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Original Article

Calcitriol levels and the stage of chronic kidney disease in children

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Abstract

Background Kidney damage in chronic kidney disease (CKD) disrupts the 1α-hydroxylase enzyme, preventing the conversion of vitamin D into the active form of calcitriol. To our knowledge, no previous studies have assessed calcitriol levels in children with CKD. Decreased vitamin D levels may occur at an early stage of the disease, so it is important to evaluate calcitriol levels in children with early stage CKD.

Objective To assess calcitriol levels in children with CKD according to disease stage and other characteristics.

Methods This cross-sectional study was conducted on 43 pediatric CKD patients at Dr. M Djamil Hospital, Padang, Indonesia. We recorded patient characteristics and performed laboratory tests, including routine hematology, blood urea nitrogen (BUN), creatinine, uric acid, electrolytes, calcium, and calcitriol levels. Based on estimated glomerular filtration rate (GFR), patients were grouped into either early-stage (stages I and II), or advanced-stage (stages III to V) CKD. Univariate and multivariate analyses were conducted to determine the association between calcitriol levels with disease stage and other characteristics.

Results The overall mean calcitriol level of our subjects was 108.77 (SD 10.79) pmol/L. Mean levels at each CKD stage from I to V were 164.28 (SD 160.90), 94.14 (SD 50.63), 72.16 (SD 13.18), 62.92 (SD 4.87), and 67.51 (SD 4.87) pmol/L, respectively. Calcitriol levels did not differ significantly by CKD stage (P=0.114) when each stage from I to V was considered separately. There was no significant difference in calcitriol levels by growth characteristics (P=0.944), etiology (P=0.311), or anemic status (P=0.104). However, low calcitriol levels were found in all subjects with advanced stage CKD, compared to 63.6% subjects with early stage CKD (P=0.004). Mean calcitriol levels were significantly lower in CKD stage IV (P=0.049) and stage V (P=0.027) compared to stage I.

Conclusions The decrease in calcitriol level occurs at an early stage in CKD. Calcitriol levels are significantly lower in advanced stage than in early stage CKD. **[Paediatr Indones. 2022;62:318-23; DOI: https://doi.org/10.14238/pi62.4.2022.318-23**].

Keywords: *calcitriol; chronic kidney disease; children*

Chronic kidney disease (CKD) is a global public health problem, with a worldwide prevalence of 9.1% in 2017.[1] Chronic kidney disease is characterized by kidney damage or a progressive decline in kidney function over time. *The Kidney Disease Improving Global Outcomes* (KDIGO) guidelines define CKD as an abnormality in kidney structure and/or function, lasting for ≥ 3 months, that impacts health. CKD is categorized into stages from I to V, indicating disease progression based on glomerular filtration rate (GFR).[2]

The clinical features of CKD in children and its long-term effects include growth disorders, hypertension, anemia, as well as bone mineralization disorders (chronic kidney disease-mineral bone disorders; CKD-MBD). Vitamin D plays an important role in the process of mineral and bone homeostasis in CKD-MBD. Kidney damage in CKD causes a decrease in phosphate clearance resulting in hyperphosphatemia, which causes a decrease in vitamin D and calcium. These changes cause suppression of 1α-hydroxylase enzyme activity, which

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prevents the conversion of vitamin D into the active form $1,25(OH)_2D_3$ (calcitriol).[3]

Most cases of pediatric CKD in Indonesia are detected at an advanced stage,[4] including those in West Sumatra and its surroundings who seek treatment at Dr. M. Djamil Hospital, Padang, West Sumatera. In addition, due to sociocultural factors, most children wear school uniforms that cover most of their body, reducing sun exposure and leading to decreased vitamin D and increasing the risk of CKD-MBD as CKD complications. There have been no previous studies to assess the active form of vitamin D, calcitriol, in children with CKD in West Sumatra. Therefore, we aimed to assess calcitriol levels in children with CKD and its association with various CKD stage. As a secondary outcome, we also aimed to assess the association between CKD and other disease characteristics.

Methods

This cross-sectional study was conducted on 43 pediatric CKD patients at Dr. M Djamil Hospital, Padang, West Sumatera, from March to October 2020. Subjects were selected by consecutive sampling from patients aged 2-18 years with established CKD etiology. Patient characteristics were recorded. We collected 5 ml of venous blood, divided into two vacutainers, from all subjects. Measurements of hemoglobin, leukocytes, differential count, hematocrist, platelets, blood urea nitrogen (BUN), creatinine, uric acid, sodium, potassium, calcium, and blood glucose were done using 3 mL specimens at the laboratory of Dr. M. Djamil Hospital, Padang, West Sumatera. The remaining 2 mL specimens were centrifuged immediately at 3,000 rpm for 20 minutes to separate the serum. The serum was sent to the Biomedical Laboratory of Universitas Andalas within four hours of sampling for calcitriol measurements. Calcitriol levels were considered low when they were <108 pmol/L.[5]

Subjects' weight and height were plotted into the WHO z-score chart for children aged ≤5 years and the *CDC 2000 Chart* for children aged >5 years. Subjects were categorized normal weight when weight-for-length z-score was ≥ -2SD on the *WHO Chart* (age ≤5 years) or weight-for-length >90% and stature >3rd percentile on the CDC 2000 growth chart. Subjects who fell below those cut-off points were categorized as having failure to thrive.

Anemia was defined as hemoglobin level ≤11 g/dL. The stage of CKD was obtained from the estimated GFR calculation using the Schwartz formula.[2] Stages I and II CKD (GFR ≥60 mL/min/1.73m^2) were categorized as early stage, while stages III, IV, and V CKD (GFR <60 mL/min/1.73m^2) were categorized as advanced stage. Based on its etiology, CKD was classified as glomerular or non-glomerular. Glomerular CKD included CKD caused by abnormalities that occur in the glomerulus, either primary or secondary. Non-glomerular CKD were those caused by causes of CKD outside the glomerulus.

Numerical data were presented as mean and standard deviation (SD), while categorical data were presented as frequency and percentage. Bivariate analysis was done using the T-test, one-way ANOVA, Chi-square, and Fisher's exact tests. Data processing was done using *SPSS version 22* (*IBM*, Armonk, New York). A P value of <0.05 was considered statistically significant. This study had been approved by the Ethics Committee of the Faculty of Medicine, Universitas Andalas, and the Ethics Committee of Dr. M. Djamil Hospital, Padang. Parents/guardians provided written informed consent after understanding the objective, procedures, and potential side effects of the study.

Results

Characteristics of the 43 pediatric CKD patients are shown in **Table 1**. The mean age of subjects was 10.91 (SD 3.41) years, with the majority aged >10 to 18 years (53.5%). More than half of subjects experienced growth failure (51.2%) and anemia (74.4%). Seventeen (39.5%) subjects had stage I CKD. Most subjects (74.4%) had glomerular etiology, and the most common etiology (55.8%) was steroid-resistant nephrotic syndrome. Overall mean calcitriol level was 108.77 (SD 10.79) pmol/L.

Table 2 shows that there was no significant difference in calcitriol levels based on growth characteristics, etiology, or anemia (P>0.05). Subjects in stage I had the highest mean calcitriol levels [164.28 (SD 160.90) pmol/L], while those in stage IV had the lowest [62.92 (SD 4.87) pmol/L]. One-way ANOVA

revealed no significant difference in mean calcitriol level among CKD stages when stages I to V were grouped separately (P=0.114).

Table 3 shows that all advanced stage and 63.6% of early stage subjects had low calcitriol levels. Fisher's exact test revealed a significant difference in calcitriol levels between subjects in the early- and advanced stage groups (P=0.004).

We compared calcitriol levels between different CKD stages using one-way ANOVA. **Table 4** shows that calcitriol levels were statistically lower in stages IV (P=0.049) and V (P=0.027), compared to stage I.

Table 1. Subject characteristics

Variables	(N=43)
Gender, n (%)	
Male	22 (51.2)
Female	21 (48.8)
Mean age (SD), years	10.91 (3.41)
Age by group, n (%)	
2-5 years	3 (6.9)
>5 - 10 years	17 (39.6)
>10 -18 years	23 (53.5)
Growth, n (%)	
Failure to thrive	22 (51.2)
Normal	21 (48.8)
Anemia, n (%)	
Yes	32 (74.4)
No	11 (25.6)
CKD staging, n (%)	
Stage I	17 (39.5)
Stage II	5 (11.6)
Stage III	5 (11.6)
Stage IV	6 (14.0)
Stage V	10 (23.3)
Etiology, n (%)	
Glomerular	32 (74.4)
Non-glomerular	11 (25.6)
Chronic kidney disease etiology, n (%)	
Post-streptococcal acute glomerulonephritis	1 (2.3)
Hydronephrosis	1 (2.3)
Urinary tract infection	7 (16.3)
Interstitial tubular necrosis	1 (2.3)
Polycystic kidney disease	1 (2.3)
Rapidly progressive glomerulonephritis	1 (2.3)
Renal tubular acidosis	1 (2.3)
Systemic lupus erythematosus	2 (4.7)
Steroid-resistant nephrotic syndrome	24 (55.8)
Acute nephritis syndrome	4 (9.3)
Outcomes, n (%)	
Died	7 (16.3)
Survived	36 (83.7)
Mean calcitriol level (SD), pmol/L	108.77 (10.79)

Discussion

In our study, there were more boys (51.2%) with CKD than girls. A previous study also had more boys in their study on the GFRs of 888 pediatric patients (62% boys and 38% girls). Gender was not significantly associated with the incidence of CKD or reduced GFR, but boys were more likely to suffer from kidney failure with non-glomerular etiologies, while glomerular etiologies were more common in girls.[6] The higher incidence of CKD in boys may be associated with the etiology of congenital anomalies of the kidney and urinary tract (CAKUT), which is more prevalent in boys.[7]

The mean age of our subjects was 10.91 (SD 3.41) years. We used the CKD definition from KDIGO for children aged 2 years and up, so we limited our sample to subjects aged 2-18 years.[7] The majority of subjects were over 10 years of age. The older age of our subjects may be explained by the most common etiology of CKD in this study being glomerular CKD (74.4%), mostly due to steroid-resistant nephrotic syndrome

Table 2. Calcitriol levels based on subject characteristics (N=43)

Variables	Mean calcitriol level (SD), pmol/L	P value
Failure to thrive		0.944*
Yes	107.59 (50.49)	
No	109.99 (81.71)	
Etiology		0.311*
Glomerular	118.91 (25.72)	
Non-glomerular	79.23 (35.66)	
Anemia		0.104*
Yes	118.76 (26.74)	
No	79.69 (22.66)	
CKD staging		0.114$
Stage I	164.28 (160.90)	
Stage II	94.14 (50.63)	
Stage III	72.16 (13.18)	
Stage IV	62.92 (4.87)	
Stage V	67.51 (7.59)	

*Independent sample T-test; $one-way ANOVA

Table 3. Calcitriol levels based on CKD stage group

Stage	Calcitriol level		P value
	Low	Normal	
Early stage, n(%)	14 (63.6)	8 (36.4)	0.004†
Advanced stage, n(%)	21 (100.0)	0	
Total	35 (81.4)	8 (18.6)	

†Fisher's exact test

Table 4. Comparison between calcitriol levels between CKD stages

CKD staging	Stage II	Stage III	Stage IV	Stage V
Stage I	0.201	0.095	0.049‡	0.027‡
Stage II		0.744	0.629	0.649
Stage III			0.886	0.936
Stage IV				0.933

‡significant difference

(55.8%). CAKUT etiology, which is associated with a younger age distribution, was found in a smaller proportion of our subjects. Lack of facilities for the early detection of structural kidney abnormalities, and the knowledge level of parents and healthcare workers, may lead to delays and misdiagnoses.

Most of our subjects had stage I CKD (39.5%), which would be expected, as most subjects had steroid-resistant nephrotic syndrome. The second most common CKD stage was stage V (23.3%). Pabuti et al. found that 50% of the pediatric CKD subjects in his study were in stage V. The large proportion of advanced stage CKD may have been due to lack of public awareness, such that patients usually consulted a physician late, or lack of competence among healthcare workers in the early detection of CKD in children.[4]

Slightly more than half of subjects had failure to thrive (51.2%), indicating that chronic nutritional disorders are common in children with CKD. Failure to thrive in children with CKD may be caused by several factors, including malnutrition, dehydration, hyponatremia, metabolic acidosis, uremia, anemia, renal osteodystrophy, and growth hormone resistance. Protein energy malnutrition is also commonly found in children with CKD.[8] However, in this study, we did not seek to determine the definite cause of failure to thrive in our subjects, since data was collected only at one point in time.

The North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) reported an anemia prevalence of 73% in children with stage III, 87% in stage IV, and >93% in stage V CKD.[9] In our study, 74.4% of subjects had anemia. Factors contributing to anemia in CKD include decreased erythropoietin production, shortened red blood cell age, urea poisoning, severe hyperparathyroidism, iron and folic acid deficiency, and blood loss, the latter occurring especially in gastrointestinal disorders due to uremic gastritis.[10]

Delayed renal replacement therapy in end-stage renal disease has been associated with mortality and complications. Death occurs in approximately 4.8 out of 100 children undergoing hemodialysis.[11] The mortality rate in our study was higher, at 16.3%. Some studies suggested the potential association between mortality and calcitriol levels. LLow calcitriol levels have been associated with mortality outcomes, impaired bone mineralization, and cardiovascular effects. A meta-analysis noted a 27% reduction in mortality risk in patients who received active vitamin D3/calcitriol therapy.[12] However, in this study, we did not seek to find this association.

Our subjects' mean calcitriol level was 108.77 (SD 10.79) pmol/L, with a ranges from 55.2 to 548.9 pmol/L. Our analysis revealed no significant difference in calcitriol levels and subject characteristics of growth status, CKD etiology, or anemia. Failure to thrive is a complication in about one-third of children with CKD. Failure to thrive in CKD is caused by reduced bone-forming minerals, reduced growth hormone, and complications of bone mineralization, including renal osteodystrophy. A previous study reported that among 729 children with failure to thrive, 42.1% had vitamin D deficiency.[13] In addition, another study reported that out of 43 patients with stage I to V CKD, 1 to 5, 25% had a glomerular etiology, and 90% had low vitamin D. Vitamin D deficiency in CKD is caused by the loss of vitamin D-binding protein (DBP) through the urine.[14]

In our study, glomerular etiologies were the smost common cause of CKD, but proteinuria and albumin levels were not recorded at the time of examination. CKD patients may experience a gradual decrease in calcitriol level and erythropoietin. Vitamin D may play a role in erythropoiesis. In CKD patients, the administration of active vitamin D has the effect of improving anemia and reducing the need for erythropoietin-stimulating agents (ESA). A study demonstrated that calcidiol and calcitriol deficiency

were associated with decreased hemoglobin levels and anemia in CKD.[15]

We found no significant differences in calcitriol levels across all CKD stages (**Table 2**). However, no standard consensus has been reached on the normal reference value of calcitriol levels in children. Ishimura *et al.*[16] reported a mean calcitriol levels of 18.8 (SD 9.2) pg/mL in non-dialyzed patients with CKD, using a reference value of 29 (SD 10) pg/mL or 69.6 (SD 24) pmol/L. Giannakopoulos *et al.*[17] used a calcitriol reference value of 70-400 pmol/L. Higgins *et al.*[5] found that in 377 healthy children, calcitriol levels were 77-471 pmol/L for 0 to 1-year-old, 113-363 pmol/L for 1-3-year-olds, and 108-246 pmol/L for 3-19-year-olds. Our subjects had a mean calcitriol level near the lower limit of the reference value for age.

When subjects were grouped into early and advanced stage CKD, there was a significant difference in calcitriol level between the two groups (**Table 3**). Decreased calcitriol levels were found in 63.6% subjects in the early stage group and in all subjects in the advanced stage group. In *The Chronic Kidney Disease in Children* (CKiD) multicenter cohort study on 586 children with GFR of 30-90 mL/min/1.73m^2, 28% had vitamin D [25(OH)D] deficiency. Calcitriol levels were significantly associated with serum 25(OH)D levels. For every 10 ng/mL decrease of 25(OH)D, calcitriol level decreased by 3 pg/mL. Other predictive factors associated with calcitriol levels were GFR value, FGF23 level, and proteinuria.[18]

A previous study found a decrease in calcitriol level in early stage CKD before a significant increase in parathyroid hormone (PTH) level occurred. A decrease in calcitriol level was significantly correlated with GFR ($P<0.0001$) and with 25(OH)D level ($P=0.0182$), but there was no significant association between GFR and 25(OH)D_3 ($P=0.8932$). In an analysis of hyperparathyroidism, in 49% of subjects, low calcitriol levels were associated with high intact PTH (iPTH) levels, while only 35% of low 25(OH)D_3 level were associated with high iPTH.[19] This suggests that calcitriol may act as a determinant of secondary hyperparathyroidism, which is associated with complications of CKD-MBD in CKD patients.[19]

Our one-way ANOVA follow-up test comparing calcitriol levels between each CKD stage (**Table 4**) showed that a decrease in calcitriol level had occurred at stage II, and at stages IV ($P=0.049$) and V ($P=0.027$) calcitriol levels were significantly lower than at stage I. The increase in FGF23 generally starts at a GFR below 70 mL/min/1.73m^2 or at stage 2, and increases with decreased GFR. In the advanced stage, FGF23 concentration increases to 1,000 times above the normal range. This dramatic increase in FGF23 is in line with a decrease in calcitriol production and the induction of secondary hyperparathyroidism.[20]

In conclusion, the decrease in calcitriol level starts at an early stage in CKD. There are significant differences in calcitriol levels between early and advanced stages of CKD. Clinicians and pediatricians should be aware of the impact of CKD on vitamin D status and calcitriol levels.

Conflict of interest

None declared.

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