Al Ameen J Med Sci 2016; 9(3):167-174 ● US National Library of Medicine enlisted journal ● ISSN 0974-1143

ORIGINAL ARTICLE CODEN: AAJMBG

A study of abnormal Calcium Phosphorus Product in Chronic Kidney Disease in Kerala population and its correlation with Acute Coronary Syndrome

Kartik Jadhav[1*] and Akash Thomas Oommen[2]

[1]Department of General Medicine, Al Ameen Medical College Hospital, Athani Road, Vijayapur-586108, Karnataka, India and [2]Department of General Medicine, Amrita Institute of Medical Sciences, Ponekkara, Kochi-682041, Kerala, India

Abstract: *Objective:* To determine the cutoff value for Calcium Phosphorus Product (CPP) in Chronic Kidney Disease (CKD) patients, above which there is a high risk of Acute Coronary Syndrome(ACS). *Methods:* Ninety five CKD patients on maintenance dialysis [2 to 3 sessions weekly] were followed up at AIMS, Kochi for a period of 2 years and any new onset acute coronary event during the following period were diagnosed and noted. All the relevant biochemical tests were performed including ECG and 2D Echocardiography. Standard statistical tests with multivariate regression analysis and ROC were performed to arrive at conclusion. *Results:* Out of 95 patients, 28 patients (29.5%) had ACS, with majority number of patients above 50 years of age [27(96.4%)]. Out of 95 patients 25(26.3%) were females and 70(73.7%) males. Out of 25 female patients 6(24%) had ACS. Out of 70 male patients, 22(31.4%) had ACS. The mean CPP was calculated for each patient and grouped into 4 groups [<40mg^2/dl^2; 40-55; 56-70; >70]. Patients with CPP>70mg^2/dl^2 had highest incidence of ACS with 92.3% patients involved [Pvalue<0.001]. Patients with CPP>55mg^2/dl^2 had odds ratio of 18.214 after multivariate regression analysis. ROC curve for CPP showed a cutoff point of 51.4mg^2/dl^2 with sensitivity of 78.6% and specificity of 73.1% for predicting ACS. *Conclusion:* This study shows that the cutoff value for CPP above which ACS is common is 51.49mg^2/dl^2 for the local population, which is quite less than the recommended KDOQI guidelines. Therefore a stricter control among the local population is recommended.

Keywords: Calcium-Phosphorus product (CPP), Serum Phosphorus and Cardiac risk, Acute Coronary Event, Acute Coronary Syndrome, Chronic Kidney Disease, ACS in CKD, Cardiovascular risk in Chronic Kidney Disease.

Abbreviations: Calcium-phosphorus product (CPP), Acute Coronary Syndrome (ACS), Coronary Artery Disease (CAD), Chronic Kidney Disease (CKD)

Introduction

Chronic Kidney Disease (CKD) encompasses a spectrum of different pathologic processes associated with progressive decline in the Glomerular Filtration Rate (GFR). The physical, social and psychological effect on the patient is immense due to its costly and long drawn/ lifelong treatment. CKD is divided into 5 stages and the 5th stage is called End stage renal disease, where the accumulation of the toxins, fluid and electrolytes normally excreted by kidneys result in Uremic syndrome. This syndrome leads to death unless the toxins are removed by renal replacement therapy, using dialysis or renal transplantation [1].

Renal transplantation is possible in patients who are medically fit, but in rest of the patients a lifelong dialysis has to be carried on. Uremic syndrome is characterized by multiple pathological changes in the body physiology which increases the overall risk of cardiovascular deaths [2-6]. Various studies have shown that cardiovascular disease is the leading cause of morbidity and mortality in patients at every stage of CKD [2-6]. This incidence is close to 30-45% of the CKD patients reaching stage 5. Also in the setting of the ACS, CKD patients are more likely to develop arrhythmias and left ventricular dysfunction [7].

There are two mechanisms by which the CKD patients suffer coronary artery disease; first is high serum Calcium Phosphorus product (CPP) which leads to accelerated vascular

calcification and atherosclerosis; second mechanism is the hemodialysis itself causing high levels of cytokines in the body leading to tissue damage [7]. Calcium Phosphorus Product (CPP) is a mathematical product of serum Phosphorus levels with serum Calcium levels. Abnormal CPP is a direct consequence of CKD. CKD with GFR below 30mL/min/1.73m^2 in adults develop Vitamin D [1, 25(OH) $_2D_3$] deficiency state. Thus condition of Vitamin D deficiency leads to hypocalcemia which in turn causes secondary hyperparathyroidism. This secondary hyperparathyroidism leads to calcium and phosphorus release from demineralization of the bone. In the initial stages of CKD the excess phosphorus is excreted by kidney, later worsening of the CKD leads to accumulation of phosphorus, causing very high levels of serum phosphorus.

This high serum phosphorus in turn causes higher levels of PTH hormone in the body leading to soft tissue and vascular calcification. This soft tissue and vascular calcification and accelerated atherosclerosis lead to coronary blockages and thus coronary artery disease [8-9]. Therefore presence of CKD in the patients is considered coronary risk equivalent and patients with CKD should therefore receive at least equally intensive risk factor modification as those with clinically recognized coronary heart disease [10].

Western medical associations and organizations have formulated various guidelines based on years of data collected during follow-up of CKD patients. These guidelines help to reduce the incidence of morbidity and mortality in the CKD patients. One such organization in USA is National Kidney Foundation (NKF) which has formulated Kidney Disease Outcome Quality Initiative (KDOQI) guidelines to guide Nephrologists to provide a better care to the CKD patients. The guidelines includes the range of various serum electrolytes and their management if found abnormal; it includes various measures taken to prevent life threatening conditions in CKD patients; various diagnostic methods and interventions required to improve the quality of life of CKD patients. The guidelines regarding Calcium Phosphorus product are

- Maintaining a target level of serum Phosphorus between 2.7-4.6 mg/dl in CKD stage 3 & 4; between 3.5-5.5 mg/dl for stage 5.
- Corrected serum Calcium should be kept within the normal range for the laboratory used, preferably towards the lower end 8.4-9.5 mg/dl.
- Calcium-Phosphorus product (CPP) should be maintained below 55 mg^2/dl^2 [11].

We have seen above that already large scale studies have been conducted and guidelines are formed and practiced in western world. The guidelines have been formed based on the data of Caucasian people for the western countries. In India similar efforts have not been made and we lack a comprehensive guideline for our population. This study is a small step towards this larger goal to form a guideline for the local population of Kerala and later for a national guideline.

Material and Methods

A prospective cohort study was conducted among CKD patients who are on regular hemodialysis at Department of Nephrology at AIMS, Kochi. The study was carried out from 2012 to 2015. Ninety Five CKD patients who were on hemodialysis for at least 1 year were followed up for a period of 2 years. All the patients in the group never had any history of cardiovascular disease in the past. Information concerning each patient (MRD number, name, age, sex, co morbid conditions, duration of dialysis, h/o smoking or alcohol intake) were recorded in Performa. Patients were followed up for 2 years and new onset acute coronary event were recorded and managed according to the protocol.

All the patients underwent the recommended management of CKD and other preexisting conditions [Diabetic control, Hypertension control, Arterial disease treatment etc] and treatment of all the abnormalities arising from the CKD condition. Hyperphosphatemia was controlled with non calcium phosphate binders. In case of hypocalcemia, adequate calcium supplementation was provided. Diet control was advised to all the patients. Patients underwent regular dialysis sessions as required by the protocol for CKD and regular dialysis were accompanied with blood

samples taken for serum calcium and serum phosphate levels [At least 3-4 samples/year]. All the calcium and phosphate levels were recorded and tabulated. Patients who were diagnosed with new onset ACS during the 2 year period of study were separated and their previous 1 year mean serum calcium and serum phosphate levels were calculated and tabulated. Blood samples were taken for Serum creatinine using Jaffe's method for know the GFR by Cockcroft Gault method; Serum Albumin levels for calculating corrected Calcium levels; Serum Calcium and Phosphate levels using Arsenazo and UV photometry methods for calculating Calcium Phosphorus product; Cardiac enzymes, Troponin I using immunoassay method and serum CK-MB for detecting ACS. ECG and 2D Echocardiography to help detect ACS.

To test the statistical significance of the association of abnormal CPP with ACS; Chi-square test applied to know the statistically significant risk factor. Multi variate analysis was done for individual association between CPP and ACS after considering and statistical correction for other variables. Variables which can lead to ACS in a person are Diabetes mellitus, Hypertension, Arterial disease, Age, Smoking, Sex, Left ventricular hypertension, Systolic dysfunction, diastolic dysfunction, Triglycerides, LDL and HDL. ROC (Receiver operating characteristic) analysis of CPP was used to know the ideal cutoff with maximum specificity and sensitivity above which ACS is more likely.

Results

This study at first considered 145 patients, out of which only 95 patients were included based on inclusion and exclusion criteria. The Inclusion Criteria involved that all the patients in the study group should not have past history of ACS at the time of initiation of the study and all the patients should have been on dialysis for at least 1 year [in our study mean, 3.8 years] and have had regular follow-ups at Amrita Institute of Medical Sciences, Kochi. The mean number of years of dialysis in Block et al was 4.5 years [1].

All the patients were followed up with for a mean period of 2 years during which patients were undergoing regular dialysis and routine blood tests at our Centre. Almost all the patients had undergone 2D Echo and fasting lipid profile as baseline according to affordability of the patient. Any new cardiac event in them would be noted and above mentioned blood parameters would be sent. An acute coronary event was diagnosed based on clinical features, cardiac enzymes, ECG changes and 2D echocardiography by an experienced faculty in the Department of Cardiology. All the patients who had ACS underwent treatment according to the AHA guidelines followed up by Department of General Medicine and Cardiology. At the end of the study, these patients were divided into 2 main groups: the patients who had ACS and the ones who didn't (control group).

The mean age of all the 95 patients in the study was 61.0 in which females were of an average age of 58.8 and males were 61.79. Out of 95 patients, 28 had ACS. In patients less than 50 years, out of 16 patients, only 1 patient had ACS (6.2 %) whereas above 50 years of age, the percentage of patient who had ACS in both the groups, i.e. 50-70 and above 70 had similar percentages of cases with 34.9% and 33.3% respectively. Therefore patients above 50 years of age had higher risk than patients less than 50 years of age. Mean age of patients who had ACS in Misiriya et al was 59 years conducted at Kottayam, Kerala [12].

In our study the mean age of patients who had ACS was 64.1 years. It was observed during univariate analysis of the variable that the P value was 0.053 which is borderline significance. Also patients above 50 years of age had 7.7 times [Odds ratio] the risk of having an ACS when compared to patients below 50 years of age. Therefore elder the patient, more the risk of having ACS. This is in accordance with the National study conducted by Block et al [1].

CPP was calculated by product of corrected calcium and phosphate levels in the serum. The corrected calcium was calculated by knowing the total serum calcium levels and albumin levels and using the formula:

Corrected total calcium (mg/dL) = Total calcium (mg/dL) + 0.8 × [4 - Serum albumin (g/dL)] [13].

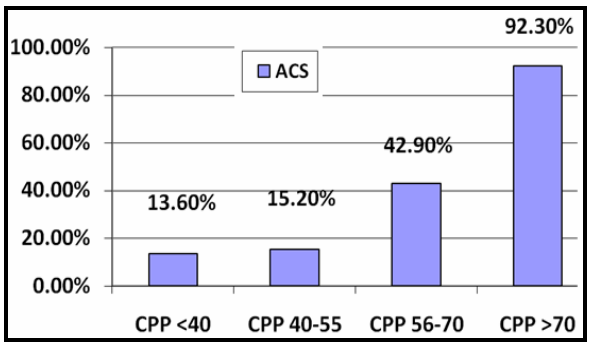
CPP for every patient was assessed at least once in 3 months as a routine follow up for patients on dialysis. For all the patients in the study, an average CPP was calculated for about 6 months. The mean CPP value for all the patients over 6 months (except for the time when patients had ACS) was 46.35 mg^2/dl^2. Any patient who had a CPP of more than 55 mg^2/dl^2 was treated with non-calcium containing phosphate binders to bring the value below 55 mg^2/dl^2.

Table-1: Percentage of ACS in each CPP group

CPP	ACS		Total
	Absent	Present	
<40 mg²/dl²	19 (86.4%)	3 (13.6%)	22
40-55 mg²/dl²	39 (84.8%)	7 (15.2%)	46
56-70 mg²/dl²	8 (57.1%)	6 (42.9%)	14
>70 mg²/dl²	1 (67%)	12 (92.3%)	13
Total	67 (70.5%)	28 (29.5%)	95

For the purpose of uni-variate analysis this variable was divided into 3 groups; group 1 consisted of patients with CPP<40; group 2 consisted of patients with CPP between 40-55 and group 3 consisted of patients with CPP>55, P< 0.001.

Fig-1: Percentage of ACS in each CPP group



The above data is clear that as the value of CPP increases the chance of getting ACS also increases.

For patients who had ACS, CPP was calculated on the values taken at that moment of time (table 1 and figure 1). Now the CPP was divided into 4 groups with the 1st group less than 40 mg^2/dl^2, 2nd group from 40-55 mg^2/dl^2, 3rd group between mg^2/dl^2 and the 4th group had patients with CPP above 70 mg^2/dl^2. CPP group less than 40 mg^2/dl^2 showed 3 patients (13.6%) with ACS in a total of 22 patients. The CPP group from 40-55 mg^2/dl^2 showed 7 patients (15.2%) with ACS among 46 patients. This particular group was taken as reference because the CPP range was considered normal according to Western guidelines. CPP group from 55-70 mg^2/dl^2 had 6 patients (42.9%) with ACS out of 14 patients.

The significant rise in the number of ACS patients in this particular group shows that higher CPP values are associated with higher percentage of ACS cases. The final group having a CPP value over 70 mg^2/dl^2 had 12 patients with ACS among a total of 13 patients, thus raising the percentage to 92.3%. This confirms the association of higher CPP with that of Acute Coronary Events. For univariate analysis these patients were divided as group 1 with CPP < 40 mg^2/dl^2, group 2 patients with CPP from 40-55 mg^2/dl^2 and group 3 patients with CPP> mg^2/dl^2. It was found that there was no significant difference in group 1 and group 2. The group 2 and 3 had P value of less than 0.001. Thus proving that the CPP value above 55 mg^2/dl^2 posed grave risk for ACS than patients with CPP less than 55 mg^2/dl^2. The risk in group 3 was 11.14 times [Odds ratio] the risk of group 1.

As ACS can be caused by multiple factors like age, sex, diabetes mellitus, hypertension, presence of LVH, presence of systolic dysfunction, presence of diastolic dysfunction, smoking and deranged lipid profile (table-2). All these variables may interfere with the associations between CPP and ACS. Therefore, a multi variant logistic regression was conducted to reduce the effect of other variables on association between CPP and ACS.

Multi variant logistic regression was performed by keeping group 1 as base; thus CPP group 2 showed P value of 0.969 with Odds ratio of 1.032. CPP group 3 showed P value of less than 0.001 with odds ration of 18.214 (table-3). Thus, this shows patients with CPP value above 55 mg^2/dl^2 have a very high risk of having ACS. This finding was in agreement with parallel studies being

conducted in the western world as well as being in agreement with KDOQI guidelines where CPP values less than 55mg^2/dl^2 is the recommended as guidelines. To know the cutoff of CPP value for our study, above which there would be a 'high risk of ACS'; was determined with the help of ROC (Receiver Operating Curve) figure-2. This showed a cutoff point of 51.49 mg^2/dl^2 CPP value with sensitivity of 78% and specificity of 74%. Thus, the above value shows that for the local population the threshold or the cut off at which there is a higher risk of ACS is much lower than the stated value of 55 mg^2/dl^2 in the guidelines. We can then safely conclude that the local population would require a stricter regulation of CPP. The western guidelines may not be applicable to the Indian population and a much larger study need to be conducted to confirm the findings and to layout the guidelines for the Indian population.

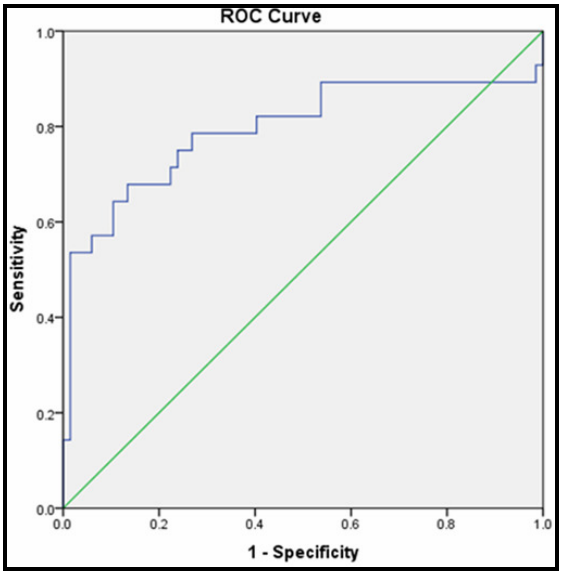
Table-2 Results of Univariate Analysis

		ACS		P value	Odds ratio	CI 95%	
		Absent	Present			Lower	Upper
DM	Not present	31 (77.5%)	9 (22.50%)	0.372			
	<20 years	20 (69%)	9 (31%)		1.55	0.526	4.571
	>20 years	16 (61.5%)	10 (38.5%)		2.153	0.728	6.364
HTN	Not Present	3 (50%)	3 (50%)	0.391			
	<10 years	30 (68.2%)	14 (31.8%)				
	>10years	34 (75.6%)	11 (24.4%)				
Age	<50 years	15 (93.8%)	1 (6.2%)	0.053	7.788	0.976	62.152
	>50 years	52 (65.8%)	27 (34.2%)				
Sex	Female	19 (76%)	6 (24%)	0.484	1.55	0.545	4.404
	Male	48 (68.6%)	22 (31.4%)				
CPP	<40	19 (86.4%)	3 (13.6%)	0.001	0.88	0.204	3.786
	40-50	39 (84.8%)	7 (15.2%)				
	>50	9 (33.3%)	18 (66.7%)		11.143	3.583	34.657
LVH	Absent	19 (70.4%)	8 (29.6%)	0.96	1.026	0.383	2.749
	Present	44 (69.8%)	19 (30.2%)				
Sys Dys	Absent	57 (70.4%)	24 (29.6%)	1	1.187	0.274	5.142
	Present	6 (66.7%)	3 (33.3%)				
DiaDsy	Absent	54 (70.1%)	23 (29.9%)	1	1.043	0.292	3.734
	Present	9 (69.2%)	4 (30.8%)				
Triglycerides	<150	40 (74.1%)	14 (25.9%)	0.366	1.667	0.547	5.074
	>150	12 (63.2%)	7 (36.8%)				
LDL	<100	28 (75.7%)	9 (24.3%)	0.395	1.556	0.56	4.322
	>100	24 (66.7%)	12 (33.3%)				
HDL	>45	15 (83.3%)	3 (16.7%)	0.241	2.432	0.623	9.492
	<45	37 (67.3%)	18 (32.7%)				
Smoking	Absent	57 (76%)	18 (24%)	0.023	3.167	1.137	8.819
	Present	10 (50%)	10 (50%)				

Table-3: Multivariate logistic regression analysis				
	P value	Odds ratio	95% C.I for odds ratio	
			Lower	Upper
Age > 50 yrs	0.032	14.123	1.264	157.846
CPP<40	0.000			
CPP 40-55	0.969	1.032	0.212	5.015
CPP>55	0.001	18.214	3.789	87.550
Smoking	0.022	4.711	1.246	17.813

Three variables the probability of which was 0.2 with univariate analysis were included for multivariate analysis; all the three variables were found to be statistically significant in multivariate analysis are given in table-3.

Fig-2: Receiver Operating Characteristic



Cut-off value: 51.49

The ROC curve showed a cut-off point 51.4 mg^2/dl^2 with the sensitivity of 78.6% and specificity of 73.1%.

Discussion

Among several potential mechanisms that explain the association of serum phosphorus levels with greater CVD risk, four are commonly cited. First, higher phosphorus levels cause direct vascular injury. Previous studies have shown higher phosphorus levels increase the propensity of mineral deposition in vascular smooth muscle cells in vitro [14]; partly explained by increased Osteopontin expression [15-16]. Secondly, serum phosphorus may also directly increase vascular calcification, especially when levels of calcium-phosphorus product are high, as observed in CKD patients [17] or in individuals without CKD (dystrophic calcification) [18].

Thirdly, inhibition of 1, 25-dihydroxyvitamin D synthesis by high serum phosphorus levels. Low levels of 1, 25- dihydroxyvitamin D are hypothesized to decrease cardiac contractility [19] and to increase coronary calcification [20]. Fourthly, high serum phosphorus levels increase circulating PTH levels even in healthy individuals [21]. High PTH levels are known to induce IL6 production and are pro-inflammatory causing increased bone resorption [21]. Higher levels of IL6 and hsCRP are known to increase CVD risk. Fifth, high serum phosphorus levels may indicate subclinical renal dysfunction, with associated cardiovascular sequelae.

As discussed above and as shown by multiple studies across the globe, it is proven beyond doubt about the association between serum phosphorus levels and CVD risk; but association between serum calcium and CVD risk is still unclear with multiple conflicting studies in past. Serum Calcium levels are known to increase blood pressure (both systolic and diastolic) [16, 22-24]. Based on multiple studies KDOQI came up with guidelines for controlling calcium levels on the lower end of the normal range for end stage renal disease [11].

According to multiple studies such as Thankappan et al and Vimala et al, it was seen that overall prevalence of risk factors for CVD among Kerala population is 50-100% more than the national average [25-26]. Therefore based on the studies epidemiologically ethnic differences are there for which further studies are required to know the exact cause. Some widely accepted hypothesis include food habits such as phosphorus rich items like meat, poultry, fish, seeds and milk products. Kerala has high per capita protein intake when compared to rest of the India.

As we saw in the results that calcium-phosphorus product (CPP) was significantly

associated with acute coronary syndrome (ACS) in chronic kidney disease (CKD) patients on continuous dialysis. Higher CPP values of more than 55 mg^2/dl^2 showed 18 times higher risk of going for ACS, which is very significant. And based on ROC curve interpretation we got a value of 51.49 mg^2/dl^2; which signifies that for the study population the risk for ACS increases significantly if the value of CPP crosses 51.49 mg^2/dl^2. Now this value is important because in KDOQI guidelines suggest the uppermost recommended value of CPP for CKD patients to be 55 mg^2/dl^2, whereas in our study the uppermost value of CPP above which ACS risk is high is 51.49 mg^2/dl^2. This shows that, the study subjects were at higher risk of suffering an ACS at comparatively lower CPP values than the western population. Even though a much larger study is required involving larger population over multiple centers to come to a conclusion but this initial study by us definitely shows that a stricter control of the CPP levels is required to reduce the risks of ACS among CKD patients.

Although, substantial progress has been made in the understanding of pathogenesis of ACS in CKD patients, majority of the studies have been carried out in western world which mostly involved Caucasian population. In India no such large scale studies have been performed to analyze ethnic differences in the risk factors. This particular study takes first step towards this larger goal. The goal being to formulate India specific guidelines for management of CKD patients on dialysis.

Conclusion

This study shows strong association of calcium phosphorus product with acute coronary event in patients suffering from chronic kidney disease on maintenance dialysis. This study also shows that the cut off value for calcium phosphorus product above which acute coronary event is 51.49 mg^2/dl^2; which is quite less than the KDOQI guideline recommendation. Therefore Kerala population would require stricter control of Calcium Phosphorus product levels. We suggest the upper limit for CCP to be 50 mg^2/dl^2.

Implications: This study might be one of the initial steps in formulating a National database and guidelines for Indian CKD patients on dialysis.

Strengths and Limitations: As this is was one the first articles to study the association between CPP and ACS in the region as far as our knowledge is; our study gives glimpse of the racial/ ethnic differences between our study population and the western population. Some of the limitations of our study deserve comment. We did not take serum 1, 25 dihydroxyvitamin D levels, serum PTH levels and hsCRP levels into consideration during our study.

References

1. Block GA, Hulbert-Shearon TE, Levin NW, Port FK. Association of serum phosphate and calcium × phosphate product with mortality risk in chronic hemodialysis patients: A national study. *Am J Kidney Dis* 1998; 31:607-17.
2. Block GA, Klassen PS, Lazarus JM, Ofsthun N, Lowrie EG, Chertow GM. Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. *J Am Soc Nephrol.* 2004; 15(8):2208-18.
3. Dhingra R, Sullivan LM, Fox CS, Wang TJ, D'Agostino RB Sr, Gaziano JM, Vasan RS. Relations of serum phosphorus and calcium levels to the incidence of cardiovascular disease in the community. *Arch Intern Med.* 2007; 167(9):879-85.
4. Robert N. Foley, Phosphorus Comes of Age as a Cardiovascular Risk Factor. *Arch Intern Med.* 2007; 167(9):873-874.
5. Kestenbaum B, Sampson JN, Rudser KD, Patterson DJ, Seliger SL, Young B, Sherrard DJ, Andress DL. Serum phosphate levels and mortality risk among people with chronic kidney disease. *J Am Soc Nephrol.* 2005; 16(2):520-8. Epub 2004 Dec 22.
6. Tonelli M, Sacks F, Pleffer M, Gao Z & Curhan G. Relation between serum phosphate level and cardiovascular event rate in people with coronary disease. *Circulation,* 2005; 112:2627-2633.
7. McCullough PA, Maynard RC. Treatment disparities in acute coronary syndromes, heart failure, and kidney disease. *Contrib Nephrol* 2011; 171:68-73.
8. Salgueira M, del Toro N, Moreno-Alba R, Jiménez E, Arresté N, Palma A. Vascular calcification in the uremic patient: A cardiovascular risk. *Kidney Int Suppl* 2003; 85:S119-21.

9. Braun J, Oldendorf M, Moshage W, Heidler R, Zeitler E, Luft FC. Electron beam computed tomography in the evaluation of cardiac calcification in chronic dialysis patients. *Am J Kidney Dis* 1996; 27:394-401.
10. Anderson JL, Adams CD, Antman EM, et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2007; 50:e1-157.
11. KDOQI, Guidelines. *American Journal of Kidney Diseases*, 2003; 42(4) Suppl 3 [October].
12. Raihanathul Misiriya KJ, Sudhayakumar N, Abdul Khadar S, George R, Jayaprakash VL, Pappachan JM. The Clinical Spectrum of Acute Coronary Syndromes: Experience from a Major Center in Kerala. *J Assoc Physicians India.* 2009; 57:377-83.
13. Portale AA. Blood calcium, phosphorus, and magnesium, in Favus MJ (ed): Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism. *Philadelphia, PA, Lippincott, Williams & Wilkins,* 1999; 115-118
14. Jono S, McKee MD, Murry CE, et al. Phosphate regulation of vascular smooth muscle cell calcification. *Circ Res*. 2000; 87:E10-E17.
15. Chen NX, O'Neill KD, Duan D, et al. Phosphorus and uremic serum up-regulate osteopontin expression in vascular smooth muscle cells. *Kidney Int*. 2002; 62:1724-1731.
16. Giachelli CM, Speer MY, Li X, et al. Regulation of vascular calcification: roles of phosphate and osteopontin. *Circ Res*. 2005; 96:717-722.
17. Oh J, Wunsch R, Turzer M, et al. Advanced coronary and carotid arteriopathy in young adults with childhood-onset chronic renal failure. *Circulation*. 2002; 106:100-105.
18. Giachelli CM. Ectopic calcification: gathering hard facts about soft tissue mineralization. *Am J Pathol*. 1999; 154:671-675.
19. Zittermann A, Schleithoff SS, Tenderich G, et al. Low vitamin D status: a contributing factor in the pathogenesis of congestive heart failure? *J AmColl Cardiol*. 2003; 41:105-112.
20. Watson KE, Abrolat ML, Malone LL, et al. Active serum vitamin D levels are inversely correlated with coronary calcification. *Circulation*. 1997; 96:1755-1760.
21. Silverberg SJ, Shane E, Clemens TL, et al. The effect of oral phosphate administration on major indices of skeletal metabolism in normal subjects. *J Bone Miner Res*. 1986; 1:383-388.
22. Jorde R, Sundsfjord J, Fitzgerald P, Bonaa KH. Serum Calcium and cardiovascular risk factors and diseases: the Tomsϕ study. *J Hypertension.* 1999; 34(3):484-90.
23. Kesteloot H, Geboers J. Calcium and blood pressure. *Lancet.* 1982; 1:813-815.
24. Yuelong Jin, Lianping He, Yingshui Yao. Serum calcium levels are not associated with coronary heart disease. *Vasc Health Risk Manag.* 2013; 9:517-520.
25. Thankappan KR, Shah B, Mathur P et al. Risk factor profile for chronic non-communicable diseases: results of community-based study in Kerala, India. *Indian J Med Res.* 2010; 131:53-63.
26. Vimala A, Ranji SA, Jyosna MT, Chandran V, Mathews SR, Pappachan JM. The prevalence, risk factors and awareness of hypertension in an urban population of Kerala (South India). *Saudi J Kidney Dis Transpl.* 2009; 20(4):685-689.

*All correspondences to: Dr. Kartik Jadhav, Assistant Professor, Department of General Medicine, Al Ameen Medical College Hospital, Athani Road, Vijayapur-586108, Karnataka, India. E-mail: drkartik303@gmail.com