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Association of vitamin D and phosphor levels with growth retardation in children with chronic kidney disease



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ABSTRACT

Introduction: Growth retardation is a complication often found in children with chronic kidney disease (CKD). Growth retardation is characterized by the failure to reach a child's potential linear growth height. Fifty percent of children with CKD will have a height below the third percentile. The causes of growth retardation in CKD are multifactorial. One of them is the electrolyte balance of phosphorus and lack of vitamin D levels which play a role in the linear growth disorders of children with CKD. This study aims to determine the relationship between vitamin D and phosphorus levels on growth retardation in children with chronic kidney disease.

Methods: This observational retrospective analytic study was conducted at the Polyclinic and Inpatient Room of the Department of Pediatrics in Saiful Anwar General Hospital, Malang from June 1, 2021 to September 2021. There were 68 subjects, divided into 2 groups: patients with CKD with growth retardation and without growth retardation, age ranging from 2 -18 years. Univariate test is used to describe the frequency distribution of each variable. The Chi-Square test used determines the correlation of each variable, the Spearman correlation test to see the strength of the relationship between the variables of vitamin D and phosphorus on growth retardation. The significance level and confidence interval were $P < 0.05$ and 95%, respectively. Data were analyzed using SPSS v.26 for windows.

Result: We found a correlation between vitamin D levels in patients with chronic kidney disease and growth retardation ($P = 0.005$), as well as a correlation between phosphorus levels in patients with chronic kidney disease and growth retardation ($p = 0.022$). Vitamin D and phosphorus had a correlation coefficients of 0.427, and 0.300 to growth retardation ($p < 0.05$). We also found a significant direct correlation between vitamin D and growth retardation ($\beta = 0.358$, $p = 0.002$), which shows a greater effect than the indirect relationship between vitamin D and phosphorus-mediated growth retardation.

Conclusion: There is a significant corr between vitamin D level and phosphorus on growth retardation in children with chronic kidney disease.

Keywords: Chronic kidney disease, Vitamin D, Phosphorus, Growth retardation.

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INTRODUCTION

Growth retardation is a failure to reach the potential linear growth in children. This growth failure implies that the child's height will be shorter than his peers.¹ One of these growth retardations is characterized by short stature as measured by height for age below the standard deviation ($< -2SD$) in reference to the growth curve by World Health Organization (WHO) in 2006 or height less than the 3rd percentile ($< P3$) in the CDC curve according to age and gender.²

Growth retardation has a negative effect on psychosocial development, education, quality of life of children and increases the incidence of morbidity

and mortality.^{2,3} Growth retardation can occur in children with chronic diseases, including chronic kidney disease (CKD) and enzymatic renal disease (ERC). Growth retardation is a problem that is often found in pediatric patients with CKD which can result in decreased quality of life.⁴ In Fivush's research, cited by Silverstein in 2018, it was stated that children with CKD will experience growth retardation, with height below the 3rd percentile, which is 50%.⁵ Data from The United States Renal Data System (USRDS) Pediatric Growth and Development Study states that pediatric patients with CKD accompanied by moderate to severe growth retardation have a higher risk of

mortality and morbidity than children with normal growth rates.⁴

Risk factors that cause growth retardation in children with CKD include malnutrition, metabolic acidosis, impaired bone mineralization, anemia, and electrolyte abnormalities. In infancy, growth retardation is often caused by impaired metabolism of growth hormone (IGF-1) which is also greatly affected by the presence of nutritional factors. Inadequate nutrition influences growth retardation, especially in children with CKD which requires at least 80% of the nutritional requirements for growth.⁶

Chronic kidney disease will cause disturbances in bone mineralization,

including vitamin D (Lang et al., 2014). Vitamin D is a hormone (steroid) derived from cholesterol which is converted into 7-dehydrocholesterol under the skin with the help of ultraviolet light from sunlight, which will be synthesized in the liver and converted into its active form in the kidneys.⁷ The activity of vitamin D 25 (OH) D in the mitochondria of the glomerulus increases when 25 (OH) D is converted to 1,25 (OH) D. Kidney disorders will cause inhibition of the synthesis of 1,25 (OH) D (active form of vitamin D3).⁸ The decrease in renal filtration rate in children with CKD will affect the formation of the 1-alpha-hydroxylation enzyme from 25-hydroxyvitamin D. A decrease in the function of phosphorus excretion could also cause increased levels of phosphorus in the blood. The process of reducing 1-alpha-hydroxylation results in reduced levels of the active form of vitamin D which causes a lack of calcium absorption in the intestine and causes hypopotassemia. Hypocalcemia stimulates the production of parathyroid hormone by the parathyroid glands and increased phosphorus levels stimulate the secretion of fibroblast growth factor 23 (FGF23) by osteocytes. Phosphorus excretion function in patients with CKD will also be impaired, and an increase in serum phosphate levels (hyperphosphatemia) could be found. Both of these mechanisms will increase the work of the parathyroid gland to stimulate the formation of parathyroid hormone, which will cause an increase in osteoclast activity and decrease osteoblasts.⁹ Vitamin D also regulates osteoblast differentiation, thereby influencing bone matrix formation and mineralization.¹⁰ This will cause growth retardation in patients with CKD. This study aims to determine the relationship between vitamin D and phosphorus levels on growth retardation in children with chronic kidney disease.

METHODS

This study is an analytical observational retrospective study on patients diagnosed with chronic kidney disease in the pediatric department of Saiful Anwar Hospital, using the medical records as secondary data. The study was performed in the inpatient room from June 1st – September 2021, using the total sampling method.

Table 1. Subject Characteristics.

Description	Normal Phosphor (n=17)	Hyperphosphatemia (n=51)
Sex		
Male	10 / 17	35 / 51
Female	7 / 17	16 / 51
Age (Mean ± SD)	10,05 (± 3,49)	8,72 (± 3,75)
Weight (Mean ± SD)	29,41 (± 10,79)	26,58 (± 13,29)
Height (Mean ± SD)	131,55 (± 14,79)	118,50 (± 24,45)
Growth retardation		
Present (57)	11/17	46/51
Absent (11)	6/17	5/51

Note: SD = standard of deviation;

Table 2. The correlation between phosphor levels and growth disorder.

Variable	Coefficient Correlation	Sig
Phosphor Level	0,318	0,013*

Note: *significant at $p < 0.05$ by Spearman Correlation test; SD = standard of deviation; p=probability.

Based on the accuracy diagnostic test, the minimum sample of this study is 46. The inclusion criteria for this study includes: subjects within the age of 2-18 years old; subject diagnosed with chronic kidney disease by the nephrology consultant pediatrician; both in and outpatients; and subjects with height < -2 SD in the WHO curve or below the 3rd percentile in the CDC curve. The exclusion criteria include: subjects with growth retardation due to syndrome disorder, congenital heart disease or hematological disorder; subjects with growth retardation administered with vitamin D, calcium, and phosphorus supplements; subjects administered with anticonvulsant therapies—such as phenytoin and phenobarbital; and subjects administered with growth hormone therapies. Data analysis in this study used an independent T-test of two unpaired samples to determine the difference in the average phosphorus levels in CKD subjects with and without growth disorders. Spearman correlation test used to determine the correlation between phosphorus category and growth disorders

RESULTS

The total population of this study is 68 children who meet the inclusion and exclusion criteria. This study aims to determine the role of phosphorus levels in

chronic kidney disease (CKD) in children with growth disorders. In completing the research subject data information, the basic characteristics will be observed including gender, age, weight, height, phosphorus levels, and the presence or absence of growth disorders as shown in table 1.

Of 68 subjects, 57 were found with growth retardation, and 11 were without growth retardation. Based on the phosphorus level, 57 subjects had increased phosphorus level while 17 had normal phosphorus level. No significant sex difference was found ($p = 0.083$) despite this study's population being dominated by males. No significant difference was found between the age ($p=0.47$) and weight ($p=0.217$) in the subjects with normal and increased phosphorus level. A significant difference was found in the height ($p=0.044$) between subjects with increased and normal phosphorus levels.

An independent T-test of two unpaired samples was conducted to determine the difference in the average phosphorus levels in CKD subjects with and without growth disorders. It was found that the average phosphorus level in 57 CKD children with growth disorders was 2.458 (SD=0.443). Meanwhile, the average phosphorus level in 11 subjects without growth disorders was 2.12 (SD =0.253). This shows that the standard deviation value in CKD children with growth disorders is greater than the

standard deviation value in CKD children without growth disorders. This shows that phosphorus levels in CKD children with growth disorders are more variable in value than children with CKD without growth disorders.

The relationship between the category of serum phosphorus levels and the incidence of growth disorders in CKD pediatric patients was tested by the Spearman correlation test, as shown in table 2.

The results of the Spearman correlation test between the phosphorus category and growth disorders obtained a significant value of 0.013 with a correlation coefficient of 0.318. These results show a significant correlation between the serum phosphorus category and the incidence of growth disorders in CKD children where the significance value is 0.013 (sig <0.05). A correlation coefficient of 0.318 was found, which means there is a weak correlation between phosphorus levels and growth disorders in children with CKD. A positive value indicates that the correlation between phosphorus levels and growth disorders is directly proportional. Children with chronic kidney disease with growth disorders have higher phosphorus levels than those without growth disorders.

DISCUSSION

This study aims to determine the role of phosphorus levels on growth disorder in children diagnosed with CKD. In the research process, 68 children with chronic kidney disease were found. The 68 subjects of this study were divided into two groups, namely children with growth disorders and children without growth disorders (normal). In terms of age characteristics from the data obtained, it was found that the lowest age of the research subjects was 2, the highest was 16; and the average age was 2-12 years. This is in line with research from Italkid-project, which reported that the prevalence of chronic kidney disease in children reached 12.1 cases/year/1 million children with an age range of 8.8-13.9 years.¹¹

In this study, it was found that CKD were found more in male children than female, but there was no significant difference (p = 0.083). This agrees with

data from the Ministry of Health, where in Indonesia the prevalence of chronic kidney disease in men is 0.3% and women 0.2%.¹² The main causes of CKD in children differ significantly from the onset of disease in adults. The main etiologic factors of CKD in children are mostly caused by Congenital Anomaly of Kidney and Urinary Tract (CAKUT), steroid-resistant nephrotic syndrome (SRNS), chronic glomerulonephritis (eg lupus nephritis, Alport syndrome) and renal ciliopathy.¹³ Less common causes of CKD in children include thrombotic microangiopathy (especially atypical hemolytic uremic syndrome), nephrolithiasis/nephrocalcinosis, Wilms tumor, infectious and interstitial disease, and others. While structural causes (eg., renal hypoplasia or posterior urethral valves) occur in younger patients, glomerulonephritis is found more in children older than 12 years old. The loss of a small number of nephrons in low birth weight and preterm newborns is an important predisposing factor for CKD. This condition, together with increasing obesity in children.⁶

This study included 68 research subjects-children diagnosed with chronic kidney disease. Of these 68 patients, 57 children with growth disorders were found and 11 children were found without. This is in accordance with previous research, which found in Chile that patients with CKD had a growth delay of 50% and in RSCM Jakarta 56% of children with chronic kidney disease had short stature. Under normal conditions, the renal glomerulus filters about 85%-90% of phosphorus. This effort is to maintain normal serum phosphate in the blood between 2.5-4.5 mg/dL. In chronic kidney disease there is a disturbance in kidney function which results in reduced phosphate excretion in the kidneys, which results in positive phosphorus balance (hyperphosphatemia). This study found that from 51 CKD subjects who had high phosphorus levels (hyperphosphatemia), 46 patients (90.2%) had growth disorders. Phosphorus levels in children diagnosed with chronic kidney disease with growth disorders were higher than in children with chronic kidney disease who did not experience growth disorders (p = 0.022). The high phosphorus level in CKD patients

is in line with previous research where research in 2019 found that of 86 patients with CKD at Gading Pluit Hospital, North Jakarta, 74.42% had hyperphosphatemia.¹⁴

Based on this study, 46 (90.2%) children with chronic kidney disease experienced an increase in phosphorus levels and experienced growth disorders. The correlation between phosphorus levels and growth disorders based on chi square analysis showed a significance value of 0.022 (p <0.05). This shows a significant correlation between phosphorus levels and growth disorders in pediatric patients with CKD. The relationship between phosphorus levels and growth disorders in this study showed a positive correlation coefficient of 0.318 with a significance value of 0.013, which means that the higher the phosphorus level in children with CKD, the higher the incidence of growth disorders and vice versa.

In this study it was found that phosphorus levels in CKD children with growth disorders varied more in value than children with CKD without growth disorders, this can be seen from the standard deviation value which was greater in CKD patients with growth disorders (0.443) than CKD patients without growth disorders. (0.253). The value of phosphorus levels in children with chronic kidney disease with growth disorders has a higher value than the value of phosphorus levels in children with CKD without growth disorders. Chronic kidney disease can cause hyperphosphatemia due to a decrease in nephron function which can cause calcium phosphate bonds to settle in the renal interstitium and blood vessels. While the balance of phosphorus in the body is very important to optimize the physical growth of early childhood, but if it is excessive it will cause pain in the bones because high levels of phosphate in the body will disrupt the process of bone growth and in the end a person's physical growth will be hampered.¹⁵

This study determined phosphorus levels' role in growth disorders in children with CKD. However, this study has limitations. In this study, the basic causes of CKD were not accounted for, and we did not classify the stages of CKD in the subjects. In addition, we also did not take the subjects' use of routine

drugs, nutritional status, daily intake, and phosphorus intake. In this study, other parameters that could affect the incidence of growth disorders in patients with chronic kidney disease were not investigated, such as vitamin D, calcium, and Fibroblast Growth Factor-23 (FGF-23).

Based on the results of data analysis and previous discussions, further research on the role of phosphorus levels on growth disorders in children with chronic kidney disease can be suggested by considering other factors that can affect growth disorders such as nutritional intake and routine medications, consumption, phosphorus intake or therapy, and other biomarkers such as FGF-23 level.

CONCLUSION

Based on the results of data analysis and discussions that have been written previously, we concluded that: There is a significant role and correlation between phosphorus levels and the incidence of growth disorders in children with chronic kidney disease; The average phosphorus level in pediatric patients with chronic kidney disease in 68 patients was 5.96 ± 2.22 mg/dL; and phosphorus levels in pediatric patients with chronic kidney disease with growth disorders are higher than children with chronic kidney disease without growth disorders.

DISCLOSURES

Ethic Approval

This study had been ethically approved by ethical commission.

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The author declares that there are no relevant or material financial interests that relate to the research described in the paper.

Conflict of Interest

The author declares that there are no relevant or material financial interests that relate to the research described in the paper.

Author Contribution

A, SK, and HPY has given contribution to this paper. All authors contributed in data collection, data analysis and interpretation. A and SK contributed additional to diagnosing and treating the subjects in the study. All authors gave contributions in writing and proofreading this study.

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