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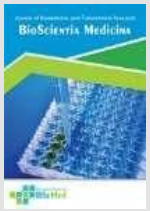

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Serum Vitamin D Levels Related to Cognitive Function in Chronic Kidney Disease Patients

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A B S T R A C T

Background: Vitamin D acts as a neuroprotector and modulator in the central nervous system. Hypovitaminosis is a risk factor for cognitive dysfunction. Hypovitaminosis D and impaired cognitive function are common in patients with chronic kidney disease. Impaired cognitive function is comorbid that can increase the morbidity and mortality of patients with chronic kidney disease. This study aims to assess the relationship between serum vitamin D levels and cognitive function in patients with chronic kidney disease. **Methods:** This research is an observational study with a cross-sectional approach. A total of 60 research subjects participated in this study. Sociodemographic data, cognitive function, and vitamin D levels were analyzed in this study. Data analysis was performed with SPSS 25 to perform univariate and bivariate tests. **Results:** The impaired cognitive function was found in 56.7% of CKD patients. The median serum vitamin D level of patients with chronic kidney disease with impaired cognitive function was 30.80 ng/mL and without impaired cognitive function 42.98 ng/mL. There was a significant relationship between serum vitamin D levels and impaired cognitive function (OR=4.125, p=0.035). The cut-off point of serum vitamin D levels associated with impaired cognitive function in CKD patients was 34.8 ng/mL (sensitivity 64.7% and specificity 69.2%). **Conclusion:** There is a significant relationship between serum vitamin D levels and the incidence of cognitive dysfunction in patients with chronic kidney disease. The cut-off point for serum vitamin D levels associated with impaired cognitive function in chronic kidney disease is 34.8 ng/mL.

1. Introduction

Vitamin D is a fat-soluble steroid hormone that plays a role in various physiological processes of the body. Vitamin D in the body exists in the form of 25-hydroxyvitamin D (25[OH]D) and 1,25-dihydroxy vitamin D (1,25[OH]$_2$D). 25-hydroxyvitamin D is the main metabolite form of vitamin D, while 1,25-dihydroxy vitamin D is the active metabolite form derived from the hydroxylation of 25(OH)D.[1,2] Vitamin D plays an important role in maintaining bone calcium metabolism homeostasis and several other extraskeletal physiological processes, such as in the central nervous system.[3] The role of vitamin D in the central nervous system is as a neuroprotector, antioxidant, anti-inflammatory, and able to prevent the accumulation of beta-amyloid (β amyloid).[4] Patients with chronic kidney disease (chronic kidney disease) are a population at high risk for hypovitaminosis D.[5] Hypovitaminosis D occurs in 40.7% of stage 3 chronic kidney disease, 61.5% of stage 4 chronic kidney disease, and increases to 74.6% of kidney disease chronic stage 5.[6] Decreased levels of vitamin D (hypovitaminosis D) increase the risk of

several neurological diseases such as mild cognitive impairment to dementia.[7,8] The general population with hypovitaminosis D has a 2.4 times greater risk of suffering from the impaired cognitive function than the population with optimal vitamin D levels.[9] Hypovitaminosis D, which occurs in patients with chronic kidney disease, will further increase the incidence of impaired cognitive function.[10,11]

Impaired cognitive function often occurs in patients with chronic kidney disease (chronic kidney disease).[12] Patients with chronic kidney disease have a higher risk of cognitive impairment than the general population.[13] The incidence of impaired cognitive function increases as kidney function worsens. The prevalence of impaired cognitive function in stage 5 chronic kidney disease undergoing hemodialysis is 70-87%.[14] Impaired cognitive function in patients with chronic kidney disease occurs due to processes related to chronic kidney disease or hypovitaminosis D.[15] Hypovitaminosis D causes neuronal degeneration through neuroprotective dysfunction, dysregulation of intracellular calcium homeostasis, oxidative stress, glutaminergic excitotoxicity, inflammation and accumulation of β amyloid in the brain. Thus manifesting as impaired cognitive function.[16] Hypovitaminosis D can also cause a worsening of the severity of chronic kidney disease, which will further worsen cognitive function. Several current studies have shown that the combination of hypovitaminosis D and chronic kidney disease causes cognitive impairment to occur more rapidly and with greater severity.[17,18] This study aims to explore the role of vitamin D levels with cognitive function in patients with chronic kidney disease.

2. Methods

The research design in this study is an analytical observational study with a cross-sectional approach. A total of 60 research subjects participated in this study, where the subjects met the inclusion criteria: patients who had been diagnosed with stage 5 chronic kidney disease (chronic kidney disease), had undergone hemodialysis for ≥ 3 months, were 18 years old, and were willing to participate in the study. This research is located in the Hemodialysis Unit of Dr. M. Djamil General Hospital Padang in April - June 2022. This study was approved by the medical and health research ethics committee of Dr. M. Djamil General Hospital Padang, Indonesia (No. 614/UN.16.2/KEP-FK/2022).

In all study subjects, basic characteristics such as age, sex, education level, hypertension, diabetes mellitus, body mass index (BMI), length of hemodialysis, and cognitive function were recorded using the Montreal Cognitive Assessment Indonesia (MoCA-Ina). Assessment of vitamin D levels was carried out using the ELISA method, according to the instructions from the ELISA kit manual book. Data analysis was carried out with the help of SPSS version 25 software. Data analysis was carried out univariate and bivariate with $p < 0.05$.

3. Results

Table 1 shows that the research subjects consisted of patients who had been diagnosed with chronic kidney disease (chronic kidney disease) and had undergone hemodialysis with or without impaired cognitive function. The mean age of the sample was 51.48 ± 11.43 years, and the male sample (53.3%) was more than the female in the current study. A total of 46 samples (76.7%) have had education for ≥ 12 years. Most of the samples (80%) suffered from hypertension, and only 4 samples (6.7%) had diabetes mellitus. The median body mass index (BMI) in the current study was 23.1 kg/m^2. The median length of hemodialysis of 60 samples was 21 months. Global cognitive dysfunction was found in 34 samples (56.7%). The median value of serum vitamin D levels in 60 samples was 34.8 ng/mL.

Table 1. Baseline characteristics of research subjects.

Characteristics	Description (n= 60)
Age (years), mean ± SD	51.48 ± 11.43
Gender, n (%) Male Female	 32 (53.3%) 28 (46.7%)
Length of education, n (%) < 12 years ≥ 12 years	 14 (23.3%) 46 (76.7%)
Hypertension, n (%)	48 (80%)
Diabetes mellitus, n (%)	4 (6.7%)
BMI, medium (min-max)	23.1 (15.40 – 34.30)
Length of hemodialysis (months), median (min-max)	21 (3-120)
Global cognitive function, n (%) Impaired Normal	 34 (56.7%) 26 (43.3%)
Serum vitamin D level (ng) /mL) medium (min-max)	34.8 (9.72 – 102.7)

Differences in serum vitamin D levels between groups with global cognitive impairment and without global cognitive function impairment are shown in table 2. Median serum vitamin D values in the global cognitively impaired group are 30.80 ng/mL with a minimum value of 10.54 ng/mL and a maximum value of 102.70 ng/mL. The median value of serum vitamin D levels in the group without global cognitive impairment was 42.98 ng/mL, with a minimum value of 9.72 mg/dL and a maximum value of 93.55 mg/dL. Serum vitamin D levels in the group with global cognitive impairment were lower than in the group without global cognitive impairment. The results of bivariate analysis using the Mann-Whitney test on serum vitamin D levels in the group with and without global cognitive dysfunction showed a statistically significant difference (p = 0.025).

Table 2. Differences in serum vitamin D levels in patients with chronic kidney disease with and without global cognitive dysfunction.

Variable	Global Cognitive Function (MoCA-Ina)		p-value
	Impaired (n= 34)	Normal (n= 26)	
Serum vitamin D level (ng/mL) median (min-max)	30.80 (10.54 – 102.70)	42.98 (9.72 – 93.55)	0.025*

* Mann-Whitney test

Provisions regarding the normal value of vitamin D in the population of chronic kidney disease patients vary. Therefore, this study calculated the cut-off point (COP) using the receiver operating characteristic (ROC) curve to obtain the area under the curve (AUC), which can be used to determine the optimal COP of serum vitamin D levels associated with impaired global cognitive function. In patients with chronic kidney disease. The results of the ROC curve analysis showed that the optimal COP of serum vitamin D levels between the group with and without global cognitive function impairment was 34.80 ng/mL. The AUC value obtained from the ROC method was 0.67 (95% confidence index, 0.526 – 0.815, p = 0.025), sensitivity 64.7% and specificity 69.2%.

Table 3 shows that in the group with impaired global cognitive function, there were 22 people (64.7%) who had serum vitamin D levels below the cut-off point, while in the group without global cognitive function impairment, there were 8 people (30.7%) who had vitamin D levels. D serum is below the cut-off point. The results of the Chi-square test showed a

significant difference in serum vitamin D levels between groups with and without global cognitive dysfunction (p = 0.019), and the odds ratio (OR) was 4.125.

Table 3. Relationship between serum vitamin D levels and the incidence of global cognitive impairment in patients with chronic kidney disease.

Variable	Global Cognitive Function (MocA-Ina)		p-value	OR (95%CI)
	Impaired (n= 34)	Normal (n= 26)		
Serum vitamin D level			0.019*	4.125 (1.38-12.27)
< cut-off point	22 (73.3%)	8 (26.7%)		
≥ cut-off point	12 (40%)	18 (60%)		

* Chi-Square Test

4. Discussion

Vitamin D is a fat-soluble steroid hormone that has an important role in various physiological processes of the skeletal and extraskeletal systems. In the central nervous system, vitamin D acts as a neuroprotector, is able to increase the synthesis of neurotransmitters, is anti-inflammatory, maintains intracellular calcium homeostasis, modulates gene expression for optimal neuronal function, is able to prevent cell damage due to oxidative stress and prevents the accumulation of beta-amyloid (β-amyloid). in the brain.[19] Patients with chronic kidney disease are a population susceptible to hypovitaminosis D. The prevalence of hypovitaminosis D increases progressively with worsening kidney function, especially in stage 3 to stage 5 chronic kidney disease.[20] The high incidence of hypovitaminosis D in patients with chronic kidney disease occurs due to decreased dietary intake, impaired intestinal absorption, loss of vitamin D binding protein through urine, and reduced 1α-hydroxylase activity which causes the decreased conversion of 25(OH)D to the active form, impaired photo biosynthesis of vitamin D_3 in the skin, reduction of renal megalin resulting in impaired 25(OH)D reabsorption tubular and increased fibroblast growth factor 23 (FGF-23) which decreases inhibition of 1α-hydroxylase activity.[21] The median serum vitamin D level in patients with chronic kidney disease with impaired global cognitive function in the current study was 30.80 ng/mL and in patients with chronic kidney disease without global cognitive impairment was 42.98 ng/mL.[22] Median serum vitamin D levels obtained in this study were still within the normal range for serum vitamin D levels. AnotMoCAher study showed a lower mean serum vitamin D level in patients with chronic kidney disease with impaired cognitive function, which was 17.2 ± 7.4 ng/mL. The study also showed that as many as 69% of patients with chronic kidney disease with impaired cognitive function experienced hypovitaminosis D.[23] The lower vitamin D levels in this study could be caused by different geographical locations that affect the intensity of sun exposure, diet, and skin pigmentation. Although still in the normal range, in the current study, it appears that serum vitamin D levels in chronic kidney disease patients with impaired global cognitive function are lower than in chronic kidney disease patients without global cognitive dysfunction.[24]

Another study showed that patients with vitamin D levels less than 30 ng/mL had a higher risk of impaired global cognitive function than the group with higher vitamin D levels. The results of the current study are also consistent with another study in which a total of 273 dialysis patients found that low vitamin D levels were an independent risk factor for the development of global cognitive impairment. Chronic kidney disease patients with vitamin D levels less than 10 ng/mL have a 1.15 times greater risk of suffering from the impaired global cognitive function than CKD patients with vitamin D levels more than 10 ng/mL. The estimated risk of impaired cognitive function was higher in the current study compared to previous

studies due to differences in the modalities of cognitive function examination and the method of examining serum vitamin D levels used. Vitamin D has been known to have an important role as a neuroprotector through glial cell-derived neurotrophic factor, nitric oxide synthase, and nerve growth factor. Vitamin D is also able to increase neuron survival, increase antioxidant activity, improve oxidative stress-induced mitochondrial dysfunction and reduce the production of excitatory neurotransmitters. Another study also stated that vitamin D was able to decrease the transcription of amyloid precursors and increase the clearance of beta-amyloid in the brain so as to prevent the accumulation of beta-amyloid. Based on this, decreased serum vitamin D levels have an impact on decreased neurological functional capacity and manifest as impaired cognitive function.[25,26]

5. Conclusion

There is a significant relationship between serum vitamin D levels and the incidence of cognitive impairment in patients with chronic kidney disease. The cut-off point for serum vitamin D levels associated with impaired cognitive function in chronic kidney disease is 34.8 ng/mL.

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