

Association between Albuminuria and Serum Phosphate Levels in Non-Dialysis Stage 3-5 Chronic Kidney Disease Patients

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ABSTRACT

Introduction: Chronic kidney disease (CKD) remains a global burden and catastrophic disease as about 697.5 million people suffering from it in 2017. About 42% of CKD mortality in Indonesia is related to cardiovascular complications. Hyperphosphatemia, a manifestation of chronic kidney disease-mineral bone disorder, could increase the risk of cardiovascular mortality. Albuminuria has been proven to inhibit the compensatory mechanisms for hyperphosphatemia, thereby aggravating this condition. This study was conducted to analyze the association between albuminuria and serum phosphate levels among CKD patients in Dr. Soetomo General Academic Hospital, Surabaya, Indonesia.

Methods: This cross-sectional study used medical records of 129 non-dialysis stage 3-5 CKD patients at the outpatient clinic of Dr. Soetomo General Academic Hospital from March-November 2021. Descriptive analysis was performed on albuminuria, serum phosphate, age, sex, body mass index, comorbid, blood chemistry tests, and CKD stages data. Correlational analysis was conducted using the Spearman Rank test on albuminuria and serum phosphate levels.

Results: The majority of the subjects in this study were male (55.81%); mean age was 55.21±11.99 years; mean BMI was 22.39±2.27 kg/m²; hypertension was found in 65.89% of the patients; mean eGFR was 25.01±16.1 ml/min/1.73 m² and dominated by CKD stage 3-5. The distribution of albuminuria grade was dominated by heavy albuminuria (>300 mg/g) and the mean serum phosphate level was 4.81±1.9 mg/dl. Spearman Rank analysis found a significant positive correlation with weak association strength ($p < 0.001$; $r_s = 0.277$) between albuminuria and serum phosphate levels.

Conclusion: There was a significant positive correlation with weak association strength between albuminuria and serum phosphate levels.

Keywords: Chronic kidney disease; mineral bone disorder; albuminuria; phosphate

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INTRODUCTION

Based on the Global Burden of Disease analysis, there are 697.5 million cases of chronic kidney disease (CKD) globally in 2017, with a global prevalence of 9.1%. CKD also accounted for 1.2 million deaths in 2017 and contributed to 7.6% or 1.4 million deaths from cardiovascular complications (GBD, 2020). In Indonesia, the main cause of CKD mortality is cardiovascular complications, with a percentage of 42% (PERNEFRI, 2018). Hyperphosphatemia, a manifestation of mineral bone disorders in CKD (CKD-MBD), has a prevalence of 55.4% in stage 3-5 CKD patients and could stimulate vascular calcifications, thereby increasing the risk of cardiovascular complications (Vikrant et al., 2016; Hruska et al., 2017).

Recent studies reported that albuminuria, a marker of kidney damage, influenced the progression of CKD-MBD through inhibition of klotho and fibroblast growth factor 23 (FGF23) action, thereby exacerbating hyperphosphatemia and increasing vascular calcifications risk (de Seigneux et al., 2017; de Seigneux et al., 2015). In children with nephrotic syndrome, serum phosphate level was found to be increased, despite the normal glomerular filtration rate (GFR). This

phenomenon indicates the existence of a mechanism other than reduced GFR, that increases serum phosphate levels. The mechanism is albuminuria/proteinuria (de Seigneux et al., 2015).

Proteinuric patients tend to exhibit higher serum phosphate levels and FGF23 with lower 24-hour fractional excretion of phosphate (FEP)/FGF23 ratio compared to non-proteinuric patients (Kim et al., 2020). Correspondingly, patients with higher serum phosphate levels tend to exhibit greater proteinuria, higher FGF23, and lower klotho levels. The FGF23/klotho ratio has a 15.4% effect on the association between proteinuria and serum phosphate levels (Jung et al., 2020).

Both elevated serum phosphate and FGF23 levels have adverse impacts on the progression and complications of CKD. FGF23 reduces vitamin D synthesis to lower serum phosphate levels, but this mechanism leads to vitamin D deficiency. Other adverse impacts of FGF23 are sodium and water retention, hypertension, and cardiac hypertrophy. FGF23 synthesis is regulated by klotho, so the decrease in klotho expression will cause resistance and overproduction of FGF23 (Waziri et al., 2019).

Hyperphosphatemia directly induces a phenotypical change of vascular smooth muscle to the osteoblastic type, thereby increasing the risk of vascular calcification in CKD (Goyal et al., 2021). In addition, hyperphosphatemia also stimulates secondary hyperparathyroidism. This condition leads to decreased bone density and increased fracture risk, a complication known as renal osteodystrophy (Hruska et al., 2017).

Research about albuminuria and serum phosphate levels could bring deeper insight into the influence of both factors on CKD progressivity. Therefore, this study aimed to analyze the relationship between albuminuria and serum phosphate levels among CKD patients in Dr. Soetomo General Academic Hospital, Surabaya, Indonesia.

METHODS

This was a correlational analytical study with a cross-sectional design from medical records of non-dialysis stage 3-5 CKD patients in Dr. Soetomo General Academic Hospital renal-hypertension polyclinic from March-November 2021. Consecutive sampling was performed based on the inclusion criteria: patients aged ≥ 18 years; diagnosed with stage 3-5 CKD; not currently or ever been on dialysis (hemodialysis or CAPD), and not being pregnant. Patients without complete data were excluded.

Information related to albuminuria grade, serum phosphate levels, age, sex, body mass index (BMI), comorbidities, blood chemistry tests, and CKD stages were extracted from the medical record. Based on the KDIGO 2012 albumin to creatinine ratio (ACR) classification, albuminuria grade was classified into normal to mildly increased (<30 mg/g), moderately increased (30-300 mg/g), and severely increased (>300 mg/g) (KDIGO, 2013). Serum phosphate levels were classified based on Dr. Soetomo General Academic Hospital clinical pathology laboratory standards into hypophosphatemia (<2.5 mg/dl), normal (2.5-4.5 mg/dl), and hyperphosphatemia (>4.5 mg/dl).

The age group was classified based on the Republic of Indonesia Ministry of Health 2009 age group classification (Kemenkes, 2019). Nutritional status was classified based on the World Health Organization (WHO) BMI classification for the Asia Pacific (WHO, 2020). The normal value of blood chemistry tests was measured and classified according to Dr. Soetomo General Academic Hospital clinical pathology laboratory standards, which are creatinine (0.6-1.3 mg/dl), BUN (7-18 mg/dl), albumin (3.4-5 g/dl), and calcium (8.5-10.1 mg/dl). CKD stages were classified based on the KDIGO 2012 GFR classification (KDIGO, 2013).

Descriptive analysis was conducted by reporting the mean and standard deviation (SD) for numerical data as well as frequency (n) and percentage (%) for categorical data. Correlation analysis was performed by Spearman Rank test on albuminuria grade and serum phosphate levels. The association was considered significant if $p < 0.05$. Based on the Spearman correlation coefficient (rs), the correlation strength was classified into negligible (0-0.09), weak (0.1-0.39), moderate (0.4-0.69), strong (0.7-0.89), and very strong (0.9-1) (Schober et al., 2018). All data analyzes were performed using Jeffrey's Amazing Statistics Program (JASP) software version 0.16.1.

RESULTS

The baseline characteristics of the patients (n=129) are presented in Table 1. Most of the patients were male (55.81%), elderly (62.02%), and having normal nutritional status (62.79%). The most common comorbid was hypertension (29.46%). Most patients with diabetes mellitus also had hypertension as another comorbid. Other comorbidities in this study were nephrolithiasis, systemic lupus erythematosus, spondylopathy, cellulitis, pyogenic arthritis, psoriatic arthritis, primary gonarthritis, coronary heart disease, hepatitis B, liver cirrhosis, hypothyroidism, polycystic kidney disease, and urogenital neoplasms.

Most of the subjects were in stage 3 (37.21%) and 5 (36.43%) CKD. The distribution of albuminuria grade was dominated by severely increased albuminuria (52.71%). The number of subjects with normal serum phosphate levels and hyperphosphatemia was almost equal, while the mean serum phosphate levels remain in the normal range (2.5-4.9 mg/dl).

The mean serum phosphate levels based on the albuminuria grade are presented in Table 2. Subjects within the normal to mildly increased albuminuria group had the lowest mean serum phosphate levels, while the severely increased albuminuria group had the highest mean serum phosphate levels. Spearman Rank analysis found a significant association between albuminuria and serum phosphate levels ($p < 0.001$) with weak association strength ($rs = 0.277$).

Table 1. Baseline characteristics

	N	%	Mean \pm SD
Sex			
Male	72	55.81	
Female	57	44.19	
Age (years old)			
Teenage (12-25)	4	3.1	
Adult (26-45)	20	15.5	
Elderly (46-65)	80	62.02	55.21 \pm 11.99
Senile (>65)	25	19.38	
Nutritional status (kg/m²)			
Underweight (<18.5)	1	0.77	
Normal (18.5-22.9)	81	62.79	22.39 \pm 2.27
Overweight (23-24.9)	30	23.26	
Obese (≥ 25)	17	13.18	
Comorbidity			
Hypertension	38	29.46	
Diabetes mellitus	4	3.1	
Others	14	10.86	
Hypertension + DM	32	24.8	
Hypertension + others	15	11.63	
DM + others	3	2.32	
None / unidentified	23	17.83	
Blood chemistry tests			
Creatinine (mg/dl)	129		4.41 \pm 4.15
BUN (mg/dl)	127		43.8 \pm 37.22
Albumin (g/dl)	112		3.51 \pm 0.41
Calcium (mg/dl)	128		9.11 \pm 1.29
CKD stages & GFR (ml/min/1.73 m²)			
3A (45-59)	18	13.95	
3B (30-44)	30	23.26	
4 (15-39)	34	26.36	25.01 \pm 16.1
5 (≤ 14)	47	36.43	
Albuminuria grade			
Normal to mildly increased	20	15.51	
Moderately increased	41	31.78	
Severely increased	68	52.71	
Serum phosphate levels			
Hypophosphatemia	4	3.1	
Normal	62	48.06	4.81 \pm 1.9
Hyperphosphatemia	63	48.84	

Table 2. Association between albuminuria and serum phosphate levels

Albuminuria grade	Serum phosphate levels (mg/dl)			r_s (p-value)
	Min	Max	Mean & SD	
Normal to mildly increased (<30 mg/g)	2.43	4.8	3.82±0.64	0.277 (p<0.001)
Moderately increased (30-300 mg/g)	2.1	12.4	4.65±1.72	
Severely increased (>300 mg/g)	1.88	12.4	5.19±2.13	

Note: all tests are one-tailed, for a positive correlation

*Correlation is considered significant if $p < 0.05$

DISCUSSION

Sex, Age, Nutritional Status, and Comorbid Characteristics.

The majority of the subjects in this study were male. Similarly, a study in Bandung reported that 203/308 (53.42%) CKD patients were male (Karim, 2019). Another study in Korea also reported that most of the CKD patients were male, as many as 1160 patients (60.8%) (Kim et al., 2020). The most dominant age group in this study was the elderly, with a mean age of 55.21±11.99 years old. A study in Madiun reported a relatively similar result, that most of the CKD patients were 46-65 years old, as many as 54 (61.4%) of 88 patients (Arianti et al., 2020). Another study in Korea also reported that the mean age of 1909 CKD patients was 53.9±12.1 years (Kim et al., 2020).

Most subjects in this study had normal nutritional status, with an average BMI of 22.39±2.27 kg/m², and were considered normal. A study in Taiwan also reported relatively similar results that 1548/4022 (38.4%) CKD patients had normal nutritional status (Chang et al., 2018). Another study in India reported that the mean BMI of 129 predialysis CKD patients was 24.8±5.5 kg/m² and considered normal according to the nutritional status of the Indian population (Jagadeswaran et al., 2019).

The most common comorbid in this study was hypertension. Diabetes mellitus (DM) became the second most common comorbid, since if the number of patients with DM as either single or multiple comorbid combined, then the result was 39 patients (30.23%). Other comorbid in this study were found to be insignificant in number. This comorbid characteristic was relatively similar to a study on 1463 stage 3-5 CKD patients in Taiwan, where the two most frequent comorbid were hypertension (66.8%) and diabetes mellitus (32.4%) (Lee et al., 2018). Another study on 176 kidney disease patients in Saudi Arabia also revealed the two most common comorbid were hypertension (57.4%) and diabetes mellitus (37.5%) (Ansari et al., 2019).

Albuminuria Grade Distribution and Mean Serum Phosphate Level.

Distribution of the albuminuria grade was dominated by severely increased albuminuria, then moderately increased, and the least is normal or mildly increased. This distribution is relatively similar to a study in 200 CKD patients (Li et al., 2018), but the percentage of severely increased albuminuria in this study was much larger than the percentage in that study. Since this study only involved advanced-stage (3-5) CKD patients and did not involve early-stage patients, then it is reasonable that most of these patients had further kidney damage and greater albuminuria grade (Haider et al., 2021).

The number of subjects with normal serum phosphate and hyperphosphatemia in this study was almost equal. The mean serum phosphate level was 4.81±1.9 mg/dl and classified as normal. These results were similar to a study by Kim et al.

(2020) that reported the mean serum phosphate level of 1909 non-dialysis stage 1-5 CKD patients was 3.7±0.7 mg/dl and classified as normal. The mean serum phosphate level in this study was higher than in that study since this study only involved advanced-stage CKD patients. In these patients, kidneys had further decrease in phosphate excretion, which could surpass the compensatory mechanisms of FGF23 and parathyroid hormone (PTH) (Waziri et al., 2019).

Association between Albuminuria with Serum Phosphate Levels.

This study revealed an increase in the mean serum phosphate level as the albuminuria grade increased. In the group of normal or mildly increased and moderately increased albuminuria, the mean serum phosphate levels were still considered normal. On the contrary, the mean serum phosphate levels of the severely increased albuminuria group were considered hyperphosphatemia. The Spearman Rank analysis also revealed a significant positive association ($p < 0.001$) between albuminuria and serum phosphate levels, but the strength of the association was weak ($r_s = 0.277$).

A previous multinational study of NephroTest data on 1738 CKD patients found similar results that serum phosphate levels were positively and significantly associated with albuminuria (de Seigneux et al., 2015). Another study on 351 CKD patients in Spain also found a similar association between ACR and serum phosphate levels, even after adjusting for GFR, age, and sex (Fernandez-Fernandez et al., 2018).

There are two phosphate excretion factors that have an important role in the association between albuminuria and serum phosphate levels, which is FGF23 and klotho. FGF23 acts as a phosphaturic hormone by decreasing the sodium phosphate cotransporter (NPT) expression in kidneys and intestines, as well as decreasing the calcitriol synthesis. In this regard, the FGF23 receptor must first be activated by klotho. In addition, klotho also has another important role in controlling the secretion of FGF23, calcitriol, and PTH. Reduced klotho expression will cause resistance and overproduction of FGF23 (Waziri et al., 2019; Hruska et al., 2017).

The experimental study (de Seigneux et al., 2015) on proteinuric mice with normal GFR revealed decreased klotho expression in the proximal tubular cells of these mice. In addition, an increase in FGF23 levels was also found but accompanied by a decrease in its signaling activity, indicated by a decrease in phosphorylation of FGF substrate 2 α receptor (FRS2 α). As the result, the number of NPT in proximal tubular cells increased, followed by an increase in serum phosphate reabsorption in these mice. The klotho reduction & FGF23 resistance underlies the main mechanism of association between albuminuria and serum phosphate levels.

At the clinical level, a study by Kim et al. (2020) revealed a negative correlation between 24-h urinary protein (24-h UP) and fractional phosphate excretion ratio/FGF23 (FEP/FGF23) as a marker of FGF23 activity. As the result of FGF23 activity downregulation, a significant increase in serum phosphate levels was found in patients with proteinuria >1g/day. Another study by Jung et al. (2020) reported that patients with higher serum phosphate levels tend to exhibit greater proteinuria, higher FGF23, and lower klotho. The FGF23/klotho ratio was found to be increased in these patients, indicating FGF23 resistance.

Several mechanisms underlie the klotho reduction in albuminuria patients. First, albuminuria could stimulate proinflammatory mediators (TNF, TWEAK, TGF β 1, and MCP1) to suppress klotho mRNA expression and induce tubular and interstitial inflammation, thereby reducing the number of klotho (Fernandez-Fernandez

et al., 2018; Fernandez-Fernandez et al., 2020) Second, albuminuria triggers endoplasmic reticulum stress in renal tubular cells, thereby suppressing the transcription of klotho mRNA (Delitsikou et al., 2020).

The third mechanism is that albuminuria directly induces lysosomal and proteasomal degradation of klotho, thereby reducing its half-life (Delitsikou et al., 2020). Fourth, albuminuria suppresses klotho expressions through epigenetic modifications. The administration of trichostatin A as histone deacetylation inhibitors had been proven to reverse the albuminuria-related decrease in klotho mRNA and protein in tubular cells (Fernandez-Fernandez et al., 2018).

There are several reasons for the weak association strength between albuminuria and serum phosphate levels in our study. The first reason is that serum phosphate levels are more affected by GFR than albuminuria. A study by Jung et al. (2020) found that 15.4% of the relationship between proteinuria and phosphate was affected by the FGF23/klotho ratio, while the remaining 67.9% was affected by the rate of phosphate excretion/GFR (EP/GFR).

In another study by Fernandez-Fernandez et al. (2018) CKD patients with low ACR and klotho levels were only found in patients with low GFR. In addition, the analysis of that study revealed a significant correlation between GFR and klotho, thus GFR also modified the association between ACR and klotho. As long as the number of preserved nephrons has not decreased significantly, as indicated by well GFR, then renal phosphate excretion is still able to compensate for the albuminuria-related klotho downregulation (de Seigneux et al., 2015).

The second reason for the weak association strength was the involvement of uncontrolled confounding variables, such as gender, age, nutritional status, comorbidities, GFR, hydration status, activity, phosphate intake, diurnal variation of phosphate, vitamin D, PTH, medications, etc (Martin et al., 2020). Subjects of this study consisted of various age groups, nutritional status, and comorbidities. However, there were some uneven distributions of subjects between groups, and multivariate analysis was also not conducted.

At an early age, the body will increase the production of vitamin D and growth factors, thus increasing serum phosphate levels to maintain optimal bone growth. On the contrary, vitamin D production tends to decrease while PTH production increases at an older age, thus decreasing serum phosphate levels (Cirillo et al., 2008). In pre-menopausal women, elevated estrogen levels could inhibit phosphate reabsorption, thereby reducing serum phosphate levels. Meanwhile, the diminished estrogen level in postmenopausal women will decrease its phosphaturic effect so they tend to exhibit higher serum phosphate levels (Koek et al., 2021; Khalil et al., 2018)

Increased nutritional status also has a negative association with serum phosphate levels, where overweight/obese people tend to exhibit increased leptin production. This hormone stimulates FGF23 release, thereby lowering serum phosphate levels. Obesity is also associated with decreased active vitamin D levels, thereby reducing phosphate absorption in the intestine (Bosman et al., 2022).

Certain comorbid affect serum phosphate levels through several mechanisms. Hypertension increases serum phosphate levels directly through renin-angiotensin-aldosterone system (RAAS) overactivation that increases angiotensin II and aldosterone levels, or indirectly through albuminuria. Both of these mechanisms reduce klotho expressions thus inducing FGF23 resistance (de Seigneux et al., 2016). In diabetic nephropathy, increased insulin levels inhibit FGF23 action. In addition, hyperglycemia

also stimulates cytokines and advanced glycosylation end-products (AGEs) synthesis that aggravates kidney damage and reduces phosphate excretion (Chen et al., 2013)

The third reason was that the measurement of albuminuria data was performed on an ordinal scale, thus decreasing the accuracy of the analysis. This was caused by the limitation of available equipment to measure albuminuria grade. The fourth reason was the time difference that sometimes occurred in urine and blood sampling. This study only extracted secondary data from the patient medical records, so the researchers did not directly involve in the sample collection process.

Two other studies investigated the association between albuminuria and serum phosphate levels, where albuminuria data were measured on a ratio scale with blood and urine samples collected simultaneously. The first study (de Seigneux et al., 2015) reported the relatively same significance and association strength between the two variables ($p < 0.001$; $r = 0.27$).⁶ On the contrary, the second study (Fernandez-Fernandez et al., 2018) reported the same significance but with moderate association strength ($p < 0.001$; $r = 0.41$).

Overall, this research still had some limitations. First, the bias due to confounding factors was not eliminated since this study did not perform multivariate analysis. This was due to technical and time limitations during the execution of this study. Third, there was an inequality in the number of subjects between variable groups due to the limited available data.

The novelty of this study is that, so far, this research was the first study about the association between albuminuria and serum phosphate levels in CKD patients in Indonesia. Thus, this study can be used as a basis for developing research on CKD-MBD in the future.

CONCLUSION

Our study presented a significant positive correlation with weak association strength between albuminuria and serum phosphate levels. However, considering the limitations of our study, further study is required with better design, involving other phosphate excretion factors, and minimizing the effects of confounding factors to obtain deeper insight into the association between albuminuria and serum phosphate levels.

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CONFLICT OF INTEREST

The authors declare there is no conflict of interest.

ETHICS CONSIDERATION

This study was approved by the ethical committee of Dr. Soetomo General Hospital with agreement number 0578/LOE/301.4.2/IX/2021.

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AUTHOR CONTRIBUTION

All author have contributed to all process in this research, including preparation, data gathering and analysis, drafting and approval for publication of this manuscript.

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