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Product of serum calcium and phosphorus ($Ca \times PO_4$) as predictor of cardiovascular disease risk in predialysis patients

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ABSTRACT

Objectives: The mortality rate of chronic kidney disease (CKD) patients is very high due to cardiovascular diseases (CVD) which cannot be fully justified by traditional CVD markers. Since, mineral bone disorder is common in CKD, product of serum calcium and phosphorus (Ca × PO4) can be a predictor of future CVD. So, our study aims to assess the utility of higher Ca × PO4 in prediction of CVD risk in predialysis CKD patients.

Design and methods: 150 CKD patients defined by NKF-KDOQI guideline not undergoing dialysis were recruited. Anthropometric and electrocardiographic parameters were recorded. We evaluated CVD risk by: i) Biochemical CVD markers, ii) NCEP ATP III guideline postulated risk factors and iii) Framingham risk scores.

Results: Higher Ca × PO4 is associated with presence of Left Ventricular Hypertrophy, oxidative stress, microinflammation, hyperhomocysteinemia, hypercholesterolemia, hypertriglyceridemia and increased LDLc. Compared to cases with Ca × PO4 <55 mg2/dL2, cases with ≥55 mg2/dL2 had relative risk (RR) of 1.82 (95% CI 1.25-2.64) for CVD, 3.24 (95% CI 2.37-4.41) for stroke and 2.43 (95% CI 1.37-4.31) for coronary heart disease (CHD). Moreover, compared to lowest quartile of Ca x PO4, the highest quartile group had RR of 2.13 (95% CI 1.06-4.28) for CVD, 2.61(95% CI 1.80-3.75) for stroke and 2.84 (95% CI 1.15-7.0) for CHD.

Conclusion: In predialysis patients, higher Ca × PO4 is independent predictor of CVD risk.

Introduction

Chronic kidney disease (CKD) is a global epidemic with its 10.2% prevalence reported in Nepal [1,2]. The mortality is very high for CKD patients [3,4]. Not all CKD patients develop kidney failure and there are thirty times more patients with stage 3 CKD than stage 5 CKD; the majority develop cardiovascular disease (CVD) [5,6]. Apart from traditional CVD markers, there has been increasing concern of novel CVD markers in CKD patients. Vascular ossification following mineral bone disorder (MBD) is common in CKD [7,8]. Product of serum calcium and phosphorus ($Ca \times PO_4$) has been established as an independent predictor of CVD and mortality in dialysis population [9–13]. NKF-KDOQI guideline [14] has recommended $Ca \times PO_4$ to maintain below 55 mg^2/dL^2 in CKD cases. Since, MBD is observed in whole range of stage 3 to stage 5 CKD [15,16], it could be a good marker to predict CVD in predialysis population as well. However, not many studies have been conducted in this regard in predialysis CKD patients. In this context, our study aims to assess the utility of $Ca \times PO_4$ in predicting CVD risks in predialysis CKD patients.

Materials and methods

Study design and participants

This hospital based study was conducted in Tribhuvan University Teaching Hospital (TUTH), Nepal from Jan 2012 to Dec 2012 (12 months). CKD was defined by NKF-KDOQI guidelines [14]. We enrolled 150 patients having CKD but not undergoing dialysis. Participants were informed about the study and written consent was taken. Anthropometric measurements were taken and fasting blood sample was obtained from every patient. Patients also underwent electrocardiogram (ECG) procedure. Among study participants, 5.3%, 53.3% and 41.3% respectively belonged to stages 3, 4 and 5 CKD [14]. Study was approved by Institutional Review Board, TUTH.

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Table 1
Mean comparison of CVD risk factors across Ca × PO4 quartiles.

	$Ca \times PO_4$ (mg^2/dL^2)				
	<41.6	41.6-51.7	51.8-59.7	≥59.8	*P*-Value
Serum creatinine(mg/dL)	3.11 ± 0.84	3.25 ± 0.73	3.76 ± 0.57	3.74 ± 0.90	0.1
eGFR(mL/min)	20.4 ± 1.0	18.4 ± 1.5	18 ± 0.9	15.5 ± 0.5	0.009
CKD duration(years)	3.1 ± 0.2	3.5 ± 0.3	4.6 ± 0.2	4.2 ± 0.3	0.002
BMI(kg/m^2)	24.3 ± 0.3	23.8 ± 0.3	23.8 ± 0.2	23.4 ± 0.4	0.28
Corrected calcium(mg/dL)	8.16 ± 0.08	8.64 ± 0.32	7.96 ± 0.08	11.6 ± 0.7	0.01
Phosphorus(mg/dL)	4.48 ± 0.1	5.68 ± 0.14	6.55 ± 0.31	7.0 ± 0.07	<0.001
PTH(pg/mL)	76 ± 4.1	79.6 ± 2.3	92.2 ± 6.1	102.9 ± 3.3	<0.001
Serum albumin (g/dL)	3.48 ± 0.35	3.44 ± 0.3	3.36 ± 0.7	3.18 ± 0.31	0.028
Serum transferrin (g/L)	2.0 ± 0.5	1.8 ± 0.5	1.6 ± 0.3	1.5 ± 0.4	<0.001
TC(mg/dL)	169 ± 5.8	199 ± 6.5	228 ± 7.7	220 ± 7.7	<0.001
TG(mg/dL)	147 ± 9.7	164 ± 9.7	170 ± 8.8	198 ± 10.6	0.002
LDLc(mg/dL)	98 ± 4.6	123 ± 5.8	146 ± 6.9	133 ± 6.5	<0.001
HDLc(mg/dL)	41 ± 1.5	42 ± 1.5	48 ± 1.5	44 ± 1.5	0.09
Non-HDLc(mg/dL)	128 ± 6.1	157 ± 6.9	181 ± 7.3	176 ± 7.7	<0.001
TC/HDL	4.96 ± 1.56	4.72 ± 1.38	4.91 ± 1.24	4.67 ± 1.35	0.055
Lp a(mg/L)	37.3 ± 2.4	44.8 ± 3.6	50.7 ± 3.7	48.6 ± 3.1	0.028
Anti-ox LDL(EU/mL)	27.8 ± 1.4	30.8 ± 1.3	32.4 ± 1.0	34.2 ± 1.0	0.003
hs CRP(mg/L)	1.64 ± 0.13	2.42 ± 0.16	2.72 ± 0.16	3.27 ± 0.1	<0.001
tHcy(μmom/L)	20.9 ± 1.1	24.4 ± 1.1	26.5 ± 1.2	26.7 ± 1.5	0.017
Hemoglobin (g/L)	11.5 ± 1.9	11.3 ± 2.3	11.2 ± 1.5	10.9 ± 1.8	0.558

eGFR: Estimated Glomerular Filtration rate; CKD: Chronic kidney disease; BMI: Body mass index; PTH: Parathyroid hormone; TC: Total Cholesterol; TG: Triglyceride; LDLc: Low-density lipoprotein cholesterol; HDLc: High-density cholesterol; Non-HDLc: Non-High-density lipoprotein cholesterol; Lp a: Lipoprotein a; Anti-oxLDL: Antibody against Oxidized Low-density lipoprotein; hs CRP: High Sensitivity C-reactive protein; tHcy: Total homocysteine.

Cardiovascular risk assessment

CVD risk was assessed by various traditional risk factors such as age, presence of diabetes, hypertension, smoking, previous history of CVD, left ventricular hypertrophy (LVH), dyslipidemia, anemia and novel risk factors, such as, homocysteine, high sensitive C-reactive protein (hsCRP), anti-oxidized low density lipoprotein antibody (anti-oxLDL) and lipoprotein a Lp(a) [8]. Presence of multiple risk factors as suggested by National cholesterol education program-Adult treatment panel III (NCEP ATP III) [17] and Framingham Predicted risk scores (FRS) [18–21] was also considered. Serum was separated within thirty minutes of blood collection. Serum calcium, phosphorus, parathyroid hormone (PTH) were also measured. We corrected calcium for albumin [22]. Glomerular filtration rate (eGFR) was estimated by Chronic Kidney Disease-Epidemiology collaboration (CKD-EPI) formula [23].

Statistical analysis

Data were analyzed by SPSS 17.0 software (SPSS Inc, USA). Continuous data were expressed as mean ± standard deviation (SD); *t*-test and one way ANOVA were used to compare means. Categorical variables were compared by Pearson's chi-square test and Fisher's exact test as appropriate. Odds ratio and relative risk (RR) were determined. Shapiro–Wilk test was used to determine distribution of parameters ($P > 0.09$ for all measured parameters). Because we compared four quartiles of $Ca \times PO_4$ with six possible combinations (Q1 vs Q2, Q1vs

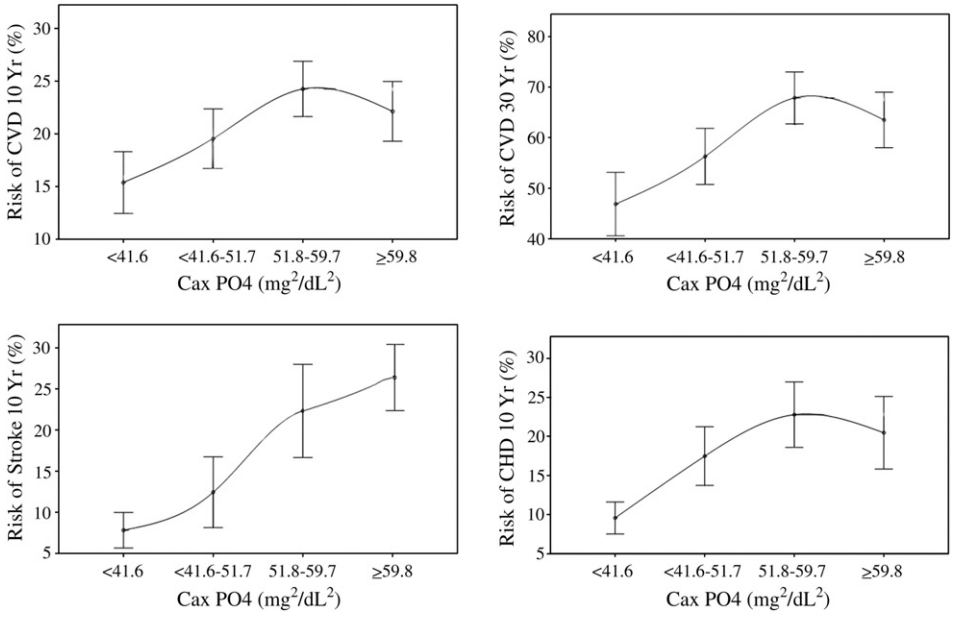

Fig. 1. Framingham predicted risk scores for Cardiovascular Disease (CVD) in 10 yr, CVD 30 yr, stroke 10 yr and coronary heart disease in 10 yr respectively for different $Ca \times PO_4$ quartile with mean and 95% confidence interval. ($P < 0.001$ for CVD 10 yr, 30 yr and CHD and $P = 0.009$ for stroke.).