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ASSOCIATION BETWEEN NUTRITIONAL STATUS, VITAMIN D AND INFLAMMATION ON VASCULAR CALCIFICATION IN NON-DIALYSIS CHRONIC KIDNEY DISEASE PATIENTS

Sumi Ramadani* — Division of Nephrology and Hypertension, Department of Internal Medicine, Faculty of Medicine, Universitas Sumatera Utara, H. Adam Malik General Hospital, Medan, Indonesia *Corresponding Author

Syafrizal Nasution — Division of Nephrology and Hypertension, Department of Internal Medicine, Faculty of Medicine, Universitas Sumatera Utara, H. Adam Malik General Hospital, Medan, Indonesia

Alwi Thamrin Nasution — Division of Nephrology and Hypertension, Department of Internal Medicine, Faculty of Medicine, Universitas Sumatera Utara, H. Adam Malik General Hospital, Medan, Indonesia

ABSTRACT

Introduction: Cardiovascular disease is the most important complication in CKD patients which contributes to high morbidity and mortality rates. Vitamin D is known to have a biphasic effect in terms of arteriocalcification and appears to have a protective role. Inflammatory markers such as hsCRP are also known to increase chronic inflammatory conditions, namely CKD and have implications for vascular calcification. Malnutrition, especially decreased albumin and body mass index.Patients with CKD were also found to be risk factors for vascular calcification, but the mechanism was unknown. **Methods:** This study is a cross sectional study using a correlative analytic design, which was conducted at the Haji Adam Malik Hospital (RSHAM). The research subjects were all patients with chronic kidney disease stages 3, 4, and 5 above or equal to 18 years old who had never undergone hemodialysis and were treated at RSHAM either inpatient or outpatient patients. hsCRP, albumin, vitamin D and calcium, phosphorus, and serum LDL levels were examined by taking blood sample from the cubital fossa area. Abdominal aortic calcification was assessed by examination of the lateral abdominal radiograph by a radiologist. **Results:** From 30 samples, 7 patients had vascular calcification and 23 patients had no vascular calcification. This study found that BMI showed a significant association with arterial calcification whereas patients with arterial calcification had a lower BMI value (p value < 0.029). None of the other risk factors included in this study showed a significant outcome for vascular calcification. **Conclusion:** BMI was significantly associated with arterial calcification in non-dialysis CKD patients in this study. There was no significant relationship between hsCRP and vitamin D levels with the formation of vascular calcifications in non-dialysis CKD patients.

KEYWORDS : BMI;CKD; Inflammation; vitamin D

1. INTRODUCTION

Chronic kidney disease (CKD) is a health problem that continues to grow and becomes a global health burden with high economic costs for the health system. CKD is also an independent risk factor for cardiovascular disease (CVD). All stages of CKD are associated with an increased risk of cardiovascular morbidity, premature death, and decreased quality of life (Hill et al., 2016). Based on data from the Ministry of Health in 2014, the highest prevalence of CKD is in continental Europe, which is around 18.38% of the entire population in Europe. (Ministry of Health RI, 2014). Based on Riskesdas data in 2013 the prevalence of CKD in Indonesia increases with age, starting to increase in the 35-44 year age group (0.3%), followed by 45-54 years old (0.4%), and 55-74 years old. (0.5y and the highest in the age group 75 years (0.6%) (Kemenkes RI, 2014).

Cardiovascular disease (CVD) is a major cause of morbidity and mortality in patients with CKD. Even the early stages of CKD, which are characterized by relatively persistent or minimally decreased overall renal function, are associated with increased de novo events and recurrent CVD events. Among CKD patients with stage 3-4, the prevalence of CVD is 4-5 times higher than in the general population. In addition, CKD patients are also known to have comorbidities such as diabetes, hypertension, and obesity -which are known as traditional CVD risk factors in the general population (Gosmaonova and Le, 2011). The three most common pathological forms of CVD include changes in heart geometry, including left ventricular hypertrophy, atherosclerosis, and arteriosclerosis (Panjiyar et al, 2017).

As the basic pathophysiology, atherosclerosis and arteriosclerosis are forms of CVD that affect morbidity and mortality in CKD patients. For this reason, current guidelines recommend screening for the presence in patients with stage 3-5 CKD (Harada et al, 2017). Based on research conducted by Gorriz et al. showed that of 742 stage 3-5 CKD patients who had not undergone dialysis, 79% of them had vascular calcification (Gorriz et al, 2015).

In addition to traditional factors such as advanced CKD, diabetes, hypertension, and aging, non-traditional factors associated with CKD must also be taken into account. Price et al. reported that low dietary protein intake markedly increased the frequency and extent of medial artery calcification in a rat model of adenine-induced uremic. Thus, recently many studies have linked malnutrition as a prognostic factor for cardiovascular events in CKD patients.

In the general population, increased BMI is a risk factor for cardiovascular events, increasing morbidity and mortality. (Mi Jung Lee, 2016). In a study of patients with CKD stage 3-5, there was a significant association between arterial calcification and an increase in the progression of kidney disease, in which an increase in BMI was very important in this regard. It was also found that patients who were overweight (BMI 25 kg/m2) or obese (BMI 30 kg/m2) had more severe kidney disease progression (Garland JS, et al, 2013).

One of the geriatric nutrition risk index (GNRI), which is calculated based on both serum albumin and body mass index (BMI), has been introduced as a simple and valuable screening tool to assess nutritional status (Harada et al, 2017). Vitamin D deficiency, another complication of CKD, is also frequently associated with vascular calcification in CKD patients. Decreased GFR, proteinuria, or tubular dysfunction will exacerbate vitamin D deficiency and reduce its pleiotropic

effect (Hou et al, 2017). Vitamin D supplementation for CKD patients provides a protective role for the endothelium through (1) inactivation of the renin-angiotensin-aldosterone system, (2) reduction of insulin resistance, (3) reduction of cholesterol and inhibition of foam cells and cholesterol release in macrophages, and (4) modulation of vascular regeneration. For arterial calcification, vitamin D supplementation provides an additional role in the deterioration of proteinuria, renal renal osteodystrophy, and restoration of calcification inhibitors (Gluba-Brzozka et al, 2018).

The effect of vitamin D in causing calcification seems to be contradictory. As previously described, vitamin D deficiency causes calcification. On the other hand, vitamin D supplementation can induce calcitriol which in turn can induce vascular calcification (Fukumoto, 2014).

Other available evidence suggests upregulation of pro-inflammatory cytokine activity in CKD, the cause of which remains unknown (Gluba-Brzozka et al, 2018). Low-grade systemic inflammation, which is frequently observed in CKD patients, is an independent risk factor for cardiovascular morbidity and mortality. High levels of inflammatory markers are known to be associated with an increased prevalence, severity and development of vascular calcifications (Dai et al, 2017; He and Massy, 2018).

Desjardins et al, in their study using an animal model of CKD, found that pro-inflammatory cytokines such as interleukins and hsCRP may be involved in vascular calcification (Dinic et al, 2017). Inflammation-induced oxidative stress is thought to be a strong inducer of osteogenic transition and vascular calcification (De Oliveira et al, 2013).

Although nutritional and inflammatory factors have been widely associated with cardiovascular events in CKD patients, very few studies have focused on nutritional and inflammatory factors in CKD patients. Therefore, the author are interested in examining the relationship between nutritional status (especially vitamin D and albumin) and inflammatory status (especially hsCRP) in causing vascular calcification in CKD patients who had never undergone dialysis.

2. MATERIALS AND METHODS

This cross-sectional study was performed in inpatient and outpatient clinic of Haji Adam Malik Hospital Medan. Subjects were patients with stage 3, 4 and 5 chronic kidney disease who had not undergone hemodialysis (eGFR < 60ml/min/1.73m2), aged 18 years old or older. Subjects who had undergone hemodialysis and in unstable condition were excluded from this study. Written informed consent was obtained from each subject. The sample was selected with consecutive sampling, namely selecting samples based on acceptance and rejection criteria until a sample size of 30 samples was met.

The analysis test will be carried out with statistical software and the results will be presented in a table. This study was approved by the Health Research Ethics Commission of the USU Faculty of Medicine and the Haji Adam Malik Hospital in Medan.

3. RESULTS

Table 1. Baseline characteristics of subjects

Characteristics	Mean ± SD	median (Min-Max)	Total (%total) n=30
Gender Male Female			 16 (53.3) 14 (46.7)
Age <45 years old 45-55 years old >55 years old			 6 (20) 11 (36.7) 13 (43.3)
Diabetes mellitus			
Yes			13 (43.3)
No			17 (56.7)
Calcium, mg/dl		7.75 (1.1-14.6)	
Phosphorus, mg/dl		4.8 (2.1-9.2)	
LDL, mg/dl		93 (28 – 307)	
HDL, mg/dl		25.5 (5 – 67)	
Albumin, mg/dl		2.9 (1.9 - 4)	
Vitamin D, mg/dl		13.55 (0.3-37.5)	
BMI, kg/m2	20.6 ± 2.29		
hsCRP, mg/dl	7.36±6.11		
Urea, mg/dl		103 (42 – 407)	
Vascular calcification Yes No			 7 (23.3) 23 (76.7)
Nutritional Status			
Based on albumin			
Malnutrition			22 (73.3)
Normal			8 (26.7
Based on BMI			
Malnutrition			8 (26.7)
Normal			22 (73.3)

BMI, body mass index; LDL, low density lipoprotein; HDL, high density lipoprotein, hsCRP, high sensitivity C-reactive protein; SD, standard deviation Table 1 shows the characteristics of the research subjects. A total of 30 subjects was enrolled in this tudy. Male subjects were dominant in this study (53.3%) accompanied by the largest age group is the age group above 55 years with a total of 13 people (43.3%) followed by the age group 45-55 years as many as 11 people (36.7 %), and <45 years as many as 6 people (20%). From a total of 30 respondents, there were 13 people (43.3%) with DM and 17 people (56.7%) without DM.

The median values (min-max) of calcium and phosphorus serum levels in all study subjects were 7.75 (1.1-14.6) mg/dl and 4.8 (2.1-9.2) mg/dl, respectively. In addition, the median (min-max) values of LDL, albumin, and vitamin D were 93 (28 – 307) mg/dl, 2.9 (1.9 - 4) mg/dl, and 13.55 (0.3-37.5) mg/dl, respectively. The inflammation marker examined in this study was hsCRP where the mean ± standard deviation obtained was 7.15 ± 6.11 mg/dl.

From table 1, it can be seen that there was an assessment of participants nutritional status based on both the serum albumin and BMI value. Serum albumin levels assessed nutritional status and classified it into malnutrition and normal. The number of respondents with malnutrition based on serum albumin values were 22 people (73.3%) and 8 people were normal (26.7%). On the other hand, based on BMI values, there were only 8 people with poor nutrition (26.7%) and 22 people with good nutrition (73.3%). Of the total 30 subjects involved in this study, it was found that a total of 7 subjects (23.3%) had vascular calcification which was observed from the results of the AP/lateral projection lumbar radiography.

Table 2. Characteristics of subjects based on the presence of vascular calcification

Characteristics	Vascular Calcification	
	Yes N(%)	No N(%)
Diabetes mellitus		
Yes	3 (23.07)	10 (76.9)
No	4 (23.5)	13 (76.4)

In Table 2 shows as many as 7 respondents who experienced vascular calcification. Of the total 7 people, there were 3 people with comorbid DM and 4 people without comorbid DM. Of the 23 people without vascular calcification, there were 10 people with comorbid DM and 13 people without comorbid DM.

Table 3. Characteristics of subjects based on calcium, phosphorus, vitamin D, HDL, LDL, eGFR, albumin, urea, hsCRP and BMI

Inspection	Vascular Calcification	
	Yes	No
Calcium*	8.8 (6.3 – 9.4)	7.6 (1.1 – 14.6)
Phosphor*	4.8 (3.9 – 8.8)	4.8 (2.1 – 9.2)
Vitamin D*	11 (0.3 – 28.2)	13.7 (6.3 – 37.5)
HDL*	40 (18 -57)	25 (5 – 67)
LDL*	110 (48 – 235)	90 (28 – 307)
eGFR*	18 (0.00 – 35)	16 (4 – 64)
Albumin*	2.9 (2.9-4)	2.9 (1.9 – 3.9)
Urea*	120 (50-407)	101 (42 -268)
hsCRP**	6.41±4.97	7.65±6.49
BMI**	20.88 ± 2.13	19.84 ± 2.7

*Data is not normally distributed, presented in the form of median (min-max)
**Data are normally distributed, shown in the form of mean ± SD

In Table 3 shows Characteristics of Research Subjects Based on calcium, phosphorus, vitamin D, HDL, LDL, eGFR, albumin, urea, hsCRP and BMI.

Table 4. Relationship of hsCRP, Vitamin D with Vascular Calcification

Inspection	Vascular Calcification		p value
	Yes (mean ± SD)	No (mean ± SD)	
hsCRP (mg/dl)	6.029 ± 5.37	7.50±6.62	0.659*
Vitamin D (mg/dl)	12.39±8.98	17.71±9.20	0.148**

*Independent T-Test
**Mann-Whitney Test

In Table 4 shows that the mean ± standard deviation of hsCRP of subjects with vascular calcification was 6.029 ± 5.37 mg/dl while in subjects without vascular calcification was 7.50 ± 6.62 mg/dl. From the two examinations, it was found that there was an insignificant relationship with a p-value of 0.659. From the table above, it can also be seen that the mean ± standard deviation of serum vitamin D levels of subjects with vascular calcification was 12.39 ± 8.98 mg/dl and from the two examinations, there was an insignificant relationship with a p-value of 0.148.

Table 5. Nutritional status with vascular calcification

Inspection	Vascular Calcification		p value
	Yes N(%)	No N(%)	
Based on albumin			
Malnutrition	5 (26.3)	14 (73.6)	0.668*
Normal	2 (25)	6 (75)	
Based on BMI			
Malnutrition	4 (50)	4 (50)	0.029*
Normal Nutrition	3 (13)	20 (87)	

*Fisher's exact test
SD, standard deviation

In Table 5 shows that in the grouping of nutritional status based on serum albumin values, there was no significant relationship between nutritional status and vascular calcification, where the p value was 0.668. On the other hand, in the grouping of nutritional status based on the calculated BMI, there was a significant relationship between nutritional status and vascular calcification, where the p value was 0.029. Of the 7 respondents who experienced vascular calcification, 3 of them were found to have poor nutritional status based on BMI values, and 3 respondents had normal nutritional status.

4. DISCUSSION

Cardiovascular disease is the main cause of death in patients with chronic kidney disease. Vascular calcification is an independent risk factor associated with cardiovascular disease and cardiovascular mortality, both in the general population and in patients with CKD. Vascular calcification is a common finding in CKD. Some literature states that the prevalence is increasing along with worsening kidney function and duration of suffering from CKD (Hill et al., 2016; Gosmanova, 2011).

The mechanism of vascular calcification in patients with CKD is multifactorial and not fully understood. The "traditional" risk factors associated with vascular calcification are age, hypertension, diabetes, and dyslipidemia. But there are also some non-traditional risk factors that are thought to have a role in arterial calcification such as calcitriol state, hyperparathyroidism, hypervitaminosis D or increased calcium levels, malnutrition and duration of dialysis (Gosmanova, 2011; Panjiyar et al., 2017).

In this study, from 30 respondents, serum albumin levels were obtained with a median (min-max) value of 2.9 (1.9 - 4) mg/dl. From the statistical tests performed, there was no significant correlation between nutritional status based on albumin values and vascular calcification. These results however were not in line with the study conducted by Choi et al. The study showed that there was a significant correlation between malnutrition and the incidence of abdominal aortic calcification. Malnutrition is a common and major problem in end-stage kidney disease. Low albumin levels are thought to play a role in the occurrence of calcification.

In addition to examination of serum albumin levels, BMI measurements were also performed to assess nutritional status and its relationship with the incidence of vascular calcification. From a total of 30 respondents, there were 8 people with BMI < 18.5 and classified as nutritional status with less nutrition, and on the contrary, 22 people with BMI ≥18.5 and classified as nutritional status with normal nutrition. This grouping showed statistically significant results with the incidence of vascular calcification. These results were in line with previous research conducted by Harada et al where in an observational study involving 392 respondents of CKD patients who did not undergo hemodialysis, found a significant relationship between GNRI values calculated based on serum albumin and BMI values with the occurrence of aortic calcification. It was found that poor nutritional status was a strong factor in the occurrence of calcification in the aorta (Fig.OR, 7.18; 95% CI: 1.92–26.82) (Harada et al., 2017). An examination of serum vitamin D levels was also performed and the median vitamin D value was 13.55 (0.3-37.5) mg/dl, where the mean vitamin D level in patients with vascular calcification was 12.39 ± 8.98 mg/dl. Statistical tests were also performed on this parameter and no significant correlation was found on vascular calcification. These results were in agreement with the cross-sectional study conducted by Canton et al. in 210 patients with CKD stages 4 and 5 who had not undergone hemodialysis. The study also found the same thing, where there was no relationship with the incidence of vascular calcification (Hou et al., 2017).

The relationship of vitamin D in the process of vascular calcification is very complex and has a biphasic pattern. Increased levels of vitamin D can trigger an increase in serum calcium and phosphate, which in turn lowers fetuin-A levels and causes vascular calcification. In addition, decreased levels of vitamin D can stimulate secondary hyperparathyroidism which in turn will trigger an increase in osteoclast activity in increasing bone mineral resorption in CKD patients and will further trigger calcification (Hou et al., 2017; Gluba-Brzozka et al, 2018) This study also looked for the relationship between inflammatory markers such as hsCRP

and vascular calcification, where the mean hsCRP level was 7.15 ± 6.30 mg/dl. In statistical tests performed on this parameter, no significant correlation was found on vascular calcification. This was in contrast to the study conducted by Choi et al., where they found a significant correlation between the incidence of vascular calcification and the inflammatory state by assessing hsCRP levels. In addition, the incidence of vascular calcification might be used as a predictor of the cause of death in patients (Harada et al., 2017).

The role of systemic and local inflammation increases the incidence of inflammatory markers such as CRP, IL-6, and TNF- which increases the incidence of vascular calcification through induction of osetogenic phenotype of vascular smooth muscle cells (VSMC) and stimulates osteoblastic genes and can reduce fetuin-A levels. In addition, inflammation can also cause a decrease in albumin levels and can exacerbate malnutrition. During the process of atherogenesis, CRP accelerates the uptake of LDL by macrophages, leading to the formation of foam cells. CRP also impairs endothelial function by reducing nitric oxide (NO) production through downregulation of endothelial nitric-oxide-synthase-mRNA and facilitating endothelial cell apoptosis. Furthermore, CRP stimulates the proliferation and migration of vascular smooth muscle cells (Dai et al., 2017; Dinic et al., 2017; Fukumoto, 2014; Harada et al., 2017; He and Massy, 2018).

This study showed that there was no relationship between serum albumin, vitamin D, and hsCRP levels on the incidence of vascular calcification. This happens because there were several limitations in this study, including the small number of samples, the use of x-ray radiography techniques in evaluating calcifications which have a lower diagnostic value, as well as a thorough evaluation of the condition of CKD in patients, including in this study all patients had not undergone hemodialysis. The incidence of vascular calcification in patients with CKD is not fully known and is usually multifactorial. Several studies showed that vascular calcification often occured in dialysis patients because in patients undergoing hemodialysis there was a decrease in magnesium levels so that it aggravates oxidative stress, increases inflammation, disruption of endothelial function, increasing vasospasm and accelerating the process of atherogenesis. In an observational study it was found that administration of magnesium carbonate inhibited the progression of coronary artery calcification after 18 months. Another study of patients aged 20-30 years, undergoing hemodialysis and peritoneal dialysis, showed that 80% of them had vascular calcification. Blood vessels undergoing dialysis also showed increased alkaline phosphatase activity and the expression of Runx2 and Osx which indicated the occurrence of osteogenic transformation of vascular smooth muscle cells (VSMC). Several studies had shown that vascular calcification in dialysis patients might play a prognostic role in cardiovascular morbidity and mortality (Dai et al., 2017; De Oliveira et al., 2013; Harada et al., 2017; Vervloet and Cozzolino, 2003).

In conclusion, there was no significant relationship between nutritional status as measured by serum albumin levels with the incidence of vascular calcification in CKD patients who had not undergone hemodialysis. There was a significant relationship between nutritional status as measured by BMI with the incidence of vascular calcification in CKD patients who had not undergone hemodialysis. There was no significant relationship between vitamin D levels with the incidence of vascular calcification in CKD patients who had not undergone hemodialysis. There was no significant relationship between hsCRP levels and the incidence of vascular calcification in CKD patients who had not undergone hemodialysis.

5. Suggestion

This study discussed whether or not there was a relationship between nutritional status and inflammation as measured by albumin levels, BMI values, vitamin D and hsCRP on the incidence of vascular calcification in CKD patients who have not undergone hemodialysis. Although statistically, this study had not been able to prove a significant relationship between albumin, vitamin D and hsCRP levels on the incidence of vascular calcification, as previous studies, good nutritional management was important for CKD patients, both those who have not and who have routinely undergone hemodialysis in order to reduce inflammation and prevent vascular calcification.

The limitations of this study mainly lied in the design of this study itself where the study was conducted cross-sectionally at a certain time and the number of samples collected was only randomly selected from the existing population. This made no similarity obtained in terms of quantity and characteristics in the group of variables being compared because it was only conducted at the same time without any outside intervention by the researcher. This certainly affected the statistical calculations so that no significant results were obtained on the hsCRP inflammation variable and vitamin D variable. In addition, the possibility of bias in sample selection could also contribute to the reason for the insignificant results.

So as a suggestion for future research, further research is needed with prospective and retrospective designs so that the case group and control group are equivalent and more varied considering the high number of CKD patients who have not undergone routine hemodialysis with various comorbidities.

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