PRODUCT OF SERUM CALCIUM AND PHOSPHORUS ($CaXP_i$) AS A PREDICTOR OF CARDIOVASCULAR DISEASE RISK IN PATIENTS WITH CHRONIC KIDNEY DISEASE

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ABSTRACT

INTRODUCTION

Most of the chronic kidney disease (CKD) patients develop cardiovascular disease (CVD) in their later stages. Various traditional CVD risk factors are highly prevalent in CKD but mortality of these patients cannot be fully justified by these CVD markers. So this study was designed to determine serum calcium and phosphorus product ($Ca \times P_i$) to predict CVD risk in CKD patients.

MATERIAL AND METHODS

We followed the guidelines of NKF-KDOQI for CKD diagnosis and staging. Further the patients were classified into 3 different groups based on $Ca \times P_i$ product; $<40\ mg^2/dl^2$ (group 1), $40\text{-}55\ mg^2/dl^2$ (group 2) and $>55\ mg^2/dl^2$ (group 3). We then evaluated CVD risk by various traditional risk factors like age, BMI, BP, smoking history, dyslipidemia, previous history of CVD, LVH, arrhythmia, VHD, cardiomyopathy, and IHD.

RESULTS

Higher level of $Ca \times P_i$ was associated with presence of LVH (32.30% in group 1, 31.42% in group 2 and 46.66% in group 3), Arrythemia (13.84% in group 1, 28.57% in group 2 and 46.67% in group 3), VHD (5.71% in group 2 and 10.00% in group 3), Cardiomyopathy (1.53% in group 1, 8.57% I group 2 and 6.66% in group 3), IHD (6.15% in group1, 11.42% in group 2 and 13.33% in group 3) and hypercholesterolemia, hypertriglyceridemia and increased LDLc.

CONCLUSION

This study found that higher $Ca \times P_i$ increases with decline in glomerular filtration rate (GFR) and associated with CVD risks and CVD. So, this study raise a potential need to evaluate the level of calcium and phosphorus in all CKD patients and the level should be monitored more thoroughly to prevent CVD.

KEYWORDS $Ca \times P_i$ product, Chronic kidney disease, Cardiovascular disease

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INTRODUCTION

Chronic kidney disease (CKD) is worldwide health problem. In Nepal approximately 10% of the population has CKD and it continues to increase.[1] The NKF-KDOQI guidelines for CKD state that patients with CKD should be considered in the highest risk group for cardiovascular disease (CVD).[2] Majority of the patients in the advance stage of CKD develops CVD and it remains the major mortality risk in dialysis patients accounting for almost 50% of deaths.[3,4] The mortality rate of CKD patients cannot be fully justified by traditional CVD risk factors like older age, diabetes mellitus, systolic hypertension, and low high density lipoprotein (HDL) which are highly prevalent in CKD.[5] There has been increasing concern of novel risk factors such as homocysteinemia, elevated inflammatory markers, oxidative stress, dyslipidemia and calcium and phosphorus product for CVD in CKD.[5-7] NKF-KDOQI guideline has recommended $CaxP_i$ to maintain below 55mg^2/dl^2 in CKD cases.[2] Elevated $CaxP_i$ products are associated with cardiovascular calcification.[7,8] Since CKD is associated with disruption of the endocrine system that distorts the balance between calcitriol, calcium, phosphorus and parathyroid hormone which in turn affects bone mineral density leading to mineral bone disorder, $CaxP_i$ could be good marker to predict CVD in patients with CKD. Thus we aimed to examine the relationship between $CaxP_i$ and CVD and its risk in renal failure patients.

MATERIAL AND METHODS

This hospital based cross-sectional study was conducted at Universal College of Medical Sciences, Bhairahawa, Nepal from January 2016 to June 2016. Total of 130 patients diagnosed with CKD was recruited in this study by using consecutive sampling technique. We followed the guidelines of NKF-KDOQI for CKD staging.[2] We excluded the patients suffering from other chronic diseases such as tuberculosis, COPD, cancer and patients previously diagnosed with CVD. Pregnant women, pediatric patients and critically ill patients were excluded in the study. The study was approved by Institutional Review Committee and patients were informed about the study. We recorded data for anthropometric and clinical history. We also obtained the data of electro cardiogram (ECG) from the participants. Fasting blood sample was taken for the analysis of biochemical parameters. Patients were classified into three different groups based on the levels of $CaxP_i$; Group 1 (<40mg^2/dl^2), Group 2 (40-55 mg^2/dl^2) and Group 3 (>55 mg^2/dl^2). Among all the renal failure patients, 13.84%, 40.76% and 45.38% were from stage 3, 4 and 5 CKD respectively. Glomerular filtration rate (eGFR) was estimated by Cockroft and Gault formula.[9] We evaluated CVD risk by various traditional risk factors like age, body mass index (BMI), blood pressure (BP), smoking history, dyslipidemia, previous history of CVD, left ventricular hypertrophy (LVH), arrhythmia, valvular heart disease (VHD), cardiomyopathy, and ischemic heart disease (IHD). Data were analyzed by SPSS version 22.0 (SPSS Inc, USA). Categorical variables were presented as number and percentage and compared by Chi-square test. Continuous data were expressed as mean ± standard deviation (SD). One way analysis of variance (ANOVA) was applied to compare means. Multiple regression analysis was used to determine the Odds ratio and relative risk. The level of significance was set at $p<0.05$.

RESULTS

Out of 130 CKD patients, 62.30% (81) was male and 37.69% (49) was female. Based on smoking habit, majority of the patients were past smokers 67.69% (88), followed by non smokers 23.07% (30), and current smokers 9.23% (12). Similarly based on alcohol intake, 14.62% (19), 20% (26), and 65.38% (85) were non-alcoholic, past-alcoholic and current alcoholic respectively. When we evaluated the participants based on the $CaxP_i$ levels, half (50%) of the CKD cases belonged to Group 1, followed by group 2 (27%) and group 3 (23%).

Table 1 shows the characteristics of CKD patients in three different groups of $CaxP_i$. Serum urea and creatinine levels were found to increase with highest value in group 3. Similarly LDLc level was the highest in group 3 as compared to group 2 and group 1. eGFR was found to decrease with increase in the levels of $CaxP_i$.

Table 1. General characteristics of patients in different $Ca\times P_i$ groups

Parameters	Group1 ($Ca\times P_i$<40mg^2/dl^2)	Group2 ($Ca\times P_i$ 40-55mg^2/dl^2)	Group3 ($Ca\times P_i$>55mg^2/dl^2)	p-value
Age (yr)	55.87±13.42	48.43±20.31	60.23±19.53	0.006
BMI (kg/m^2)	28.44±4.40	28.10±4.78	27.02±4.54	0.36
SBP (mmHg)	128.31±23.82	134.87±25.48	126.33±22.20	0.29
DBP (mmHg)	79.54±12.92	80±15.52	77±16.22	0.66
Urea (mg/dl)	130.6±57.58	128.2±49.60	171.5±61.04	0.002
Creatinine (mg/dl)	4.99±6.07	5.0±2.67	7.67±4.94	0.04
Calcium (mg/dl)	8.51±1.89	8.97±1.53	10.09±2.41	0.002
Phosphorus (mg/dl)	3.58±1.21	5.28±1.01	7.4±2.00	0.001
$Ca\times P_i$ (mg^2/dl^2)	29.02±7.10	46.24±4.50	72.05±16.25	0.001
TC (mg/dl)	140.14±44.03	154.15±57.62	165.07±53.10	0.69
HDLc (mg/dl)	32.66±10.12	33.45±11.09	33.65±10.73	0.89
TG (mg/dl)	155.55±59.80	148.53±73.69	149.1±45.99	0.82
VLDLc (mg/dl)	31.11±11.96	29.70±14.73	29.82±9.1	0.82
LDLc (mg/dl)	76.36±38.16	90.99±55.24	101.62±48.45	0.03
eGFR (ml/min)	20.75±10.87	19.15±11.04	13.40±10.16	0.009

Figure 1 shows the number of cases with various types of CVD in three different groups of CaxP$_i$. In general it was found that the incidence of CVD diseases increases with increase in CaxP$_i$ level. Chi-square analysis showed significant association between CaxP$_i$ and arrhythmia (p=0.003), VHD (p=0.05). However LVH (p=0.38), cardiomyopathy (p=0.14) and IHD (p=0.46) did not show any association with CaxP$_i$.

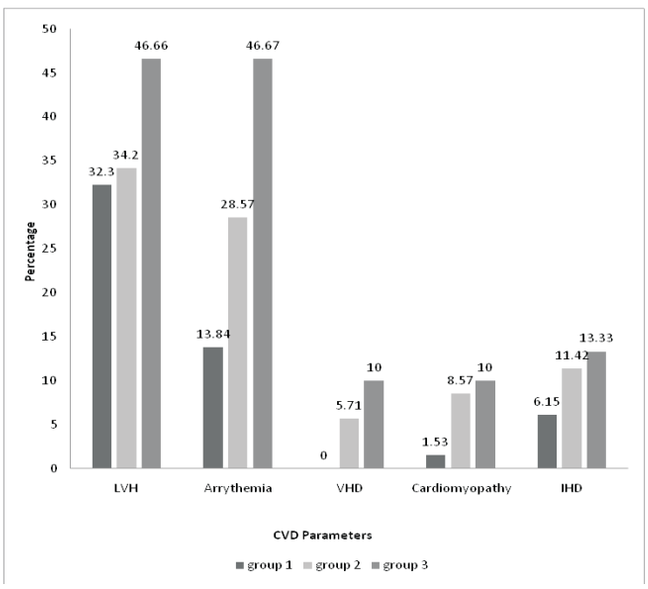

Figure 1. Number of cases with various types of CVD in three different CaxP$_i$ groups.

Table 2 shows the categorization of the patients based on their lipid level in three different groups. We found that the number of the patients in these groups increases with increase in the level of TC (3.1% vs 5.7% vs 6.7%) and LDLc (0% vs 8.5% vs 10%). In contrast, the number of the patients decreases in these groups with increasing level of HDLc (7.6% vs 5.7% vs 3.3%).

Table 2. Distribution of patients based on lipid level in different Ca×P$_i$ Groups

Lipid profile	Range (mg/dl)	N (%)		
		Group 1	Group 2	Group 3
TC	<200	60(92.3)	29(82.8)	20(66.6)
	200-239	3(4.6)	4(11.4)	8(26.6)
	≥240	2(3.1)	2(5.7)	2(6.7)
TG	<150	32(49.2)	19(54.2)	14(46.6)
	150-199	19(29.2)	9(25.7)	10(33)
	≥200	14(21.5)	7(20)	6(20)
LDLc	<100	51(78.4)	26(74.2)	14(46.6)
	100-129	7(10.7)	2(5.7)	6(20)
	130-159	5(7.7)	3(8.5)	5(16.6)
	160-189	2(3.1)	1(2.8)	2(6.6)
	≥190	0(0)	3(8.5)	3(10)
HDLc	<40	43(66.1)	22(62.8)	21(70)
	40-59	17(26.1)	11(31.4)	8(26.6)
	≥60	5(7.6)	2(5.7)	1(3.3)

CaxP$_i$ was positively correlated with TC (r=0.24, p=0.005), and LDLc (r=0.26, p=0.002). In contrast, eGFR showed negative correlation (r=-0.32, p=0.001) with CaxP$_i$. Multiple regression analysis (Table3) demonstrated that CaxP$_i$ is an independent predictor for high TC and LDLc in renal failure patients.

Table 3. Ca× P$_i$ as a predictor of lipid disorder

Lipid profile	ß	p- value
TC	0.124	0.002
HDLc	0.041	0.42
TG	0.006	0.915
LDLc	0.081	0.046

DISCUSSION

We assessed CVD risk based on the level of Ca×P$_i$ in renal failure patients. CVD risk was found to increase with increase in the level of Ca×P$_i$. With increase in the level of Ca×P$_i$, number of CVD patients was also found to be increased; LVH (32.30% vs 34.20% vs 46.66%), arrythemia (13.84% vs 28.57% vs 46.67%), VHD (0% vs 5.71 vs 10%), cardiomyopathy (1.53% vs 8.57 vs 10%), and IHD (6.15 vs 11.42% vs 13.33%). Similarly, TC and TG level were found to increase with increase in Ca×P$_i$ level, unlike HDLc level which was found to decrease with increase in the value of Ca×P$_i$. eGFR showed negative correlation with Ca×P$_i$ (r= -0.32, p= <0.001).

A similar study by Regmi et al[10] found that higher Ca×P$_i$ is associated with presence of LVH, oxidative stress, microinflammation, hyperhomocysteinemia, hypercholesterolemia, hypertriglyceridemia and increased LDLc. In addition, Ganesh et al[7] found the progressive association between CaxP$_i$ and death from coronary artery disease (Relative risk (RR) 1.06) and sudden death (RR 1.07) per 10 mg^2/dl^2 increase in CaxP$_i$. More evidences from Young et al[11] and Block et al[12] further supported these findings. Young et al demonstrated that CaxP$_i$ is independent predictor of all-cause and CVD mortality with RR 1.02 and 1.05 per 5 mg^2/dl^2 increase in the level of CaxP$_i$ respectively. In a study of Block et al multivariable RR of death associated with CaxP$_i$ products of 45 to 50 mg^2/dl^2 and 50 to 55 mg^2/dl^2 were 1.06 and 1.14 respectively.

Similarly study conducted in Chinese patients with renal insufficiency showed that the CVD risk is significantly increased in patients with CKD. Even minor CKD has a major impact on the CVD risk.[13] This is further supported by the findings of the study from Kahnooj M et al[14] in which they illustrated that CaxP$_i$ level more than 42 mg^2/dl^2 was the optimal value in terms of sensitivity and specificity for

predicting the presence of vulvular insufficiency. Aortic insufficiency was directly associated with a high $CaxP_i$ level after adjustment for additional known mortality predictors p=0.01). Similarly a study conducted in Polish population also found that 55% of CKD patients had abnormal left ventricular heart structure.[15]

The serum total $CaxP_i$ product is an indicator of the risk of calciphylaxis, in particular cardiovascular calcification. The positive balance of this product is mainly due to high bone turnover in CKD which activate vascular smooth muscle cell (VSMC) to differentiate into osteo/chondrocyte-like cells by up regulation of RUNX-2 and MSX-2 transcription factors. These cells form collagen and noncollagenous proteins in the intima or media and incorporate calcium and phosphorus into matrix vesicles to initiate mineralization.[16] Our study found high levels of calcium and phosphorus. Higher phosphorus levels are associated with coronary artery calcification and vascular stiffness in humans. In *in vitro* conditions, higher extracellular phosphorus concentrations induce aortic VSMC to transform into osteoblast-like cells and to calcify the vascular extracellular matrix.[17] Similarly positive calcium balance may also be a factor in the pathogenesis of arterial calcification by altering VSMC functions and affecting NFAT cell signalling.[18]

CONCLUSION

This study showed that $CaxP_i$ increases with decrease in GFR and associated with various CVD and CVD risks. So this study raise a potential need to evaluate the level of calcium and phosphorus in all CKD patients and the level should be monitored more thoroughly to reduce morbidity and mortality in these patients due to CVD.

CONFLICT OF INTEREST

None

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