



CORRELATION OF CALCIUM-PHOSPHATE LEVELS WITH ABDOMINAL AORTIC CALCIFICATION IN HEMODIALYSIS PATIENTS

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ABSTRACT

Background: Mineral metabolism disorders (hyperphosphatemia, hypercalcemia) are common in patients with chronic hemodialysis. Hyperphosphatemia, hypercalcemia and high CaxP products are associated with increased cardiovascular morbidity and mortality through vascular calcification formation.

Objective: To determine the correlation between Ca-P levels and abdominal aortic calcification in patients with chronic hemodialysis.

Methods: Ca-P and lateral lumbar plain film examinations were conducted on chronic hemodialysis patients in Dr. Soetomo General Hospital that met the inclusion and exclusion criteria in order to identify calcification in abdominal aorta. The results were analyzed using Spearman test.

Results: In the 35 patients involved in this study, the age mean was 42.6 ± 12.9 years. Most patients were male (71.4%). The mean of hemodialysis duration was 39.4 ± 26.8 month. The means of corrected Ca levels, P and CaxP products were 9.24 ± 0.86 mg/dl, 6.40 ± 1.60 and 58.82 ± 14.49 respectively. Abdominal aortic calcification occurrence was 46.87%. The mean ($\pm$ SE) of AAC score was 3.4 ± 5.28 . The correlation between Ca levels and Abdominal aortic calcification score was 0.031 with $p=0.861$, between P levels and Abdominal aortic calcification score was 0.075 with $p=0.670$, and between CaxP product and Abdominal aortic calcification score was 0.0111 with $p=0.572$.

Conclusion: There was no significant correlation between Ca-P levels and abdominal aortic calcification in chronic hemodialysis patients involved as the sample in this study.

KEYWORDS. chronic hemodialysis, hypercalcemia, hyperphosphatemia, vascular calcification.

INTRODUCTION

Mineral metabolism disorders (calcium or Ca-Phosphate or P) are common in patients with chronic kidney diseases (CKD) stage 5 undergoing dialysis. Hyperphosphatemia, hypercalcemia and CaxP product are associated with vascular calcification and increased cardiovascular morbidity and mortality [Ganesh S et al., 2001; Block G et al., 2004]. A lot number of studies showed a strong correlation between Ca, P and CaxP product and cardiovascular mortality. In vitro studies showed

calcium and phosphate independently and synergistically induce calcification in vascular smooth muscle cells (VSMC) [Negri AL, 2010].

Vascular calcification (VC) quite greatly contributes toward the high cardiovascular mortality in CKD patients undergoing dialysis [Bellasi AE et al., 2006; Toussaint ND et al., 2009; Noordzij M et al., 2011]. Vascular calcification in dialysis patients might result in progressivity if not detected and thoroughly managed. Inadequate control of mineral metabolism disorder, especially hyperphosphatemia will worsen vascular calcification [Jean G et al., 2006]. The patient's longer hemodialysis duration will cause the complications to be more severe. If the disorder is not overcome, it will cause a very high cardiovascular mortality in CKD

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patients and the economic burden will be unable to suppress [Khan S, Amedia CA Jr, 2008].

In advanced CKD patients, hyperphosphatemia is caused by disruption of P excretion by the kidneys. High levels of serum P are thought to be "vascular toxins" that accelerate the progression of VC [Covic A. et al., 2010]. It is currently known that VC is not only a passive process of accumulating Ca and P on the walls of blood vessels, but also an active process. VC will cause increased vascular stiffness, which then increases the pulse pressure known as the predictor of cardiovascular death [Shanahan C et al., 2011]. Several methods that are accurately considered as gold standards for identifying vascular calcification are electron-beam computed tomography and multislicespiral computed tomography.

Several studies have shown that aortic calcification has been shown to correlate with those obtained in coronary arteries [Honkanen E et al., 2008]. The abdominal calcification obtained from the lateral lumbar plot images is then assessed using a previously validated system of AAC [Bellasi AE et al., 2006].

Good control of Ca-P levels is expected to slow the progression of vascular calcification and thus is expected to contribute to decreased cardiovascular mortality. This study attempted to analyze whether there was a correlation between Ca-P levels and the occurrence of abdominal aortic calcification in CKD patients undergoing hemodialysis identified by using lateral lumbar plain film in accordance with Kidney Disease Improving Global Outcomes recommendations.

MATERIAL AND METHODS

This is an observational analytical study with cross-sectional design. The samples of this study were selected through inclusion and exclusion criteria from CKD patient population undergoing chronic hemodialysis at dr. Soetomo General Hospital Surabaya during September-November 2013. The inclusion criteria were men and women aged of ≥ 18 years old who were undergoing chronic hemodialysis (≥ 3 months) 2x/week and were willing to be involved in this study as confirmed by their signing the informed consent..

These CKD sufferer had undergone periodic hemodialysis within ≥ 3 months. Abdominal aortic

calcification is the calcification that appears in lateral lumbar plain film. Lumbar lateral plain photos were taken in a standing position using standard radiographic equipment and an estimated radiation dose of about 15mGy using computed radiography. Abdominal aortic calcification was assessed using a system that has been previously validated. The scores were summarized using two methods: a composite score for anterior-posterior severity and the affected segment total number of aortic segments indicated the severity of calcification level (maximum score of 4).

Calcium levels are total serum Ca content with samples taken just before hemodialysis, and is stated in mg/dl unit. The results of the examination were then categorized into three, namely hypercalcemia, normal, and hypocalcaemia. Hypercalcemia occurs if blood Ca levels is >9.5 mg/dl. The nominal blood Ca level is 8.4-9.5 mg/dl, while hypocalcemia occurs if blood Ca level is <8.4 .

Phosphate levels are serum P levels with samples taken just before hemodialysis, and is stated in mg/dl unit. The results of the examination were then categorized into three, namely hyperphosphatemia, normal, and hipofosfatemia. Dikatakan hipofosfatemia adalah jika kadar P darah $> 5,5$ mg/dl. Normal blood phosphate levels are 3.5-5.5 mg/dl. Hypophosphatemia occurs if blood P level was <3.5 mg/dl. Ratio measurement scale.

After the samples were collected according to inclusion criteria, Ca-P and lateral lumbar photo examination were conducted to identify the presence of abdominal aortic calcification. All data were then using a statistical program (SPSS). Correlations between Ca-P levels and AAC scores was assessed using Spearman test.

RESULTS

The samples consisted of 35 CKD patients undergoing routine hemodialysis at dr. Soetomo General Hospital Surabaya who met inclusion and exclusion criteria. In this section we describe the general characteristics of CKD patients involved as the study samples (Table 1). Most samples were male (71.4%), while women patients were only 10 (28.6%). The mean of the patients' age was 42.6 years old, with the youngest being 20 years old and the oldest 66. The highest proportion in the age group of 40-49 years age group was 25.6% (10).

TABLE 1.

Patients' general characteristics

Characteristics	Number (n=35)	Mean± SD	Range
Age (year)		42.6 ± 12.9	20 – 66
Gender n (%)			
Male	25 (71.4%)		
Female	10 (28.6%)		
HD Period (month)		39.4 ± 26.8	4 – 120
Ca Ca-based P binder	16 (45.7%)		

Distribution of subjects in dialysis duration showed 1 (2.9%) subjects had undergone hemodialysis of <6 months, 4 patients (11.4%) had hemodialysis of 6-11 months, 25 patients (71.4%) had hemodialysis ≥24 months.

The distribution of calcium content was categorized as <8.4 mg/dl for 5 subjects (14.3%), optimal level of 8.4-9.5 mg/dl of 17 (48.6%), >9.5 mg/dl of 13 subjects (37.1%). Dari 13 subyek dengan kadar > 9.5 mg/dl tersebut sebanyak 5 subyek (38.46%) mengalami hiperkalsemia (>10 mg/dl) (Fig. 1).

Phosphor level distribution was categorized as <3.5 mg/dl of 5.7%, the optimal grade was between 3.5-5.5 mg/dl of 20%, while the P level was >5.5 mg/dl of 74.3% (Fig. 2). The value of calcium-phosphorus products was categorized as optimal value <55 mg²/dl² of 31.4%, while for not optimal category was ≥55 mg²/dl² of 68.6% (Fig. 3). HPTi levels are divided into the level of <150 pg/ml of 25.7%, 150-299 pg/ml of 28.6%, 300-499 pg/ml of 14.3%, 500-799 pg/ml of 14.3%, and 800 pg/ml of 17.1% (Fig. 4).

The description and degree of calcification in the abdominal aorta media tunica was determined by radiologists. Kappa's alignment test was performed to obtain agreement among the radiologists (Table 2). The results of SPSS analysis showed Kappa value of 0.828, categorized as excellent. The probability value (Ap prox. Sig) was 0 or <0.05.

TABLE 2.

Abdominal aortic calcification radiology results

	Radiologist		Total
	Calcification	No Calcification	
Radiologist 1			
Calcification	15	2	17
No Calcification	1	17	18
Total	16	19	35

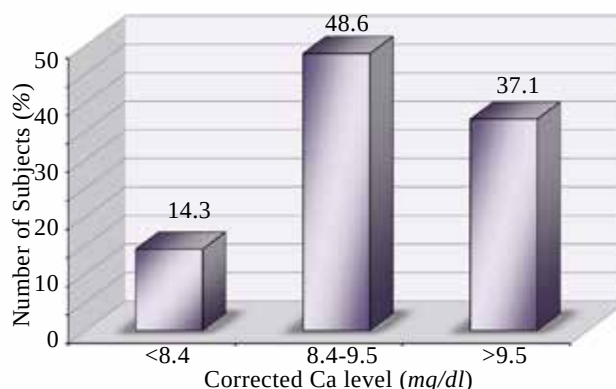


FIGURE 1. Subject distribution based on corrected calcium levels

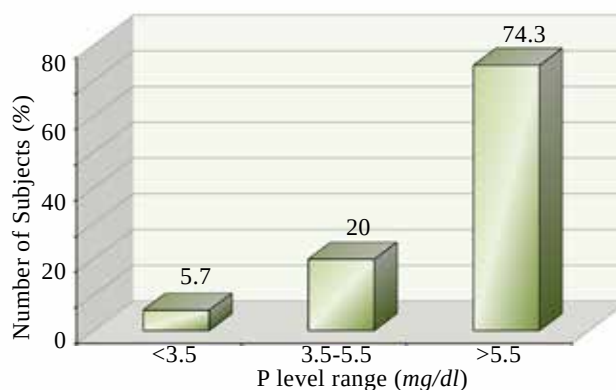


FIGURE 2. Subject distribution based on P level value

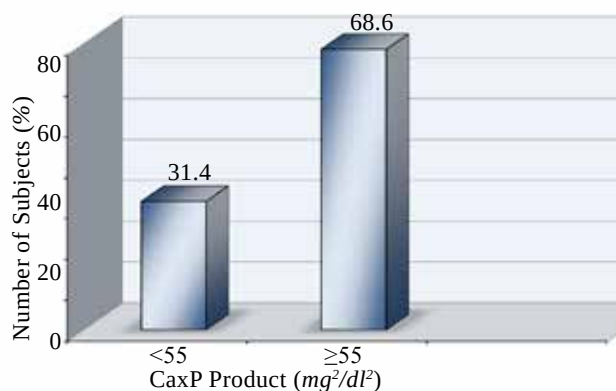


FIGURE 3. Subject distribution based on the CaxP product level value

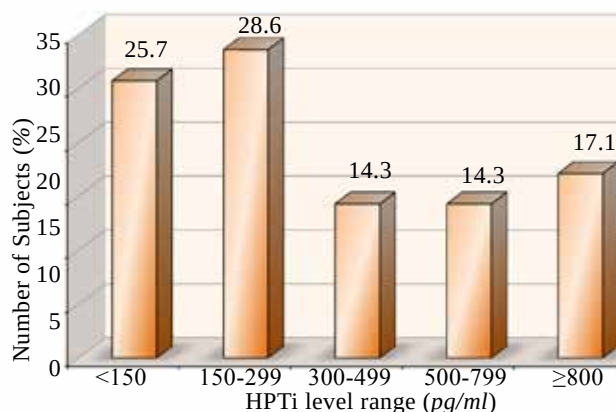


FIGURE 4. Distribution based on intact parathyroid hormone value

This indicates that the Kappa size was significant.

ACC scores of individual aortic segments for both the anterior and the posterior wall were summed. The mean ($\pm$ SE) AAC score was 3.4 ± 5.28 . The average AAC score in male subjects was 4.36 ± 5.93 , whereas in the female subjects were 1.0 ± 1.65 . AAC scores on the L1-L4 segment are depicted in figure 5. Spearman correlation test did not show any significant relationship between Ca, P, CaxP and abdominal aortic calcification ($p > 0.05$).

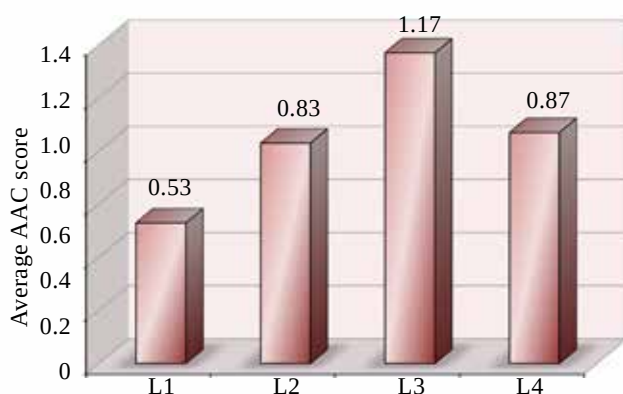


FIGURE 5. The average AAC score in L1-L4 segments

DISCUSSION

The mean age of the subjects in this study was lower than in the previous studies. [Kraśniak A et al., 2006; Honkanen E et al., 2008; Toussaint ND et al., 2011]. A research in Australia showed the highest age mean which is 69 years old [Toussaint ND et al., 2011]. The largest proportion was in the age group of 40-49 years old. The number of male subjects was higher than that of women patients with the ratio of 2.5:1. This is higher compared to the previous studies [Kraśniak A et al., 2006; Honkanen E et al., 2008; Toussaint ND et al., 2011] with the ratios of 1.03:1, 1.55:1, and 1.5:1 respectively.

In this study, the mean of HD duration was 39.4 months, almost the same as the obtained results which were 38.2 and 38 months respectively [Honkanen E et al., 2008; Toussaint ND et al., 2011]. Meanwhile, other studies obtained much longer HD mean which is 73.8 months [Kraśniak A et al., 2006]. The difference is because several studies included research subjects based on the old criteria in which the HD duration varied and this affects the mean results. The subjects of this study were those who had undergone HD for more than 3 months.

The mean of HD duration was longer [Kraśniak A et al., 2006] compared to the results of this study.

The mean of P level is higher when compared to that of the previous studies whose P mean of 5.65 [Kraśniak A et al., 2006], 5.3 [Honkanen E et al., 2008], and 4.97 [Toussaint ND et al., 2011]. When viewed from the distribution of P levels, it was found that many patients (74.3%) had serum P levels excluding the target serum levels recommended by Bailie GR, Massry SG, (2005).

The mean of corrected calcium level is higher compared to that of the previous studies. Another study obtained higher corrected calcium level, which is 9.6 [Honkanen E et al., 2008]. Tingginya hasilrerata kadar kalsium terkoreksi penelitian ini diakibatkan oleh komposisi dialisat dan pemberian terapi pengikat fosfat yang mengandung kalsium. Dialisate in this installation is a bicarbonate dialysate Ca concentration of 1.7 mmol/L which was generally applied to all patients. The calcium concentration in the dialysate is considerably higher than the recommendation from NKF-K/DOQI [Bailie GR, Massry SG 2005].

In this study we found that 46.87% of subjects had abdominal aortic calcification detected with lateral lumbar plain film. This is much lower than in the previous studies. The low prevalence of abdominal aortic calcification in this study compared with that of the previous studies [Honkanen E et al., 2008; Toussaint ND et al., 2011] probably due to the high elderly population in both studies.

A study showed that calcification of the aorta is proven to correlate with coronary blood vessels [Honkanen E et al., 2008]. There are several diagnostic modalities to detect abdominal aortic calcification. The use of CT scans to measure aortic calcification is reliable, sensitive and can give quantitative calcification results. For a significant prognosis of vascular calcification, Kidney Disease Improving Global Outcomes recommends the use of lateral lumbar plain photo instead of CT imaging. Several studies have shown that aortic calcification that is detected using lumbar lateral plain images can predict the occurrence of heart failure, ischemic heart disease, stroke and incidence of overall CV disease and death in the general population and in patients with CKD.

AAC scores is proven to correlate well with electron-beam CT scores of coronary arteries in

chronic hemodialysis patients and are associated with all cardiovascular causes and mortality in CKD. In a study conducted on 140 patients undergoing dialysis, there was a good correlation between lateral lumbar plain photo and Electron-beam CT, with sensitivity and specificity reaching 67% and 91% [Bellasi AE et al., 2006; Okuno S, 2007].

Evaluation of AAC scores in 933 patients showed an average score of 10.3 [Honkanen E et al., 2008]. Meanwhile, the evaluation of AAC scores on 132 patients obtained the average score of 11 [Toussaint ND, 2011]. In this study, the AAC score is lower than the two studies.

Aortic calcification is associated with all cardiovascular causes and mortality among patients undergoing dialysis. Some of the risk factors associated with the occurrence of VC in patients with chronic hemodialysis were increased age, long dialysis, CaxP products, P levels, and the use of Ca-based binders [Reslerova M, Moe S M, 2003].

The effect of P concentration on VC is supported by the argument that coronary artery calcification detected using an ECT is associated with high serum calcium and phosphate [Raggi and Bellasi, 2007]. It is similar studies with serum concentrations of P, CaxP products, and daily calcium intake that were higher in patients with coronary artery calcification detected by using Electron-beam CT [Goodman WG et al., 2000].

In populations with chronic kidney diseases, age and duration of dialysis are said to be associ-

ated with the occurrence of aortic calcification in some previous studies [Toussaint ND, 2011]. In this study we found a correlation between age and abdominal aortic calcification, while no correlation was found for the duration of dialysis although some reports in the general population indicate that males are more likely to occur calcification.

There is no significant association between AAC scores and mineral serum metabolism markers. This might also result in a one-time examination, whereas both Ca and P levels are fluctuated by many factors, including the effects of hemodialysis processes.

Patients with hemodialysis often have cardiovascular events with the onset of atherosclerosis and vascular calcification. Some reports suggest that excess calcium, for example is the administration of a calcium-based P binder, is associated with the occurrence of arterial calcification. NKF-K / DOQI recommends a concentration of calcium dialysate 2.5 mEq/l (1.25 mmol/L) to prevent calcification caused by excess calcium during the process of HD [Yamada, K. et al., 2007].

CONCLUSION

There was no significant correlation between Ca-P levels and abdominal aortic calcification in patients with chronic kidney diseases undergoing chronic hemodialysis that were involved as the study sample.

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