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The relation between vitamin D, calcium, and phosphor in growth retardation of child with chronic kidney disease

Radwika Swastanti Wijaya[1*], Ariani[2], Krisni Subandiyah[3]

[1]Pediatric Department, Faculty of Medicine, Universitas Brawijaya;
[2]Growth Development and Social Pediatric Division, Pediatric Department, Faculty of Medicine, Universitas Brawijaya;
[3]Nephrology Division, Pediatric Department, Faculty of Medicine, Universitas Brawijaya;

*Corresponding to:
Radhika Swastanti Wijaya;
Pediatric Department, Faculty of Medicine, Universitas Brawijaya;
radwikasw@gmail.com

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ABSTRACT

Background: Growth retardation was a complication in chronic kidney disease (CKD). It is a condition that a child can not achieve linear potential growth. Fifty percent of children with CKD will have a height below the third percentile. The causes of growth disorders in CKD are multifactorial. Electrolyte hemostasis (calcium and phosphorus) and lack of vitamin D play a role in growth in children with CKD. The aim of this study was to determine the relationship between growth problems in children with chronic kidney disease and the correlation with vitamin D, calcium, and phosphorus.
Method: This study was a retrospective observational analytical study design. The research subjects were taken from medical records from Saiful Anwar General Hospital in Malang from January 1st to December 2019. 68 pediatric patients aged 2 – 18 years old were diagnosed with chronic kidney disease, divided into 2 groups (with growth retardation and normal stature). Data were analyzed using SPSS v.26 for windows.
Results: There was significant correlation between low vitamin D levels and growth retardation ($p = 0.005$), and significant correlation between calcium levels ($p = 0.026$) and phosphor levels ($p = 0.222$) and the incidence of growth retardation. Levels of vitamin D, calcium, and phosphor have a positive correlation with growth retardation 0.427, 0.277, dan 0.300 ($p<0.05$). Path analysis found a significant direct relationship between vitamin D on growth retardation ($\beta = 0.358$, $p = 0.002$) and had a greater effect when compared to the indirect relationship between vitamin D and growth retardation mediated by calcium and phosphorus.
Conclusion: there is a correlation between vitamin D, calcium, and phosphorus with growth retardation in children with chronic kidney disease.

Keywords: Chronic Kidney Disease, Vitamin D, Calcium, Phosphorus, Growth Retardation.
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INTRODUCTION

Failure of children to attain a linear height of growth potential is known as growth retardation. This lack of growth suggests that the youngster will be shorter than their classmates in height.[1] Short stature, as determined by height according to age under standard deviation (-2SD) in accordance with the growth curve from the World Health Organization (WHO) in 2006, or height less than the third percentile (P3) in accordance with the applicable CDC curve according to age and sex, is one of the signs of growth retardation.[2] Children's quality of life, psychosocial development, education, and the frequency of sickness and mortality are all negatively impacted by growth retardation.[3,4]

According to Fivush's findings, which Silverstein cited in 2018, 50 percent of kids with chronic kidney illness may experience growth failure, resulting in a height below the third percentile.[5] According to data from The United States Renal Data System (USRDS) Pediatric Growth and Development Study, children with CKD with moderate to severe growth retardation are more likely to die and suffer other health problems than kids with normal growth rates.[4]

Bone mineralization will be disturbed by chronic renal illness (calcium, phosphorus, and vitamin D) The parathyroid glands will have to work harder to induce the production of parathyroid hormone as a result of the calcium and phosphorus imbalance, which will increase osteoclast activity and reduce osteoblast activity. Additionally, vitamin D controls osteoblast differentiation, which has an impact on the production of bone matrix and bone mineralization.[6] Patients with CKD will experience growth retardation as a result. Therefore, the aim of this study was to determine the relationship between growth problems in children with chronic kidney disease and the correlation between vitamin D, calcium, and phosphorus.

METHODS

This study is an observational analytic study with retrospective observations on patients diagnosed with Chronic Kidney Disease in the Pediatric Department of Dr. Saiful Anwar Hospital Malang from January 2019 to December 2019.

The target population in this study were all children diagnosed with chronic

kidney disease who received outpatient and inpatient care at the Pediatric Department of the Dr. Saiful Anwar Hospital Malang who met the inclusion and exclusion criteria. The number of samples used in this study was 68 samples. The technique of taking research subjects with total sampling.

The inclusion criteria for the short stature group were 2-18 years of age, diagnosed with chronic kidney disease, outpatients/inpatients who did not receive vitamin D/calcium/phosphorus supplements, and height measurements were less than -2 standard deviations. While the exclusion criteria were growth retardation due to syndromic disorders, congenital heart disease, hematological disorders, or growth retardation in patients who have received vitamin D, calcium, and phosphorus supplements, patients receiving anti-convulsive drug therapy such as phenytoin and phenobarbital and patients who have received growth hormone therapy.

The independent variables in this study were ferritin, vitamin D, calcium, and phosphorus. The dependent variable in the study was chronic kidney disease patients with growth retardation and chronic kidney disease patients with normal stature. The instrument used in this study was secondary data taken from the patient's medical record.

Univariate analysis was carried out to describe the frequency distribution of each variable. The relationship between various levels of vitamin D, calcium, and phosphorus on growth retardation in children with chronic kidney disease was measured by the chi-square test. The correlation test used Spearman correlation to determine the relationship between two or more variables at an ordinal scale, while to determine the direct and indirect relationship between the three variables (vitamin D, calcium, and phosphorus), path analysis (pathPLS) was used. The level of significance and the confidence interval used was P <0.05 and 95%, respectively.

RESULT

The research conducted was to determine whether there was a relationship between the incidence of short stature and serum ferritin, vitamin D, calcium, and phosphorus levels in chronic kidney disease patients. The following is the demographic data of the subjects in this study in table 1.

Table 1. Demographic Characteristics of Research Subject.

Variables	Growth retardation (n= 57)	Normal stature (n= 11)
Gender (male / female)	35 / 22	10 / 1
Age, mean (SD)	9.25±3.76	8.09±3.42
Weight, Median (IQR)	21 (18-35.25)	26 (20-48)
Height, Median (IQR)	122 (103.5-143)	128 (111-142)
Duration of disease, median (IQR)	1 (0.88 – 1.75)	1 (0.5 – 2)
Aged at diagnosed, mean (SD)	8.24±3.69	6.87±2.9
Hemodialysis therapy (n)		
No	50 /57	11 /11
Yes	7 / 57	0 (0)
Etiology of CKD, n		
Nephrotic Syndrome	35 / 57	7 / 11
Nephritis Lupus	10 / 57	3 / 11
GNAPS	7 / 57	1 / 11
Nephritis HSP	2 / 57	0 / 11
CAKUT	3 / 57	0 / 11

Table 2. Relationship between Vitamin D and Growth Retardation in Chronic Kidney Disease.

Variables	Growth Retardation		P value
	Yes	No	
Vitamin D status			
Vitamin D Insufficiency	2 (33.3%)	4 (66.7%)	0.005
Vitamin D Deficiency	55 (88.7%)	7 (11.3%)	
Calcium status			
Normal	16 (69.9 %)	7 (30.4%)	0.029
Hypercalcemia	41 (91.1%)	4 (8.9%)	
Phosphor status			
Normal	11 (64.7%)	6 (35.3%)	0.022
Hyper-phosphatemia	46 (90.2%)	5 (9.8%)	

Table 3. Correlation Vitamin D levels, Serum Calcium levels and Serum Phosphorus levels with Growth Retardation in Chronic Kidney Disease.

Variable	Correlation coefficient (r)	Sig
Vitamin D	0.427**	0.000
Calcium	0.277*	0.022
Phosphorus	0.300*	0.013

Result of this study Patients who have vitamin D levels <20 ng/mL are categorized as vitamin D deficiency, while vitamin D insufficiency if the vitamin D levels are 20-29 ng/mL. Of the 68 patients with chronic kidney disease, the majority had vitamin D deficiency, and deficiency vitamin D in 62 patients, such as in Table 2.

From the analysis, the chi-square value of sig = 0.005 (sig <0.01) indicates

a significant relationship. There was a significant difference between vitamin D deficiency and the incidence of growth retardation in patients with chronic kidney disease.

We obtained low levels of calcium levels in 45 study subjects, and we performed a chi-square test with the results of sig = 0.029 which showed a significant relationship between hypocalcemia and the incidence of growth retardation in patient with chronic kidney disease as in table 2.

Based on our findings, we found 45 subjects with a high level of phosphorus, while 23 other subjects were normal. We performed the chi-square test and the resulting sig was 0.029 which means a significant correlation between serum levels of phosphorus are low with short stature incidence such as in Table 2.

The results of the Spearman correlation test between the vitamin D and growth retardation is a significant relationship (sig <0.05). A positive coefficient is interpreted as a decrease in vitamin D levels, so patients with CKD will experience growth retardation.

The a significant relationship between the serum calcium and the incidence of growth retardation in children with CKD (sig <0.05). A positive coefficient is defined as the decrease in the serum calcium category, so patients with CKD will experience growth retardation.

The correlation between serum phosphorus and growth retardation is also significant. A positive coefficient is defined as a higher serum phosphorus category, so patients with CKD will experience growth retardation. On the other hand, the more normal the serum phosphorus level is, the children with CKD will not experience growth retardation.

DISCUSSION

This study consisted of 68 children with chronic kidney disease, which were divided into 2 groups, growth retardation, and normal stature. In the data characteristics, the average age is 2-12 years old. This result agrees with the research conducted by Halle *at all* in 2017 that chronic kidney disease in children is found at the age of 7 to 12 years old. According to the Italkid-project investigation, 1 million youngsters between the ages of 8.8 and 13.9 were found to have 12.1 instances of CKD per year.[7,8]

Our study result found that male patients were more dominant, but there was no significant difference (p = 0.083). Previous research data conducted in Europe also showed that the prevalence of male gender had more chronic kidney disease than girls with a ratio of 2:1. Likewise Prambudi's research at dr. Kariadi Semarang in 2011-2015 with 28 boys and 12 girls with chronic kidney disease.[8,9]

The results of this study were 68 children diagnosed with chronic kidney disease, while 57 children experienced growth retardation and 11 children did not experience growth retardation. This is in accordance with the reference that 50% of children with chronic kidney disease will experience growth failure which is indicated by a height below the 3rd percentile. Seikaly's research in 2006 obtained data from 5,615 chronic kidney disease children studied and found that 36.9% experienced growth retardation.[10]

The age when the child patient was diagnosed with chronic kidney disease who had growth retardation or not growth retardation was not much different, namely the age of 5 to 11 years with insignificant different test results (p=0.347). This study is similar to epidemiological studies in Europe where the youngest age at diagnosis of CKD is the age at a median of 3 years and the oldest is 11.3 years old.[11]

The most common aetiologies of chronic kidney disease in this study were nephrotic syndrome, lupus nephritis, GNAPS, HSP nephritis, and CAKUT. However, the etiology of CKD did not have a significant difference between patients with growth retardation or normal. According to the theory, the causes of CKD in children can be in the form of structural abnormalities (CAKUT, ciliopathy, nephrolithiasis) and glomerular diseases (nephrotic syndrome, glomerulonephritis, or thrombotic microangiopathy).[11]

According to this study, the primary cause of CKD in children is nephrotic syndrome, and the majority of these children have growth retardation. This is explained by Park and Shin's study from 2011, which found that reduced insulin-like growth factors (IGFs) and/or IGF-binding proteins (IGFBPs), as well as the side effects of corticosteroid therapy in patients with nephrotic syndrome, are the two most common causes of growth retardation in patients with nephrotic syndrome.[12]

In this study, 57 patients with CKD experienced growth retardation and 7 of them received hemodialysis therapy, but this study did not differ significantly between patients with growth retardation and normal stature (p = 0.588). Research conducted by Salas in 2013 wrote that 50% of CKD patients will experience growth retardation, and dialysis therapy for 6-12 months cannot improve the height of CKD patients.[4]

The findings revealed that 55 patients with high serum vitamin D levels and growth retardation were children with CKD, making up 88.7% of their total population. Chi-square analysis with p = 0.005 shows a correlation between vitamin D levels and the likelihood of experiencing growth retardation. Similar research was done in 2009 by Seeherunvong et al., who examined the prevalence of vitamin D status in kids and teenagers with chronic renal disease. According to the study's findings, people with CKD and vitamin D deficiency (25 (OH) D levels < 20ng/dL) will be shorter than people with levels above that level.[13]

Kidney 1,25(OH)2D deficiency is caused by kidneys losing the ability to convert vitamin 25(OH)D to vitamin 1,25(OH)2D. This mechanism is caused by a number of factors, including: (1) a rise in serum phosphate levels and FGF-23, which control the kidney's 1-hydroxylase enzyme; (2) suppression of the enzyme by uremia and acidosis; (3) decreased preparations of 25 (OH) D and 1-hydroxylase in CKD patients; and (4) decreased expression of renal megalin, which is crucial for moving 25 (OH) D from the glomerulus to 1-hydroxylase in the proximal tub.[14]

The results showed that there were 23 patients with normal calcium category where 16 patients had growth retardation (69.6%) while 7 patients (30.4%) did not. Meanwhile, the number of patients who had decreased calcium category was 45 patients, of which 41 patients (91.1%) had growth retardation and 4 patients (8.9%)

did not experience growth retardation. The significant value obtained is 0.029 (sig <0.05) which indicates that there is a relationship between the calcium category and the incidence of growth retardation.

Chronic kidney disease can be accompanied by a decrease in the glomerular filtration rate which will result in impaired excretion of phosphate. Reduced 1-alpha- hydroxylation enzyme from vitamin D due to kidney disorders, will cause decreased absorption of calcium from the intestinal organs leading to a state of hypocalcemia. Increased phosphate can induce the secretion of fibroblast growth factor-23 (FGF23) by osteocytes, and hypocalcemia will enhance the parathyroid glands' production of parathyroid hormone. This will result in significant bone calcium absorption and phosphaturia. The renal phosphate sodium co-transporter will be affected by parathyroid hormone, which will promote bone resorption and release calcium from the bones, impairing bone mineralization. Growth retardation will eventually result from increased bone resorption.[10] The findings of our study, which demonstrate a correlation between the category of serum calcium levels and the occurrence of growth retardation, support this.

Reduced proximal tubular 1-hydroxylase expression is caused by decreased renal function and the development of tubulointerstitium nephritis, which in turn decreased calcitriol levels and gastrointestinal calcium absorption. It is possible for CKD to gradually limit calcium and phosphorus excretion, which results in an increase in blood phosphorus and a decrease in serum calcium. Osteocytes and osteoblasts create FGF-23 in response to an increase in serum phosphorus. FGF-23 inhibits 1,25(OH)2D synthesis, which in turn affects phosphorus and calcium absorption in the intestine, leading to hypocalcemia, which can increase PTH expression. The quantity of Npt2a and Npt2c in the kidney's proximal tubule is decreased by parathyroid hormone, which also decreases proximal tubular phosphorus reabsorption.[15]

The research data showed that high phosphorus results were found in patients with CKD as many as 51 patients and among those with growth retardation as many as 46 patients (90.2%). The relationship between serum phosphorus levels in CKD children with growth retardation was shown to be higher than those in children with normal chronic kidney disease (P = 0.022). A similar study we obtained from Seikaly et al's 2006 study examined the correlation between height and acidemia, anemia, serum phosphorus, PTH, and albumin levels. The results showed that hyperphosphatemia levels (phosphorus levels above 7 mg/dL) had a significant relationship with the child's height and CKD (P <0.001).[11]

CONCLUSION

Levels of vitamin D, calcium, and phosphorus have a major impact on growth retardation in kids with chronic kidney disease. To stop growth retardation in children with chronic renal disease, it is important to address the underlying causes of the disease, supplement with calcium and vitamin D, and keep track of each serum's phosphorus and calcium levels.

CONFLICT OF INTEREST

None of the authors has a conflict of interest to declare.

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ETHICAL CLEARANCE

This research has received a certificate of ethical acceptance from the Ethics Commission of Dr. Saiful Anwar Hospital Malang with the number 400/179/K.3/302/2020 before the research was conducted.

AUTHOR CONTRIBUTION

All authors equally contribute to the study from the conceptual framework, data acquisition, and data analysis until interpreting the study results through publication.

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