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CORRELATION BETWEEN GLOMERULAR FILTRATION RATE WITH CALCIUM-PHOSPHATE PRODUCT LEVELS IN CHRONIC KIDNEY DISEASE

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Abstract

Background: In chronic kidney disease (CKD) patients, calcium and phosphate homeostasis disorders occur. Decreased renal function will result in a decrease in phosphate excretion. In stage 3b CKD, the kidney is no longer able to compensate for phosphate burden adequately, and as a result hyperphosphatemia arises. The decline in renal function also causes calcitriol level to decline, which will be followed by undermined calcium absorption in the intestine. The application of calcium-phosphate binders and calcitrion in CKD will normalize phosphate and

calcium levels in the blood. However, it can bring about hypercalcemia episodes. This research attempted to figure out the relationship between glomerular filtration rate (GFR) and calcium-phosphate (CaxP) product in CKD.

Methods: This is an observational study with a cross-sectional approach that involved 80 CKD subjects, distributed into stage 3 (n = 20), stage 4 (n = 20), non-dialysis stage 5 (n = 20), and dialysis stage 5 (n = 20) CKD patients at Wahidin Sudirohusodo Hospital and Unhas Hospital of Makassar from April to August of 2021. Phosphate levels were measured using ELISA kit (Immutopics). The results of the statistical tests conducted would be considered significant if $p < 0.05$.

Results: The CaxP product averages across stages were as follows: stage 3: 32.82 ± 10.77 mg^2/dL^2; stage 4: 32.95 ± 8.11 mg^2/dL^2; non-dialysis stage 5: 47.93 ± 21.28 mg^2/dL^2; and dialysis stage 5: 45.58 ± 24.74 mg^2/dL^2. The figures above showed that stage 3 was not significantly different from stage 4 ($p = 0.986$), but it was significantly different from non-dialysis stage 5 ($p = 0.009$). A significant difference was also found between stage 4 and non-dialysis stage 5 ($p = 0.009$). The proportion of subjects with high CaxP product (CaxP $\geq$ 55 mg^2/dL^2) in CKD stage 3 was 5% (n = 1), in CKD stage 4 5% (n = 1), in non-dialysis stage 5 25% (n = 5), and in dialysis stage 5 35% (n = 7).

Conclusion: The lower the GFR the greater the CaxP product. The proportion of subjects with high CaxP product increased with the decrease in GFR.

Keywords: Phosphate; Calcium-Phosphate Product; Glomerular Filtration Rate; Chronic Kidney Disease

1. Introduction

Chronic kidney disease (CKD) is among the world's high-cost health issues. About 1 in 10 in the global population has been identified to suffer from CKD.[1] The disease has a direct role in the increases of morbidity and mortality. Global Burden of Disease (GBD) data in 2015 indicated that approximately 1.2 million people died from renal failure, up by 32% from the figure in 2005.[2]

In CKD patients, calcium and phosphate homeostasis disorders occur. The decline in renal function will cause the α1-hydroxylase expression in the proximal tubule undermined, which will decrease the calcitriol level and calcium absorption rate in the intestine. The decreased nephron mass in CKD can drive calcium and phosphate excretion to fall. Meanwhile, an increase in serum phosphate stimulates fibroblast growth factor 23 (FGF-23) production by osteocytes and osteoblasts. FGF-23 reduces calcitriol production, which also reduces phosphate and calcium absorption in the intestine, causing hypocalcemia.[3,4]

In stage 3b CKD, the concentration of phosphate begins to rise, showing that the compensation mechanism is no longer adequate to preserve the phosphate balance and to prevent hyperphosphatemia.[4,5] The application of calcium-phosphate binders and calcitriol in CKD normalizes phosphate and calcium levels in the blood. However, it can bring about hypercalcemia episodes and contribute to a calcium-phosphate (CaxP) product increase.[6] This research attempted to figure out the relationship between glomerular filtration rate (GFR) and calcium-phosphate (CaxP) product in chronic kidney disease. Various studies as those conducted by Ganesh et al.,[7] Block et al.,[8] Yasin et al.,[9] Menon et al.,[10] and Slawuta et al.[11] reported that CaxP product would increase with the decrease in GFR.

2. Methods and Patients

2.1 Research design

This research is an observational cross-sectional study that was conducted at Dr. Wahidin Sudirohusodo Hospital and Universitas Hasanuddin Hospital of Makassar.

2.2 Research population and sample

The population of this research was stage 3, 4, and 5 CKD patients who were undergoing dialysis and non-dialysis therapies on outpatient and inpatient medication at RSWS since April 2021. The inclusion criteria were CKD patients aged 18–65, not on phosphate decreasing therapy, calcitriol therapy, and calcium supplementation, and willing to participate in the research as shown by signed informed consent.

2.3 Data analysis

Data analysis comprised a descriptive method and some statistical tests. The descriptive method aimed to gather general information on the research sample. The statistical tests used included Kruskal-Wallis test, Mann-Whitney test, and Spearman's rho test. The results of the statistical tests would be considered significant if $p < 0.05$. The data were analyzed with SPSS 25.

3. Results

This research involved 80 CKD subjects, consisting of 42 males (52.5%) and 38 females (47.5%). The age range was 18–65, and the average age was 48.28 ± 12.65. The phosphate level was in the range 1.5–11.4 mg/dL, with an average of 5.04 ± 2.58 mg/dL. Meanwhile, the calcium level was in the range 5.4–11.4 mg/dL, with an average of 8.08 ± 1.05 mg/dL (Table 3). Diet effect was not analysed in this research.

In this research, the CaxP product average in each CKD stage was as follows: stage 3: 32.82 ± 10.77 mg^2/dL^2; stage 4: 32.95 ± 8.11 mg^2/dL^2, non-dialysis stage 5: 47.93 ± 21.28 mg^2/dL^2; and dialysis stage 5: 45.58 ± 24.74 mg^2/dL^2 (Table 1). This shows that there was an increase in CaxP level with every increase in CKD stage; the higher the CKD stage the higher the CaxP level ($p = 0.011$).

Tabel 1. Average calcium-phosphate product concentration by CKD Stage

Stage	CaxP Product Concentration	
	N	Mean±SD (mg^2/dL^2)
3	20	32,82 ± 10,77
4	20	32,95 ± 8,11
5 Non-dialysis	20	47,93 ± 21,28
5 Dialysis	20	45,58 ± 24,74

**Kruskal-Wallis test,* p=0,011

The proportion of subjects with high CaxP product (CaxP product > 55 mg^2/dL^2) in each stage was found in this research as follows: stage 1: 35% (n = 1); stage 4: 5% (n = 1); non-dialysis stage 5: 25% (n = 5); and dialysis stage 5 (n = 7) (Tabel 2). This shows that the proportion of subjects with high CaxP product increased with the increase in CKD stage. From means comparison it was found that non-dialysis stage 5 was significantly higher than stage 3 (p = 0.009), dialysis stage 5 was higher than stage 3 (p = 0.025), non-dialysis stage 5 was higher than stage 4 (p = 0.009), and dialysis stage 5 was higher than stage 4 (p = 0.026).

Table 2. The proportions of CaxP product subjects in different CKD stages

CKD Stage		CaxP Product Group		Total
		<55	≥55	
3	n %	19 95%	1 5%	20 100,0%
4	n %	19 95%	1 5%	20 100,0%
5 Non-Dialysis	n %	15 75%	5 25%	20 100,0%
5 Dialysis	n %	13 65%	7 35%	20 100,0%
Total	n %	31 82,5%	49 17,5%	80 100,0%

*Uji Chi-square, p= 0,025

4. Discussion

The results of the phosphate level average analysis by CKD stage in this research demonstrated that there was an increase in CaxP level in each increase in CKD stage. The greater the CKD stage the significantly higher the CaxP level (p = 0.011). This finding is in line with the findings of Slawuta et al.[10] and Yasin et al.[9] that, with every increase in CKD stage, the CaxP product will increase.

The finding revealed that CaxP product increased when the CKD stage increased. This mirrored the findings of Wen Ting et al.[11] and Isakova et al.[12] that there was a progressive rise in CaxP product as the CKD stage increased.

In early CKD stage, the phosphate metabolism is already disturbed, but the serum phosphate level will typically be maintained within the normal range by FGF-23 and parathyroid hormone increases to the final stage of the kidney disease. The prevalence of hyperphosphatemia in CKD patients is heightened with the decline in renal function.[3,4] A rise in serum phosphate level occurs upon CKD progression, showing that the phosphate homeostasis compensation mechanism may remain effective up until stage 3a of CKD.[13] In advanced-level CKD (stage 3b), the kidney will no longer be able to compensate for phosphate burden adequately when the eGFR falls below 45 mL/min/1.73 m^2, leading to hyperphosphatemia.[14] The decline in renal function will cause the α1-hydroxylase expression in the proximal tubule undermined, which will decrease the calcitriol level and calcium absorption rate in the intestine. The application of calcium-phosphate binders and calcitrion in CKD will normalize the phosphate and calcium levels in the blood. However, it can bring about hypercalcemia episodes.[6]

5. Conclusion

A decrease in GFR will cause an increase in CaxP product.

Acknowledgements

Limitations of the study

In our observational study, we did not assess phosphate intake in study subjects.

Authors' contribution

RP, HK and SB were the principal investigators of the study. HR, AML, EA and AS were included in preparing the concept and design. HK and SB revisited the manuscript and critically evaluated the intellectual contents. All authors participated in preparing the final draft of the manuscript, revised the manuscript and critically evaluated the intellectual contents. All authors

have read and approved the content of the manuscript and confirmed the accuracy or integrity of any part of the work.

Ethical considerations

The research followed the tents of the Declaration of Helsinki. The Ethics Committee of Hasanuddin University of Medical Sciences approved this study. The institutional ethical committee at Hasauddin University of Medical Sciences approved all study protocols (Recommendation Letter No. 76/UN4.6.4.5.31/PP36/2022, under protocol number UH20110690. Accordingly, written informed consent taken from all participants before any intervention. Additionally, ethical issues (including plagiarism, data fabrication, double publication) were completely observed by the authors.

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