate and significant negative correlation between GFR value and phosphate levels, with a correlation coefficient of r = -0.527 (p = 0.000). Based on CKD stage grouping, the distribution of median phosphate levels also shows an increasing trend with the decrease in GFR value.

Specifically, from 3.86 mg/dL in stage G3a, 3.27 mg/dL in G3b, 4.59 (3.45-6.03) mg/dL in G4, to 5.72 (2.85-12.07) mg/dL in G5. Several previous studies have also shown a significant correlation between a decrease in GFR value and an increase in phosphate levels, as demonstrated by Kovesdy, Anderson, et al. and Levin et al.[18,25] The decrease in kidney function leads to a reduction in phosphate excretion, resulting in the accumulation of serum phosphate.[27] Increased phosphate levels stimulate the production of PTH and FGF-23 to decrease the expression of Npt2a and Npt2c in the proximal renal tubules, thereby increasing phosphate excretion.[11] However, the continuous decrease of calcium levels and increase of phosphate levels stimulate sustained PTH production, contributing to secondary hyperparathyroidism.[27] Secondary hyperparathyroidism can lead to various complications such as cardiovascular disorders and calciphylaxis, which is the accumulation of calcium in blood vessels, fat, and skin tissues.[28,29] Hypocalcemia and hyperphosphatemia, which trigger secondary hyperparathyroidism, are major issues in the management of CKD patients. So that the administration of active vitamin D supplements and phosphate-binding medications in advanced CKD patients can help maintain calcium and phosphate concentrations within the normal range.[2]

CONCLUSION

In conclusion, there was no significant correlation between GFR and calcium levels, but there was a significant moderate correlation between GFR and phosphate levels in pre-dialysis CKD patients in this study. Further study is needed to discover other variables that correlate with GFR and to obtain a stronger correlation between GFR value and calcium levels. In this study, it was observed that a decrease in GFR is correlated with an increase in phosphate levels, which can be taken into consideration in the management of CKD-MBD.

REFERENCES

1. Kahdina M, Mardiana N, Fauziah D. Levels of Hemoglobin, Leukocytes, and Platelets of Chronic Kidney Disease Patients Undergoing Hemodialysis in Surabaya. Biomol Heal Sci J. 2018;1(1):29.
2. Chen TK, Knicely DH, Grams ME. Chronic Kidney Disease Diagnosis and Management: A Review. JAMA - J Am Med Assoc. 2019;322(13):1294–304.
3. Maharani, Pramana IBP, Oka AAG. Studi Meta-Analisis Hipertensi Dan Diabetes Melitus Sebagai Faktor Risiko. J Med Udayana. 2022;11(9):49–53.
4. Xie Y, Bowe B, Mokdad AH, Xian H, Yan Y, Li T, et al. Analysis of the Global Burden of Disease study highlights the global, regional, and national trends of chronic kidney disease epidemiology from 1990 to 2016. Kidney Int [Internet]. 2018;94(3):567–81. Available from: https://doi.org/10.1016/j.kint.2018.04.011
5. Brück K, Stel VS, Gambaro G, Hallan S, Völzke H, Ärnlöv J, et al. CKD prevalence varies across the European general population. J Am Soc Nephrol. 2016;27(7):2135–47.
6. Liyanage T, Toyama T, Hockham C, Ninomiya T, Perkovic V, Woodward M, et al. Prevalence of chronic kidney disease in Asia: A systematic review and analysis. BMJ Glob Heal. 2022;7(1):1–9.
7. Romagnani P, Remuzzi G, Glassock R, Levin A, Jager KJ, Tonelli M, et al. Chronic kidney disease. Nat Rev Dis Prim. 2017;3.
8. Kemenkes. Riset Kesehatan Dasar (RISKESDAS). Badan Penelit dan Pengemb Kesehat. 2018;
9. KDIGO. KDIGO 2020 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease. Kidney Int. 2020;98(4):S1–115.
10. Waziri B, Duarte R, Naicker S. Chronic Kidney Disease–Mineral and Bone Disorder (CKD-MBD): Current Perspectives. Int J Nephrol Renovasc Dis. 2019;12:263–76.
11. Blaine J, Chonchol M, Levi M. Renal control of calcium, phosphate, and magnesium homeostasis. Clin J Am Soc Nephrol. 2017;10(7):1257–72.
12. Webster AC, Nagler E V., Morton RL, Masson P. Chronic Kidney Disease. Lancet [Internet]. 2017;389(10075):1238–52. Available from: http://dx.doi.org/10.1016/S0140-6736(16)32064-5
13. Ferrè S, Neyra JA, Moe OW. Calcium, Phosphate, and Magnesium Metabolism in Chronic Kidney Disease. Chronic Ren Dis. 2019;(Cvd):661–79.
14. Felsenfeld AJ, Levine BS. Pathophysiology of Calcium, Phosphorus, and Magnesium in Chronic Kidney Disease [Internet]. Chronic Renal Disease. Elsevier Inc.; 2017. 391–405 p. Available from: http://dx.doi.org/10.1016/B978-0-12-411602-3.00033-0
15. Dahlan MS. Statistik untuk Kedokteran dan Kesehatan deskriptif, Bivariat, dam Multivariat. 6th ed. Jakarta: Salemba Medika; 2017.
16. Anthoni A, Supriyadi R, Fatimah SN. Serum Calcium Levels in Chronic Kidney Disease Patient Stratified By Body Mass Index. Althea Med J. 2019;6(2):55–9.
17. Kovesdy CP, Kuchmak O, Lu JL, Kalantar-Zadeh K. Outcomes associated with serum calcium level in men with non-dialysis-dependent chronic kidney disease. Clin J Am Soc Nephrol. 2017;5(3):468–76.
18. Levin A, Bakris GL, Molitch M, Smulders M, Tian J, Williams LA, et al. Prevalence of abnormal serum vitamin D, PTH, calcium, and phosphorus in patients with chronic kidney disease: Results of the study to evaluate early kidney disease. Kidney Int. 2017;71(1):31–8.
19. Glassock RJ, Winearls C. Ageing and the glomerular filtration rate: truths and consequences. Trans Am Clin Climatol Assoc. 2017;120:419–28.
20. Nojima J, Meguro S, Ohkawa N, Furukoshi M, Kawai T, Itoh H. One-year eGFR decline rate is a good predictor of prognosis of renal failure in

patients with type 2 diabetes. Proc Japan Acad Ser B Phys Biol Sci. 2017;93(9):746–54.
21. Jamshidi P, Najafi F, Mostafaei S, Shakiba E, Pasdar Y, Hamzeh B, et al. Investigating associated factors with glomerular filtration rate: Structural equation modeling. BMC Nephrol. 2020;21(1):1–8.
22. Lim LM, Kuo HT, Kuo MC, Chiu YW, Lee JJ, Hwang SJ, et al. Low serum calcium is associated with poor renal outcomes in chronic kidney disease stages 3-4 patients. BMC Nephrol. 2017;15(1):1–9.
23. Carrero JJ, Hecking M, Chesnaye NC, Jager KJ. Sex and gender disparities in the epidemiology and outcomes of chronic kidney disease. Nat Rev Nephrol [Internet]. 2018;14(3):151–64. Available from: http://dx.doi.org/10.1038/nrneph.2017.181
24. García GG, Iyengar A, Kaze F, Kierans C, Padilla-Altamira C, Luyckx VA. Sex and gender differences in chronic kidney disease and access to care around the globe. Semin Nephrol. 2022;42(2):101–13.
25. Kovesdy CP, Anderson JE, Kalantar-Zadeh K. Outcomes associated with serum phosphorus level in males with non-dialysis dependent chronic kidney disease. Clin Nephrol. 2017;73(4):268–75.
26. Janmaat CJ, Van Diepen M, Gasparini A, Evans M, Qureshi AR, Ärnlöv J, et al. Lower serum calcium is independently associated with CKD progression. Sci Rep. 2018;8(1):1–9.
27. Tang PK, Geddes RF, Jepson RE, Elliott J. A feline-focused review of chronic kidney disease-mineral and bone disorders — Part 2: Pathophysiology of calcium disorder and extraosseous calcification. Vet J [Internet]. 2021;275:105718. Available from: https://doi.org/10.1016/j.tvjl.2021.105718
28. Westphal SG, Plumb T. Calciphylaxis. StatPearls [Internet] [Internet]. 2023; Available from: https://www.ncbi.nlm.nih.gov/books/NBK519020/
29. Muppidi V, Meegada SR, Rehman A. Secondary Hyperparathyroidism. StatPearls [Internet] [Internet]. 2023; Available from: https://www.ncbi.nlm.nih.gov/books/NBK557822/