Vitamin D Levels in Chronic Kidney Disease Stage 3, 4, and 5

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Abstract

Background: Hypovitaminosis D is highly prevalent in chronic kidney disease (CKD). This conditionmay increase CKD progression and cause various complications, since kidney has a pivotal role in metabolizing the vitamin D. The aim of this study was to find the difference in vitamin D levels among CKD stage 3 to 5.

Methods: A cross-sectional study involving patients aged over 18 years with CKD stage 3 to 5 who visited Dr. Hasan Sadikin General Hospital, Dustira Hospital, and Kidney Special Hospital Ny. R.A. Habibie in 2017 was conducted. CKD stages were determined based on glomerular filtration rate (GFR). Kruskal-Wallis test was used to analyzethe difference in vitamin D levels among CKD stage 3 to 5.

Results: One hundred subjects consisting of 57 men and 43 women met the study criteria. There were 97% of subjects experienced hypovitaminosis D, with 20% having vitamin D insufficiency and 77% having vitamin D deficiency. In subjects with vitamin D insufficiency, a decrease in the mean vitamin D levels was observed along with advancing stages of CKD (p=0.255). No vitamin D level difference was observed among CKD stage 3 to 5 [11.1 (3.8-27.7) ng/mL vs 14.45 (5.10-50.90) ng/mL vs 11.7 (4.2-38.0) ng/mL, p>0.05].

Conclusions: There is no difference in vitamin D levels among CKD stage 3, 4 and 5.

Keywords: Chronic kidney disease, deficiency, vitamin D

Introduction

Chronic kidney disease (CKD) is abnormalities of kidney structure or function for more than 3 months.[1] About 10% of the world's population suffer from CKD, and every year there are millions of people die from its complications.[2] The results of Global Burden of Disease study in 2010 showed that CKD experienced an increase in the ranking of causes of death in the world, from 27th to 18th in 1990-2010.[3] As one of non-communicable diseases, CKD is a health problem that is still increasing in Indonesia. Based on Indonesia Basic Health Research (*Riset Kesehatan Dasar)* 2013, the prevalence of CKD increased along with increasing life expectancy with a peak at over 75 years of age.[4]

Chronic kidney disease occurs when there is decreased glomerular filtration rate (GFR) for more than 3 months, namely GFR <60 mL/min/1.73m^2 which indicates CKD stage 3-5.[1] At those stages, the decreased GFR has caused various complications, one of which is hypovitaminosis D which includes vitamin D deficiency (25(OH)D <20 ng/mL) and vitamin D insufficiency (25(OH)D <30 ng/ml).[5-7] A decrease in GFR that occurs along with advancing stages of CKD may cause a decrease in vitamin D levels in patients with CKD through/ decreased 25(OH)D (25-hydroxyvitamin D/ calcidiol) supply into the kidney, increased fibroblast growth factor-23 (FGF-23) level, and reduced megalin receptor function inside proximal convoluted tubule (PCT).[1,6,8] Hypovitaminosis D is also common in the general population including Indonesia. About 75% of healthy children aged 7 to 12 years in Indonesia experience vitamin D insufficiency

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and 15% experience vitamin D deficiency.[9] While in CKD, 70–80% patients experience vitamin D deficiency.[10] Hypovitaminosis D in CKD may increase CKD progression, as well as morbidity and mortality.[6,11] Hypovitaminosis D may also cause mineral and bone disorder which leads to osteopenia and osteoporosis that may increase the risk of fracture.[12,13] Therefore, mineral and bone disorder may cause disability and reduce the quality of life of patients with CKD. Kidney disease itself is a disease with the second largest funding from Healthcare and Social Security Agency (*Badan Penyelenggara Jaminan Sosial Kesehatan, BPJS Kesehatan)* after heart disease.[4] The mineral and bone disorder will certainly increase the burden of health costs in Indonesia.

Based on above explanation, it is important to know vitamin D levels difference among stages of CKD. This study aimed to determine the vitamin D levels difference among CKD stage 3, 4 and 5, and is expected to add information and data about vitamin D level in CKD so that it canprovide information to help determine cut-off point of vitamin D and proper vitamin D therapy in predialysis CKD.

Methods

This study was a cross-sectional study with comparative analysis conducted in April–August 2018, and carried out using secondary data from previous studies taken from Dr. Hasan Sadikin General Hospital, Dustira Hospital, and Kidney Special Hospital Ny. R.A. Habibie in 2017. The subjects were patients participated in previous research entitled "Correlation of Total Antioxidant Capacity, Vitamin D, Calcium, and Sclerostin to Body Composition of Patients with CKD Stage 3-5". This study was approved by the Health Research Ethics Committee Universitas Padjajaran Bandung (No.295/UN6.KEP/EC/2018).

Inclusion criteria of this study were all data of patients over the age of 18 who had a diagnosis of CKD stage 3–5. Exclusion criteria of this study were patients who had undergone hemodialysis; patients who had a diagnosis of severe diseases, infectious diseases, and malignancy; patients who regularly consumed supplements of antioxidants, vitamin D and calcium; and incomplete patient data, namely data that did not include the variables sought, including vitamin D level and stage of CKD.

Research variables used in this study include: an independent variable, namely stage of CKD; a dependent variable, namely vitamin D (25(OH)D) level; and confounding variables namely age, gender, and body mass index (BMI).

The stage of CKD was determined based on the glomerular filtration rate (GFR) in accordance with Kidney Disease Improving Global Outcomes (KDIGO) 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease (stage 3–GFR=30-59 mL/min/1.73m^2; stage 4–GFR=15-29 mL/min/1.73m^2; stage 5–GFR <15 mL/min/1.73m^2).[1]

The GFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation. Vitamin D (25(OH)D) level was measured using chemiluminescent microparticle immunoassay from ARCHITECT 25-OH Vitamin D assay. Then, the vitamin D level was categorized as normal (25(OH)D = 30-100 ng/mL), insufficiency (25(OH)D <30 ng/mL), and deficiency (25(OH)D <20 ng/mL).[7]

Sampling method used in this study was total sampling, in which all samples contained in secondary data were collected. The collected data were then grouped according to stage of CKD. Then, to see the difference in vitamin D levels among stages of CKD, Kruskal-Wallis test was performed. Hypothesis testing revealed significant results if p <0.05. Multiple linear regression analysis was also conducted to control confounding variables (age and BMI). The data were analyzed using IBM SPSS Statistics 25.

Results

The number of subjects who met the criteria of this study was 100 subjects. Table 1 shows characteristics of study sample which grouped according to the stages of CKD. Most subjects with CKD stage 3, 4 and 5 were found to bemale. Subjects with CKD stage 4 were found to have the highest median age of 65 years, while subjects with CKD stage 3 had the lowest median age of 54 years. Most patients with CKD stage 3, 4 and 5 had over 50 years of age. There was a significant age difference among CKD stage 3, 4 and 5 (p=0.002) and there was a significant correlation between age and CKD stages (p=0.013).

Table 2 shows vitamin D levels (25(OH) D) in patients with CKD stages 3, 4, and 5. The overall median of vitamin D level in this study was 12.25 (3.80-50.90) ng/mL. Subjects with CKD stage 4 had the highest median vitamin D of 14.45 ng/mL, whereas subjects with CKD stage 3 had the lowest median vitamin D of 11.1 ng/mL. The results

Table 1 Subject Characteristics According to CKD Stages

Characteristics	CKD			P Value
	Stage 3 (n=21)	Stage 4 (n=34)	Stage 5 (n=45)	
Gender, n(%)				
Male	11(52.38%)	21(61.76%)	25(55.56%)	0.765*
Female	10(47.62%)	13(38.24%)	20(44.44%)	
Age (years),median (min-max)	54 (24-69)	65 (28-77)	59 (33-78)	0.002**
>50 year, n(%)	11(52.4%)	30(88.2%)	32 (71.1%)	0.013*
≤50 year, n(%)	10 (47.6%)	4 (11.8%)	13(28.9%)	
BMI, median (min-max)	23.75(17.65-37.99)	24.39(18.75-36.36)	22.11 (10.54-35.39)	0.067**

Note:*chi-square test; **Kruskal-Wallis test; BMI, body mass index; CKD, chronic kidney disease

showed no significant difference in vitamin D (25(OH)D) levels among CKD stage 3, 4, and 5 (p=0.089). Most subjects with CKD stage 3, 4, and 5 CKD had vitamin D deficiency, and there were no subjects who had normal vitamin D level in subjects with CKD stage 3. In subjects with vitamin D insufficiency, the highest mean of vitamin D level was found in CKD stage 3, while the lowest mean of vitamin D level was found in CKD stage 5. In subjects with vitamin D deficiency, the highest mean of vitamin D level was found in CKD stage 4, while the lowest mean of vitamin D level was found in CKD stage 3. In those subjects, there was also an increase in the number of subjects with advancing stages of CKD. In subjects with vitamin D insufficiency and deficiency, there were no significant differences in vitamin D levels among CKD stage 3, 4 and 5 (p=0.255 and p=0.596), but in subjects with vitamin D insufficiency there was a decrease in mean vitamin D levels with advancing stages of CKD.

Figure 1 shows a graph of vitamin D (25(OH)D) levels in CKD stage 3, 4, and 5. In the graph, it was found that most subjects with CKD stage 3, 4, and 5 had vitamin D (25(OH) D) levels below 30 ng/mL, particularly below 20 ng/mL.

Figure 2 shows a graph of the number of subjects based on hypovitaminosis D category in CKD stage 3, 4, and 5. In the graph, it was found that there was an increase in the number of subjects with vitamin D deficiency along with advancing stages of CKD.

Table 3 shows the result of multiple linear regression test to control confounding variables. After multivariate test was performed to control confounding variables (BMI and age), the result showed that there was no significant difference in vitamin D levels among CKD stage 3, 4 and 5 (p=0.335 and p=0.736). The classical assumption test showed that there was no multicollinearity and error distribution had not followed

Table 2 Vitamin D (25(OH)D) Levels in CKD Stage 3, 4, and 5

	CKD			P value
	Stage 3	Stage 4	Stage 5	
Vitamin D levels (ng/mL),median (min-max)	11.1 (3.8-27.7)	14.45 (5.10-50.90)	11.7 (4.2-38.0)	0.089*
Normal, n(%)	0 (0%)	2 (5.9%)	1 (2.2%)	
Vitamin D levels (ng/mL), $\bar{x}$±SD	-	41.75±12.94	38	-
Insufficiency, n(%)	4 (19%)	10 (29.4%)	6 (13.3%)	
Vitamin D levels (ng/nL), $\bar{x}$±SD	24.38±2.62	23.35±2.48	21.95±1.43	0.255**
Deficiency, n(%)	17 (81%)	22 (64.7%)	38 (84.4%)	
Vitamin D levels (ng/mL), $\bar{x}$±SD	10.14±3.99	11.42±3.97	10.62±4.06	0.596**

Note:*Kruskal-Wallis test; **one-way ANOVA test; CKD, chronic kidney disease

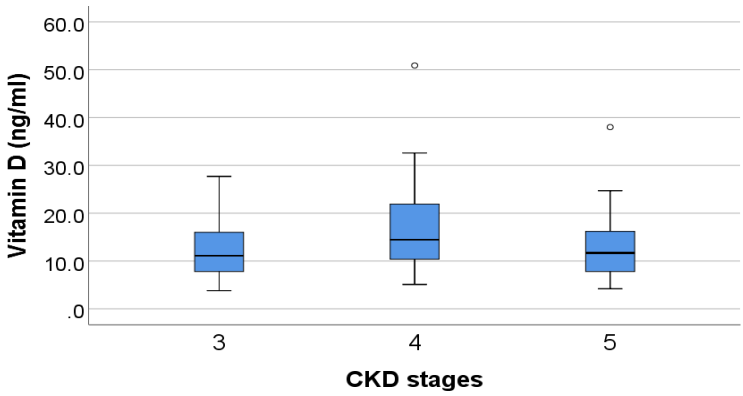

Figure 1 Graph of Vitamin D (25(OH)D) Levels in CKD Stage 3, 4, and 5

normal distribution pattern. Transformation of the dependent variable was needed so that the error distribution followed the normal distribution pattern.

Discussion

Based on the results of the study, it was known that the general characteristics of the study subjects were predominantly male and most had an age above 50 years (Table 1). These results are consistent with the results of research conducted by Diniz et al.[14] in Brazil involving 125 subjects with CKD who had an average age of 57.4 years and 55% of subjects were male. These results are also consistent with the results of research conducted by Rozita et al.[15] in Malaysia involving 50 subjects with CKD who had an average age of 53 years and 58% of the subjects were male. The result of this study also showed a correlation between age and CKD stages. CKD is more common in older age due to decreased renal function with increasing age and the presence of various risk factors for CKD such as diabetes and hypertension in older individuals.[16]

Vitamin D (25(OH)D) level in the body can be classified into 3 categories: normal, insufficiency, and deficiency. Vitamin D level is classified as normal if the 25(OH) D concentration in the body is 30–100 ng/mL. Vitamin D insufficiency occurs when 25(OH)D concentration is below 30 ng/mL, while vitamin D deficiency occurs when 25(OH)D concentration is below 20 ng/mL.[7] Based on the results of the study, there was no significant difference in vitamin D levels among CKD degrees 3, 4 and 5 (Table 3), but the results showed that almost all (97%) study subjects had hypovitaminosis D (Table 2). Hypovitaminosis D had occurred from CKD stage 3, and most subjects with CKD stage 3, 4, and 5 had vitamin D deficiency. These results are consistent with the research conducted by Rozita et al.[15] in Malaysia involving 50 subjects with CKD stage 2-4 and showed vitamin D deficiency was found in CKD stage 2, 3, and 4 with a mean 25(OH)D levels of 15.7 ng/mL, 16.5 ng/mL, and 15.5 ng/mL, respectively, and also there was no significant difference

Table 3 Multiple Linear Regression Analysis with Vitamin D Level as the Dependent Variable n=100)

Predictor Variables	B Value	P Value	Confidence Interval 95%	
			Lower Bound	Upper Bound
Constant	1.835	<0.001	0.939	2.732
Stage 3vs4	0.146	0.335	-0.152	0.444
Stage 3vs5	-0.047	0.736	-0.321	0.228
BMI	-0.002	0.845	-0.026	0.021
Age	0.012	0.022	0.002	0.022

Note:dependent variable=vitamin D; BMI, body mass index; CKD, chronic kidney disease

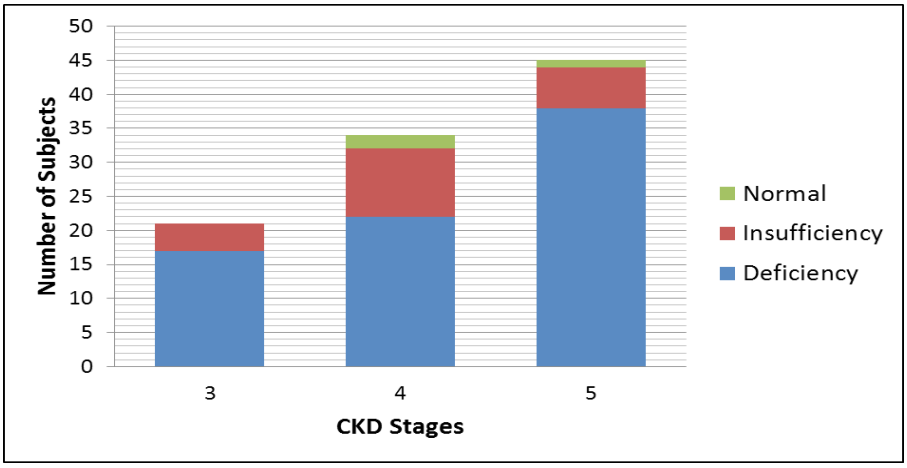

Figure 2 Graph of the Number of Subjects Based on Hypovitaminosis D Category in CKD Stage 3, 4, and 5

in vitamin D levels among CKD stage 2, 3 and 4. These results are also consistent with the results of research conducted by Diniz et al.[14] in Brazil involving 125 subjects with CKD stage 2–5 and showed the majority of subjects had 25(OH)D levels below 30 ng/mL and also there was no significant difference in vitamin D levels among CKD stage 2–5. Similar results are also found in children with CKD. Study conducted by Lee et al.[17] in South Korea involving 113 children aged 1–18 years with CKD stage 2–5 showed that most subjects had 25(OH)D levels below 30 ng/mL.

Hypovitaminosis D is a common problem in the general population. The prevalence of vitamin D deficiency in South Asia is about 70% or higher, while the prevalence of vitamin D deficiency in Southeast Asia varies from 6–70%.[18] Hypovitaminosis D is also quite common in Indonesia characterized by 75.8% of healthy children aged 7–12 years old experience vitamin D insufficiency and 15% experience vitamin D deficiency.[9]

Hypovitaminosis D occurs in the general population in Indonesia even though Indonesia receives a lot of sunlight because it is located in the equatorial region. In addition, CKD can also cause decreased vitamin D level.[6] The occurrence of CKD will certainly cause a decrease in vitamin D levels in the community. This is evidenced by the results of research conducted by Rozita et al.[15] stating that in subjects with vitamin D deficiency, it was found that 25(OH)D levels were significantly lower in the group of subjects with CKD compared to the control group. Hypovitaminosis D in CKD may cause worsening renal function, increased CKD progression, and increased morbidity and mortality. This is because vitamin D has renoprotective effects that can reduce inflammation in the kidney, produce antifibrotic and antiapoptotic effects, prevent podocyte damage, and reduce intraglomerular pressure.[6,11]

Based on the results of the study, there was no significant difference in vitamin D levels among CKD stage 3, 4, and 5, but it was found that there was an increase in the number of subjects with vitamin D deficiency along with advancing stages of CKD and a decrease in the mean 25(OH)D levels along with advancing stages of CKD in the group of subjects with vitamin D insufficiency (Table 2). Increased stages of CKD indicate a decrease in GFR as a marker of renal filtration function.[1] A decrease in GFR may cause a decrease in vitamin D level. Decreased GFR may cause a decrease in supply of 25(OH)D to proximal convoluted tubule (PCT), an increase in fibroblast growth factor-23 (FGF-23) level in the body, and a decrease in megalin receptor function in PCT.[6,8] A decrease in the supply of 25(OH)D to PCT cells may cause a decrease in the synthesis of 1,25(OH)2D (1,25-dihydroxyvitamin D/ calcitriol).[8] Elevated FGF-23 level may be caused by hyperphosphatemia. This may results from a decrease in renal phosphate excretion which occurs along with decreasing GFR.5 Increased level of FGF-23 may cause synthesis of 1,25 (OH)2D decreases due to disruption of 1α-hydroxylase enzyme activity. The increased FGF-23 level may also promote the degradation of vitamin D (25(OH)D and 1,25(OH)2D) due to the

increase of 24-hydroxylase enzyme activity.[6] Megalin receptors require active vitamin D to work properly, so a decrease in 1,25(OH)2D level in the body may reduce the function of the megalin receptor in 25(OH)D tubular reabsorption.[6,8] Decreased function of megalin receptors may causes loss of 25(OH)D-vitamin D binding protein complex in urine. This leads to a decrease in the levels of 25(OH)D and 1,25(OH)2D in the body.[6]

Based on these mechanisms, it was hypothesized that there was a difference in vitamin D levels among CKD stages. The high prevalence of hypovitaminosis D in the general population in Indonesia may cause decreased vitamin D levels that occur in CKD patients does not show a significant difference. In addition, based on the results of the study, there was no decrease in vitamin D levels with advancing stages of CKD, whereas CKD stage 3 had the lowest median of vitamin D and CKD stage 4 had the highest median of vitamin D. This may be caused by factors not measured in this study that may affect vitamin D levels in this study, such as sun exposure, skin pigmentation, and the use of sunscreen.[19]

Hypovitaminosis D may cause mineral and bone disorder in chronic kidney disease-mineral and bone disorder (CKD-MBD), decreased intestinal calcium absorption and renal calcium reabsorption which induce hypocalcemia. Hypocalcaemia may promote increased parathyroid hormone production which causes secondary hyperparathyroidism.[12] High bone turnover due to secondary hyperparathyroidism leads to high bone resorption (higher than bone formation) that induces hypercalcaemia, hyperphosphatemia, osteopenia and osteoporosis.[12,13] Cardiovascular disease in form of vascular wall calcifications may occur due to hyperphosphatemia and hypercalcaemia.[5] Calcification and stiffness of blood vessels may cause increased systolic blood pressure and left ventricular hypertrophy.[13]

The results of this study indicate that there was hypovitaminosis D starting from CKD stage 3 (Table 2). This study did not measure vitamin D levels in CKD stage 1 and 2 because at those stages, there are no signs and symptoms of CKD yet.[5] Research conducted by Diniz et al.[14] and Rozita et al.[15] also showed that hypovitaminosis D had occurred since CKD stage 2. It is important to note that there are no studies that have measured normal value of vitamin D level for Indonesians. Based on the results of these studies, vitamin D (25(OH)D) testing as well as vitamin D supplementation in patients with CKD can be started from CKD stage 3 or earlier. If hypovitaminosis D is found, it is important to immediately provide vitamin D supplements to reduce CKD progression, prevent mineral and bone disorder, and reduce the risk of all-cause and cardiovascular mortality.[14,20] These things can be achieved through several effects of vitamin D, namely reducing the renin-angiotensin system, increasing insulin secretion and sensitivity, preventing proliferation vascular smooth muscle cells proliferation, protecting normal endothelial cells function, controlling inflammatory processes, preventing myocardial cells proliferation and hypertrophy, and inhibiting anticoagulants activity.[20] Renoprotective activity of vitamin D may also reduce proteinuria and repair kidney damage by decreasing the renin-angiotensin system, decreasing activation of NF-κB (nuclear factor-kappaB) transcription factors, inhibiting Wnt/β-Catenin pathway, and maintaining the integrity of slit diaphragm and protecting glomerular filtration membrane.[11]

The limitation of this study is that the factors that can affect vitamin D levels in patients with CKD were not measured. These factors include factors that can affect vitamin D production in the skin such as sun exposure (can be measured through daily activities or types of clothing that are often used), skin pigmentation/race and sunscreen use. Therefore, hypovitaminosis D in the subjects of this study was not solely caused by decreased GFR alone, but there were various other influential factors (confounding factors) that were not measured in this study. Substantially based on theory and literature, there is difference in vitamin D levels among CKD stage 3, 4, and 5, but statistically this study showed a conclusion that is not significant to the hypothesis made.

Based on the results of the study it can be concluded that there is no difference in vitamin D levels among CKD stage 3, 4, and 5, but hypovitaminosis D can be found since CKD stage 3 to 5 so that examination of vitamin D level and vitamin D supplementation are important things to do. Various limitations found in this study cause the results of the study could not significantly detect difference in vitamin D levels among stages of CKD. Thus, further research is needed by paying attention to and taking into account other factors that can affect vitamin D levels in patients with CKD.

References

1. Eknoyan G, Lameire N, Eckardt K, Kasiske B, Wheeler D, Levin A, et al. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int. 2013;3(1):1–150.
2. World Kidney Day. World kidney day: chronic kidney disease. 2018. [cited 2018 August 5]. Available from: http://www.worldkidneyday.org/faqs/chronic-kidney-disease/.
3. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380(9859):2095–128.
4. Kementrian Kesehatan Republik Indonesia. Pusat data dan informasi kementrian kesehatan republik indonesia: situasi penyakit ginjal kronis. Jakarta: Kementrian Kesehatan Republik Indonesia; 2017.
5. Bargman JM, Skorecki K. Chronic Kidney Disease. In: Kasper DL, Fauci AS, Hauser SL, Longo DL, Jameson JL, Loscalzo J, editors. Harrison's Principles of Internal Medicine. 19th ed. New York: McGraw-Hill Education; 2015. p. 1811–21.
6. Kim CS, Kim SW. Vitamin D and chronic kidney disease. Korean J Intern Med. 2014;29(4):416–27.
7. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2011;96(7):1911–30.
8. Inda Filho AJ, Melamed ML. Vitamin D and kidney disease: what we know and what we do not know. J Bras Nefrol. 2013;35(4):323–31.
9. Soesanti F, Pulungan A, Tridjaja B, Batubara JR. Vitamin D profile in healthy children aged 7-12 years old in Indonesia. Int J Pediatr Endocrinol. 2013;2013(Suppl 1):P167.
10. Nigwekar SU, Tamez H, Thadhani RI. Vitamin D and chronic kidney disease-mineral bone disease (CKD-MBD). Bonekey Rep. 2014;3:498–503.
11. Li YC. Vitamin D in chronic kidney disease. Contrib Nephrol. 2013;180:98–109.
12. Mac Way F, Lessard M, Lafage-Proust MH. Pathophysiology of chronic kidney disease-mineral and bone disorder. Joint Bone Spine. 2012;79(6):544–9.
13. Seifert ME, Hruska KA. The kidney-vascular-bone axis in the chronic kidney disease-mineral bone disorder. Transplantation. 2016;100(3):497–505.
14. Diniz HF, Romao MF, Elias RM, Romao Junior JE. Vitamin D deficiency and insufficiency in patients with chronic kidney disease. J Bras Nefrol. 2012;34(1):58–63.
15. Rozita M, Afidza MN, Ruslinda M, Cader R, Halim AG, Kong CTN, et al. Serum vitamin D levels in patients with chronic kidney disease. EXCLI J. 2013;12:511–20.
16. Prakash S, O'Hare AM. Interaction of aging and chronic kidney disease. Semin Nephrol. 2009;29(5):497–503.
17. Lee K, Lee S, Cho H. Optimal vitamin d levels in children with chronic kidney disease. J Nephrol Ther. 2015;5(4):207–10.
18. Nimitphong H, Holick MF. Vitamin D status and sun exposure in Southeast Asia. Dermatoendocrinol. 2013;5(1):34–7.
19. Tsiaras WG, Weinstock MA. Factors influencing vitamin D status. Acta Derm Venereol. 2011;91(2):115–24.
20. Zheng Z, Shi H, Jia J, Li D, Lin S. Vitamin D supplementation and mortality risk in chronic kidney disease: a meta-analysis of 20 observational studies. BMC Nephrol. 2013;14(1):199–211.