Title: Prevalence and Risk Factors of Vascular Calcification in Peritoneal Dialysis Patients

Introduction

Cardiovascular disease (CVD) is a major cause of death in dialysis patients worldwide. In addition, the conventional risk factors for CVD as diabetes mellitus (DM), hypertension (HT) and dyslipidemia, the calcium-phosphate imbalance among these patients is also important for cardiac morbidity and mortality. Calcium-Phosphate abnormality is a common mineral problem, found both in continuous ambulatory peritoneal dialysis (CAPD) and hemodialysis (HD) patients, resulting in calcium-phosphate precipitation within the vessel wall, so called vascular calcification (VC) which causes acute coronary syndrome and sudden cardiac arrest. There are 2 types of VC, first is intimal calcification which is associated with atherosclerosis and the other is medial calcification, more common in dialysis patients. Besides mineral abnormality, the risk factors of VC in dialysis consist of older age, male, increasing of dialysis vintage, usage and dose of calcium-based phosphate binder, high serum calcium or phosphate level, DM[1-10] and inflammation.[11-12] VC can be detected at many sites like carotid or coronary artery, abdominal aorta, ileo-femoral and femoro-popliteal axis. Various techniques have been used for VC detection such as plain radiography, ultrasonography, Computed Tomography (CT) [13-15], depending on the vessels. Although CT is used for gold standard in VC assessment, substantial cost and radiation exposure are problems for routine application, so plain radiography is used instead because it can provide a solid and inexpensive approach. Moreover, it is also a technique, recommended by National Kidney Foundation (NKF) and K/DOQI guideline for CVD in CKD-V patients[10]. The severity of VC is usually reported as vascular calcium score by using the technique of Bellasi and NKF[10, 13]. The previous studies showed high prevalence of coronary calcification among HD and CAPD patients about 40-100% and 60-80% [1, 15-17], respectively but there is still limited data in CAPD. At present, there are some research which studied about the correlation between VC and clinical outcomes, concluded that the presence and extent of VC are strong predictors of all-cause mortality and cardiovascular death in ESRD and HD patients [14-15, 18], so CVD is the major cause of death in dialysis. It should be considered if early VC detection, early management and risk modification are provided to high risk patients, the death rate will be decreased while improving the quality of life.

The PD First Policy in Thailand has been established since 2008 for free of charge PD and is provided to Thai population, most are poor, to improve their quality of life. During 2008-2011, more than 12,000 ESRD patients all over the country had been treated with CAPD under this policy. The main causes of death in the patients are CVD such as myocardial infarction, congestive heart failure and sudden cardiac arrest, these events are still the important health problems and the government has to pay more for annual expenditure.

This study aimed to determine prevalence and risk factors of VC in CAPD patients under the Policy, in order to develop a preventive program for decreasing the risk factors and improving the patient survival and gaining better outcomes.

Material & Methods

A multicenter cross-sectional study of CAPD patients under the PD First Policy from 10 hospitals (1.Chaiyapoom hospital, Surin hospital, Udonthani hospital, Roi-Et hospital, Nongbualumpoo hospital, Srinagarind hospital, Nakonrachasima hospital, Ta Bor Crown Prince hospital, Khon Kaen

hospital and Benjaluck hospital) in the Northeast of Thailand, was conducted during January-December 2011. The inclusion criteria were 1. CAPD patient who is under Thai PD First Policy 2. Age 15-90 years 3. CAPD outpatient. The study information was given to all patients and they had to sign a consent form if they were interested in joining this research and then took a plain radiograph of lateral lumbar spine to detect VC of abdominal aorta and a plain radiograph of pelvis was used instead for ilio-femoral axis. All radiographs from 10 centers were sent to Srinagarind hospital and were read by single radiologist, using the diagnostic criteria of Bellasi [13] for VC score assessment. The demographic data: age(year), gender, diabetes, dialysis vintage (month), daily dose of calcium-based phosphate binder(elemental calcium; mg/day) and laboratory parameters: levels of serum phosphate(mg/dL), calcium(mg/dL), parathyroid(PTH)(ng/ml) and albumin(g/dL) were measured and recorded in each center and were sent to Srinagarind hospital by PD doctors or PD nurses. The outcome of this study was prevalence of VC which is a categorical variable and the risk factors which had to be considered in this setting were: age 40-49 years, gender, DM, dialysis vintage more than 24 months, serum calcium more than 10.2 mg/dL, serum phosphate more than 5.5 mg/dL , calcium×phosphate products(CaxP) more than 55 mg/dL, PTH level more than 315 ng/ml, calcium based phosphate binder dose(elemental calcium dose) more than 1,800 mg/day and serum albumin less than or equal to 3 g/dL. For statistical analysis, Mean±SD was used for numerical continuous data and Percentage was used for counting or discrete data. The multivariate logistic regression with log likelihood analysis was used to assess the association between the risk factor and VC. Based on these results, we computed the prevalence ratio and its 95% Confidence Interval (95% CI) by using Stata version 10.

Results

Total of 633 CAPD patients were enrolled from 10 hospitals (Chaiyapoom hospital n= 100, Surin hospital n=95, Udonthani hospital n=82, Roi-Et hospital n=76, Nongbualumpoo hospital n=76, Srinagarind hospital n=74, Nakonrachasima hospital n=55, Ta Bor Crown Prince hospital n=44, Khon Kaen hospital n=21, Benjaluck hospital n=10), male in 325 patients (51.34%) and 34.43% of all had DM. The mean age was 52.5±13.40 years and mean dialysis vintage was 21.05±12.55 months. Average level of CaxP product was 36.44±14.55 mg/dL but only 9.3% had CaxP product more than 55 mg/dL. Mean dose of calcium-based phosphate binder was 1,550±628.20 mg/day (elemental calcium dose) and mean serum PTH level was in normal range, 244.33±309.78 ng/ml. Most patients (85.78%) had hypoalbuminemia (albumin less than 4 g/dL) with mean level of 3.25±0.76 g/dL. There were 162 patients (25.60%) had VC at abdominal aorta, female predominant in 54.32%. The low VC rates were also reported both in iliac artery and femoral artery of 14.13% and 18.29%, respectively. Mean vascular calcium score of abdominal aorta was 6.43±5.47. Regarding to VC group, average age was higher than non-VC (53±14.18 vs. 52±13.18 years, $p = 0.91$) and the highest rate of VC was presented in age group more than or equal to 60 years. The number of patients with dialysis vintage more than 24 months in VC was not different too much when compared to Non-VC group (38.80% vs. 36.94%) and DM patients were equally found about 34% in each group. Mean serum phosphate level was reported in 4.13 mg/dL in both groups and similar rate of hyperphosphatemia (phosphate more than 5.5 mg/dL) could be found in VC and Non-VC group (15.13% vs. 15.07%). Patients with CaxP product more than 55 mg/dL were detected more in VC group because their serum calcium level was higher than the other group. Although the mean PTH levels in VC and non-VC group were in normal limits (251.32 ± 362.48 vs. 266.78±346.78 ng/ml), hyperparathyroidism (PTH level more than 315 ng/ml) was reported more in non-VC (26.86%). The average dose of calcium-based phosphate binder in VC was lower than non-VC group (1,476.23±582.77 vs. 1,574.67±641.61 mg/day). In this study, we defined “malnutrition” as serum albumin less than or equal to 3.5 g/dL and it could be seen in both VC and Non-VC groups with the mean level of 3.24±0.58 g/dL and 3.33±0.62 g/dL, respectively and the number of the patients with serum albumin less than or equal to 3 g/dL was not different between two groups (27.77% vs. 28.45%). (Table 1.)

To determine the risk factors for VC, multivariate logistic regression with log likelihood analysis was used and we reported in the prevalence ratio (PR) with 95% CI. We found the 2 potential risk factors which were the longer dialysis vintage more than 24 months (PR=1.03, 95% CI [0.78-1.36]) and serum calcium level more than 10.2 mg/dL (PR=1.14, 95% CI [0.67-1.91]), furthermore we also found that PTH level more than 315 ng/ml (PR= 0.77, 95% CI [0.52-1.13]) and dose of calcium based phosphate binder more than 1,800 mg/day (PR=0.77, 95% CI [0.55-1.09]) might be the 2 potential protective factors.

TABLE 1 Comparison of demographic and clinical characteristics of the patients with VC and Non-VC of total 633 CAPD patients

Characteristic	VC N= 162	Non VC N= 471	p-value
1. Gender (Number)(%) 1.1 Male 1.2 Female	 74(22.77%) 88(28.57%)	 251(77.23%) 220(71.43%)	0.09
2. Age (year)(mean±SD) 2.1 Age <30 2.2 Age 30-39 2.3 Age 40-49 2.4 Age 50-59 2.5 Age ≥60	53±14.18 12(27.91%) 13(28.26%) 34(26.36%) 48(23.65%) 54(27.27%)	52±13.18 31(72.09%) 33(71.74%) 95(73.64%) 155(76.35%) 144(72.73%)	0.91
3. DM (Number)(%) Non DM	55(25.23%) 107(25.78%)	163(74.77%) 308(74.22%)	0.87
4. Dialysis Vintage (Month)(mean±SD) 4.1 Dialysis vintage <12 months (Number)(%) 4.2 Dialysis vintage 12-24 months 4.3 Dialysis vintage >24 months	21.90±13.04 40(24.69%) 55(26.32%) 63(26.58%)	20.75±12.37 122(75.31%) 154(73.68%) 174(73.42%)	0.90
5. CaxP Product (mg/dL)(mean±SD) 5.1 CaxP >55 mg/dL (Number)(%)	36.93±15.02 17(28.81%)	36.26±14.40 42(71.19%)	0.55
6. Serum Phosphate (mg/dL)(mean±SD) 6.1 Serum Phosphate >5.5 mg/dL (Number)(%)	4.13±1.72 23(25.84%)	4.13±1.61 66(74.16%)	0.98
7. Serum Calcium (mg/dL)(mean±SD) 7.1 Serum Calcium >10.2 mg/dL (Number)(%)	8.94±0.99 11(28.95%)	8.81±0.97 27(71.05%)	0.62
8. PTH (ng/ml)(mean±SD) 8.1 PTH >315 ng/ml (Number) (%)	251.32±362.48 26(20.47%)	266.78±346.48 101(79.53%)	0.17
9. Calcium based phosphate binder dose	1,476.23±582.77	1,574.67±641.61	

(mg/day)(mean±SD) 9.1 Calcium based phosphate binder dose >1,800 mg/day (Number) (%)	62(22.79%)	210(77.21%)	0.15
10. Serum Albumin (g/dL)(mean±SD) 10.1 Serum Albumin ≤ 3g/dL(Number)(%)	3.24±0.58 45(25.14%)	3.33±0.62 134(74.86%)	0.81
11. Vascular calcium score >0 of orta (mean±SD)	6.43±5.47	0	
12. VC at iliac artery (Number)(%)	21(14.58%)	0	
13. VC at femoral artery (Number)(%)	27(18.75%)	0	

Table 2. Prevalence ratio of risk factors for vascular calcification

VC Risk Factor	Prevalence Ratio	95% CI
1. Female vs. Male	1.25	0.96-1.63
2. Age (year) 2.1 Age <30 2.2 Age 30-39 2.3 Age 40-49 2.4 Age 50-59 2.5 Age ≥60	 1.05 1.07 1 0.89 1.03	 0.60-1.85 0.62-1.84 0.61-1.31 0.71-1.49
3. DM vs. Non DM	0.97	0.73-1.29
4. Dialysis Vintage (months) >24 vs. ≤24	1.03	0.78-1.36
5. CaxP Product (mg/dL) >55 vs. ≤55	1.13	0.74-1.74
6. Serum Phosphate (mg/dL) >5.5 vs. >5.5	1.00	0.68-1.47
7. Serum Calcium (mg/dL) >10.2 vs.<10.2	1.14	0.67-1.91
8. PTH (ng/ml) >315 vs. <315	0.77	0.52-1.13
9. Calcium based phosphate binder dose (mg/day) >1,800 vs. ≤1,800	0.77	0.55-1.09
10. Serum Albumin (g/dL) ≤3 vs. >3	0.96	0.71-1.30

Discussion

Cardiovascular disease was a leading cause of death in dialysis patients because these patients exposed to both conventional and kidney-related CVD risk factors, especially mineral abnormality. Although some new treatments would be provided in high risk patients, prevalence of CVD in dialysis was still high of 45%[19] and not only causing a major health problem, it also was a big burden to the community. Many treatments had been used to reduce the mortality rate, the early detection of CVD was the important one. VC was recently recognized as a marker of CVD and its presentation was associated with cardiac and all-cause mortality in dialysis patients. VC could be easily detected by using plain radiograph, so the early detection, the early treatment and this strategy could help to improve patient survival and quality of life. "The Thai PD First Policy" has been set up for PD supporting among the poor population all over Thailand. Most PD patients died from CVD as in Western countries and in order to alleviate their sufferings, this study was conducted to determine the prevalence and risk factors of VC for decreasing the mortality rate.

The prevalence of VC at abdominal aorta from our study was 25.60%, lower than previous studies [1, 15-17] which was about 60-80% in CAPD and 40-100% in HD. The low VC prevalence was also shown both in iliac and femoral artery of 14.58% and 18.75%, respectively. The underlying conditions that brought about low VC prevalence may be from malnutrition with low phosphate intake (< 700 mg/day) [20] and the short duration of dialysis.

Malnutrition is commonly found in Northeast region of Thailand about 30% of population[21] who have low protein and dairy products intake, malnourished patients could be seen all over our country, especially in poor people and this situation also affected on PD patients, sometimes it might be severe because some patients were usually advised to have low protein intake to avoid uremic state and have low phosphate diet for balancing their mineral abnormality in pre dialysis stage but when they have already turned to dialysis, they still have continued the same diet restriction. A number of malnourished PD patients were increasing gradually. Besides the low protein and phosphate intake from low socioeconomic status and uremia itself, PD patients might have the concurrent protein loss via dialysate about 5-15 grams protein/day and dialysate phosphate loss 2,000- 2,800 mg/week [22], influencing the severity of malnutrition.

From our series, 28.27% of all cases had malnutrition with serum albumin less than 3 g/dL. In addition, hypoalbuminemia could be found in chronic illness from inflammation, the poor dietary intake of protein among our patients would be causing both hypoalbuminemia and hypophosphatemia. Dialysis patients generally had hyperphosphatemia from inadequate clearance but in this study, the mean serum phosphate level was in normal limits, this finding confirmed the low protein and phosphate intake in these patients and moreover, using of calcium based phosphate binder could reduce the phosphate level as well. Therefore, it was very difficult to calcium-phosphate precipitation and VC progression in the condition of low to normal serum phosphate as in our patients setting. Although the recent study[23] found that malnutrition was associated with VC, explained by the expressions of Bone morphogenetic protein 2 (BMP2) and Matrix Gla protein (MGP) as new inducers but this research was studied only in HD patients who usually had hyperphosphatemia than PD patients and it could not be applied as in PD. Whenever in the condition of low substrate of phosphate and calcium, the VC could be rarely occurred despite having an inducer, so hypophosphatemia might become a protective factor for VC.

The short duration of dialysis with mean duration of 21.90±13.04 months in our series was the other reason of lower VC prevalence. VC formation rate would be increasing according to the longer dialysis duration from multifactorial factors like chronic inflammatory state, atherosclerotic process, chronic uremia [11-12], prolonged used of calcium based phosphate binder, resulting in hypercalcemia and

mineral disturbances with hyperphosphatemia for a long time[24]. Though the actual mechanism of VC formation in prolonged dialysis vintage were not completely understood, all factors accelerated the process of calcification. The longer dialysis vintage, the longer risk exposure. Therefore, the short dialysis vintage of nearly 2 years might cause the lower VC prevalence.

The older age [1, 3-5], increasing duration of dialysis[1, 2, 4], disturbed mineral metabolism with hyperphosphatemia [2-5, 7], usage and dose of calcium based phosphate binder [2, 7] and diabetes[3] were determined as a contributing factor of VC but from our data, we found only prolonged dialysis vintage (duration more than 24 months) and hypercalcemia (serum calcium more than 10.2 mg/dL) were the potential risk factors to VC. As in our study, the increasing number of VC patient was found in the longer dialysis duration and especially in patient with dialysis vintage more than 24 months, the prevalence risk was 1.03(95% CI: 0.78-1.36) and the explanations of prolonged dialysis increased risk to VC were explained as above. Furthermore, the cut-off point at 2 years after dialysis initiation might be suggested as an appropriate timing for VC detection in PD.

Hypercalcemia was relatively common condition in PD. The prolonged usage of such medications like calcium salts for phosphate binding or vitamin D for PTH suppression usually caused hypercalcemia and when it was concurrent with hyperphosphatemia, the calcium- phosphate crystal was easily precipitated and finally turned to VC. We also found that the patient who had hypercalcemia of serum calcium more than 10.2 mg/dL would have been increased risk to VC with prevalence risk of 1.14(95% CI: 0.67-1.91) and this was identified as the potential risk from our finding. Despite the calcium salts were used for phosphate binding in our patients but only 6.8% in VC group had serum calcium level more than 10.2 mg/dL, it might be from the low calcium intake and malnutrition in our patients. However, it was good for our patients to have low serum calcium because the possibility of VC formation rate would be decreased. According to K/DOQI Guideline for BMD [25], serum calcium level should be maintained in range of 8.8-9.5 mg/dL for avoiding the metabolic disturbance and for our suggestion, calcium supplements should not be given regularly without serum calcium monitoring and kept its level not more than 10.2 mg/dL for prevention of VC formation.

Interestingly, serum PTH more than 315 ng/ml and calcium dose equivalent of more than 1,800 mg/day were also reported from this study as protective factors. From our data, the number of patients with hyperphophatemia (PTH more than 315ng/ml) was found in Non-VC more than VC group and this finding could be explained by the type of dynamic bone change in each group. There were 2 common types, first was high bone turnover which was usually seen in secondary hyperparathyroidism and the other type was low bone turnover which was the condition seen in low serum PTH. Although both types of bone change could be the cause of VC by different mechanisms, it was found more common in low bone turnover which was usually occurred in peritoneal dialysis patients. Regarding to VC patients, they had lower PTH level than in Non-VC, so the trend of low bone turnover would be taken place in these VC patients and consequently with VC formation. The minimally disturbed of serum calcium and phosphorus from malnutrition in VC group, causing in low to normal level of serum PTH and if PTH level less than 315 ng/ml, the increased chance to have VC as concluded from our series.

In addition, the recommendation of the KDIGO Guideline for MBD [26], maintained PTH level about 2-9 times of the upper reference limit and the calcium and phosphate level should be in normal limits and we would suggest that PTH level should not be kept lower than 315 ng/ml in order to prevent low bone turnover, increasing VC formation rate in PD setting. Previous studies [27-29] also supported our finding of low serum PTH is associated with increased VC and cardiac calcium deposition, this concept was based on low bone turnover and the major influencing key factors for VC formation were hyperphosphatemia and hypercalcemia.

Nowadays, many phosphate binders were used, including calcium and non-calcium based

phosphate binders, for balancing the mineral metabolism in dialysis. In spite of causing hypercalcemia, calcium salts were still widely used because it was easily available and its cost-effectiveness. Dose of calcium salts varied to individual patients, depending on serum phosphate level. In order to avoid the calcium deposition in vessels and tissue, calcium salts should not be added in hypercalcemic patient. Although both hypercalcemia and hyperphosphatemia could accelerate VC formation easily, meticulous using of calcium salts with appropriate dose would help to reduce these problems.

All our patients received calcium carbonate for phosphate binding with a mean calcium dose of 1,550±628.20 mg/day; because the using dose of calcium was not high, so only 6% of all had serum calcium more than 10.2 mg/dL. From our data, the element calcium dose more than 1,800 mg/day was determined as potential protective factor. As in Non-VC patients, using the higher calcium dose than in VC group. The higher calcium dose, the more phosphate reduction and finally the VC formation rate would be decreased. However, hypercalcemia was also important, so calcium based phosphate binder should not be given routinely and serum calcium level should always be monitored. We suggest that the calcium dose more than 1,800 mg/day is probably safe for phosphate binding til hypercalcemia or other metabolic abnormality does not occur.

Age had been reported as a risk factor for VC by previous studies, however there is no evidence from our study and it might not be a real risk factor. The assumption of premature atherosclerosis from prolonged dialysis or chronic uremic state with inflammation in PD patients would be a proper explanation of increasing in VC formation, independently to the older age.

DM was determined as one of the risk factors, hyperglycemia with hyperinsulinemia and advanced glycation end products were proposed as possible mechanisms. Hyperglycemic state induced cell proliferation and expression of osteopontin in cultured VSMCs, causing VC formation [3, 30-31] but strong supportive data were still unclear. However our study could not be demonstrated clearly that DM was a risk factor or associated with VC, so the further study should be needed to identify the actual mechanism and confirm which one was a strong risk factor. Although DM might not be a risk factor, the good glycemic control was important in dialysis patients for other mechanisms for CVD prevention.

Regarding strength of our study, this multicenter study may be the largest study which was designed to determine the prevalence and risk factor of VC, so the results would be valid and reliable, especially in PD setting, it could be represented the PD data of Thailand. From our study, not only the risk factors, we also found the protective factors and these findings would be applied to improve the treatment. This research had some limitations, we had some missing data from some hospitals, however that missing data was just a small part of the study. The other limitation was the lack of population diversity, so our findings could be used only in Thai or Asian people.

Conclusions

The Prevalence of VC in CAPD patients from our study is quite low when compared to HD patients, may be due to low protein and phosphate intake from malnutrition and the short duration of dialysis. Dialysis vintage more than 24 months and hypercalcemia of serum calcium more than 10.2 mg/dL are at high risk for VC, so every patient who has one of them needs to be monitored for VC and treated properly to prevent cardiac mortality.

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