

Original Research Article

Role of serum phosphate level in cardiovascular events in non-CKD patients

Arvind Kumar, Prem Singh*, Mohd. Imran Khan, Mehtab Alam

Department of Medicine, Ganesh Shankar Vidyarthi Memorial Medical College, Kanpur, Uttar Pradesh, India

Received: 13 February 2019

Revised: 13 May 2019

Accepted: 30 May 2019

*Correspondence:

Dr. Prem Singh,

E-mail: drpremsingh22gsvm@gmail.com

Copyright: © the author(s), publisher and licensee Medip Academy. This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License, which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

ABSTRACT

Background: Serum phosphate level correlate with atherosclerosis in both animal models and humans with advanced chronic kidney disease and coronary calcification is a known impact of higher serum phosphate, but whether this relationship exists among individuals with Non-CKD is unknown. we conducted this study to observe role of higher serum phosphate level in cardiovascular comorbidities like MI and CHF in Non-CKD patients.

Methods: In this observational study, 300 patients were enrolled, half of the patients having Clinical features or positive biochemical markers (Troponin-I for MI and serum BNP for CHF) suggestive of myocardial infarction and heart failure were taken as case group and half of the subjects were taken as control group with similar baseline characteristics. All participants in this study were consenting and more than 18 years of age.

Results: The mean value of serum phosphate level in case group was 4.41 ± 1.40 while in control group was 3.19 ± 1.07 showing statistically significant difference (p-value <0.001). In case group 65% patients were having MI with higher serum phosphate level (4.22 ± 1.40).

Conclusion: Higher serum phosphate level is related to increased cardiovascular morbidities even in non-CKD patients.

Keywords: Cardiovascular morbidities, Congestive heart failure, Myocardial infarction, Serum phosphate level

INTRODUCTION

Phosphorus is essential for life and exists in the body as phosphate. Phosphates are components of RNA, DNA, adenosine triphosphate (ATP), cell membrane, and bone. Despite its importance, the accumulation of phosphate can produce deleterious effects. However, the accumulation of phosphate occurs long before the rise in serum phosphate above the upper normal limit since several observational studies in both general population and early-stage CKD patient have identified the relationship between high-normal serum phosphate and adverse cardiovascular outcomes.^{1,2} FGF 23 is produced

by osteoblasts and osteocytes in the bone under physiological condition. In the kidney, FGF-23 binds to FGF receptor in the proximal tubule in the presence of co-receptor klotho resulting in inhibition of proximal tubular phosphate reabsorption and a suppression of 1,25-dihydroxy vitamin D synthesis.³ Current knowledge remains incomplete, but clearly prevention of vascular calcification is a dynamic, multifaceted process. Endogenous inhibitors of crystal formation and of osteogenic differentiation of vascular smooth muscle cells have been identified, including matrix Gla protein and fetuin-A, experimental studies have shown that exposure of experimental animals to high ambient

phosphorus is followed by expression of an osteogenic phenotype in vascular smooth muscle cells and by vascular calcification.⁴⁻⁸ Other potential mechanisms linking rising phosphorus levels to vascular disease include inhibition of 1,25-dihydroxy vitamin synthesis and increased parathyroid hormone (PTH) production.⁹⁻¹¹ Phosphorus levels correlate with atherosclerosis in both animal models and humans with advanced chronic kidney disease, but whether this relationship exists among individuals with normal kidney function is unknown. Several observational studies of dialysis populations have shown that high serum phosphorus levels are antecedent associations of mortality and cardiovascular events, independent of calcium and PTH levels.¹²⁻¹⁵ If high phosphorus levels truly cause vascular disease, then it seems natural to hypothesize that this relationship also applies within the normal range of phosphorus levels, even in the presence of normal kidney function.

Coronary artery calcium levels are believed to reflect accurately the overall burden of atherosclerosis and to exhibit dosage-response relationships with the incidence of future cardiovascular events.¹⁶⁻¹⁸ Studying phosphorous levels and coronary artery calcification can potentially reveal the mechanisms by which serum phosphorous may lead to cardiovascular disease and, perhaps, suggest the existence of novel mechanisms for developing atherosclerosis.

METHODS

This observational study was conducted in a Tertiary Centre, department of medicine, GSVM Medical College, Kanpur from December 2016 to October 2018. 300 patients were included in the study.

All consenting patients more than 18 years of age having Clinical features or positive biochemical markers (Troponin-I for MI and serum BNP for CHF) suggestive of myocardial infarction and heart failure. Subjects less than 18 years of age, Pregnant females, CKD patients, Patients with hypoparathyroidism, patients with hypovitaminosis D and non-consenting were excluded from study. A brief medical history of subjects related to study was taken followed by blood investigations like complete blood count, Liver function test, Kidney function test, Serum Na⁺/K⁺/Ca⁺⁺, Trop I / serum BNP, Serum Phosphate, vitamin D3 level, iPTH along with USG whole abdomen, Urine Routine/Microscopic examination and ECG.

Statistical analysis

The data was processed in Excel sheet and analysis was carried out using SPSS Software. Quantitative variables were analyzed using mean and Standard Deviation. Comparison between groups was done using Independent t test (for 2 groups) and ANOVA (for more than 2 groups). p-value of <0.05 was taken as statistically significant.

RESULTS

In this study, author included 300 patients. Further they divided it into Case and Control Group, each containing 150 patients. Case group is subdivided into myocardial infarction (n=98), heart failure (n=27) and patients which have both myocardial infarction and heart failure (n=25) subgroups. Baseline characteristics were comparable. Mean age of patients in case group was 58.43±13.54 years while in control group 53.41±12.54 years. Half of the patients in both groups were in 41-60 years age group. 60% patients were male in case group while in control group 56.7%. Risk factors like smoking, alcohol intake and diabetes were comparable in both groups. Mean HbA1c in case group was 5.8±0.9 while in control group was 5.1±0.5. Serum Cholesterol in case group was 165.07±33.80 which was comparable to control group 147.87±21.14. Serum triglyceride level in case group was 162.29±44.87 as compared to control group having 124.72±21.17. Serum LDL level in case group was 121.57±25.59 comparable to control group 112.73±21.56 (Table 1).

Table 1: Demographic Profile, baseline characteristics and risk factors.

Parameters	Case Group (n=150)	Control Group (n=150)
Age (in years)		
18-40	13 (8.7%)	16 (10.7%)
41-60	74 (49.3%)	74 (49.3%)
>60	63(42%)	60 (40%)
Sex		
Male	90 (60%)	85 (56.7%)
Female	60 (40%)	65 (43.3%)
Risk factors		
Smoking	52(34.6%)	50 (33.3%)
Alcoholism	37(24.7%)	35(23.3%)
Diabetes	14(9.3%)	12(8%)
HbA1C (Mean±SD)	5.8±0.9	5.1±0.5
Serum cholesterol (Mean±SD)	165.07±33.80	147.87±21.14
Serum triglycerides (Mean±SD)	162.29±44.87	124.72±21.17
Serum LDL (Mean±SD)	121.57±25.59	112.73±21.56
Serum HDL (Mean±SD)	54.11±8.89	57.19±5.91

Case group was subdivided as per etiology into 3 groups: Myocardial infarction (MI) subgroup, congestive heart failure (CHF) subgroup and subgroup of patients having both MI and CHF. In case group majority of patients were having MI (65.3%), with CHF were 18% and patients having both MI and CHF were 16.7%.

Serum Phosphate level was compared in these subgroups. Serum Phosphate level in MI subgroup was 4.22 ± 1.40 , in

CHF subgroup was 4.94 ± 1.33 and in subgroup having both MI and CHF were 4.59 ± 1.33 (Table 2).

Table 2: Serum phosphate level in etiological subdivision of patients in case group.

Etiology	No. of patients	Percentage	Serum phosphate level (Mean \pm SD)
Myocardial infarction (MI)	98	65.3	4.22 ± 1.40
Heart failure (HF)	27	18	4.94 ± 1.33
Both MI and HF	25	16.7	4.59 ± 1.33

Correlation of serum BNP level with serum Phosphate level was also tested in CHF patients using Pearson correlation coefficient (0.025) which was statistically insignificant. (p-value 0.903) while correlation of Trop-I and Serum Phosphate Level was also tested in MI patients using Pearson correlation coefficient (0.133) which was showing positive correlation but no statistically significant difference was observed (p-value 0.081) (Table 3).

Table 3: Correlation between serum BNP, Trop-I and serum phosphate level.

Correlation	N	Pearson's correlation coefficient	P value
BNP and serum PO4 level	27	0.025	0.903
Trop-I and serum PO4 level	98	0.133	0.081

There is significant difference in serum Phosphate level among control group (3.19) and case group with various cardiovascular morbidities. The mean value of serum Phosphate level in case group was 4.41 ± 1.40 while in control group was 3.19 ± 1.07 showing statistically significant difference (p-value < 0.001) (Table 4).

Table 4: Comparison of Serum Phosphate Level between Case and Control Group.

	Case group	Control group	P-value
Serum PO4 level (Mean \pm SD)	4.41 ± 1.40	3.19 ± 1.07	≤ 0.001

DISCUSSION

Serum phosphate level in subjects showed a complex relationship with classic cardiovascular risk factors. Although Higher Serum Phosphate levels were associated with higher cardiovascular morbidity among Non-CKD patients. Most observational studies examining association between serum phosphate level and

cardiovascular morbidities come from advanced chronic kidney disease (CKD) patients. These studies have shown consistent associations between abnormal Serum Phosphate level and cardiovascular outcomes; in contrast, associations with calcium levels and PTH levels have been inconsistent in the same studies.¹⁹⁻²² These findings have been extended to phosphorus levels within the normal range by a retrospective analysis of the Cholesterol and Recurrent Events (CARE) trial among individuals with previous MI.²³ There are some studies exploring associations between serum Phosphate level and cardiovascular comorbidities in community adults without apparent kidney disease.

A report from participants in the Framingham Offspring Study, the average age of the study population was approximately 20 years older than in Cardia study. Several associations of higher serum Phosphate level mirrored the findings in our study. contributions of genetic and environmental factors to the associations remain speculative. Unlike many cardiovascular risk factors uncovered in observational studies, potential interventions that can address some of the hypotheses suggested by this study may already exist.

Present study findings suggest that extending these studies to high-risk individuals without CKD in the general population has the potential to improve public health. Quite apart from the underlying determinants, the associations seen in this study suggest that high phosphorus levels might be a modifiable risk factor among cardiovascular comorbidities that should be screened and managed accordingly.

Limitations of study

This was single center study having small study population. It was Non-experimental design, observational study. Majority of data comes from studies showing correlation between serum Phosphate level and cardiovascular disease comes from advanced CKD patients. So, large population studies should be carried out to determine role of serum Phosphate level in cardiovascular comorbidities in patients not having apparent kidney disease.

CONCLUSION

Serum Phosphate level is emerging as a risk factor for cardiovascular disease in advanced kidney disease. But role of serum Phosphate level in cardiovascular comorbidities among Non-CKD patients is still under debate. There are only few studies for the same. In our study we concluded that higher Serum Phosphate level in Non-CKD patients is also related to increased cardiovascular comorbidities like MI and CHF. Large epidemiological studies to be done to generalize the results of this study in general population.

ACKNOWLEDGEMENTS

Authors would like to thank Dr. Richa Giri and Samreen Imran to support this study.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

- McGovern AP, de Lusignan S, van Vlymen J, Liyanage H, Tomson CR, Gallagher H, et al. Serum phosphate as a risk factor for cardiovascular events in people with and without chronic kidney disease: a large community based cohort study. *PLoS One*. 2013;10(8):e74996.
- Da J, Xie X, Wolf M, Disthabanchong S, Wang J, Zha Y, et al. Serum phosphorus and progression of CKD and mortality: a meta-analysis of cohort studies. *Am J Kid Dis*. 2015;1:66(2):258-65.
- Shimada T, Hasegawa H, Yamazaki Y, Muto T, Hino R, Takeuchi Y. FGF-23 is a potent regulator of vitamin D metabolism and phosphate homeostasis. *J Bone Mineral Res*. 2004;19(3):429-35.
- Jono S, McKee MD, Murry CE, Shioi A, Nishizawa Y, Mori K, Morii H, Giachelli CM. Phosphate regulation of vascular smooth muscle cell calcification. *Circ Res*. 2000 Sep 29;87(7):e10-7.
- Steitz SA, Speer MY, Curinga G, Yang HY, Haynes P, Aebersold R, Schinke T, Karsenty G, Giachelli CM. Smooth muscle cell phenotypic transition associated with calcification: upregulation of Cbfa1 and downregulation of smooth muscle lineage markers. *Circ Res*. 2001 Dec 7;89(12):1147-54.
- Wada T, McKee MD, Steitz S, Giachelli CM. Calcification of vascular smooth muscle cell cultures: Inhibition by osteopontin. *Circ Res*. 1999;84(2):166-178.
- Chen NX, O'Neill KD, Duan D, Moe SM. Phosphorus and uremic serum up-regulate osteopontin expression in vascular smooth muscle cells. *Kidney Int*. 2002;62(5):1724-31.
- Luo G, Ducy P, McKee MD, Pinero GJ, Loyer E, Behringer RR, et al. Spontaneous calcification of arteries and cartilage in mice lacking matrix GLA protein. *Nature*. 1997;386(6620):78.
- Portale AA, Halloran BP, Morris RC. Physiologic regulation of the serum concentration of 1,25-dihydroxyvitamin D by phosphorus in normal men. *J Clin Invest*. 1989;83(5):1494-9.
- Zittermann A, Schleithoff SS, Tenderich G, Berthold HK, Korfer R, Stehle P. Low vitamin D status: a contributing factor in the pathogenesis of congestive heart failure?. *J Am Coll Cardiol*. 2003;41(1):105-12.
- Smogorzewski MI, Zayed MA, Zhang YB, Roe JA, Massry SG. Parathyroid hormone increases cytosolic calcium concentration in adult rat cardiac myocytes. *Am J Physiol Heart Circulatory Physiol*. 1993;1:264(6):H1998-2006.
- Block GA, Hulbert-Shearon TE, Levin NW, Port FK. Association of serum phosphorus and calcium x phosphate product with mortality risk in chronic hemodialysis patients: a national study. *Am J Kid Dis*. 1998;1:31(4):607-17.
- Ganesh SK, Stack AG, Levin NW, Hulbert-Shearon T, Port FK. Association of elevated serum PO₄ (4), Ca x PO₄ (4) product, and parathyroid hormone with cardiac mortality risk in chronic hemodialysis patients. *J Am Soc Nephrol*. 2001;12(10):2131-8.
- Stevens LA, Djurdjev O, Cardew S, Cameron EC, Levin A. Calcium, phosphate, and parathyroid hormone levels in combination and as a function of dialysis duration predict mortality: evidence for the complexity of the association between mineral metabolism and outcomes. *J Am Soc Nephrol*. 2004 Mar 1;15(3):770-9.
- Slinin Y, Foley RN, Collins AJ. Calcium, phosphorus, parathyroid hormone, and cardiovascular disease in hemodialysis patients: the USRDS waves 1, 3, and 4 study. *J Am Soc Nephrol*. 2005 Jun 1;16(6):1788-93.
- Mautner GC, Mautner SL, Froehlich J, Feuerstein IM, Proschan MA, Roberts WC, et al. Coronary artery calcification: Assessment with electron beam CT and histomorphometric correlation. *Radiol*. 1994;192(3):619-23.
- Detrano R, Hsiai T, Wang S, Puentes G, Fallavollita J, Shields P, et al. Prognostic value of coronary calcification and angiographic stenoses in patients undergoing coronary angiography. *J Am Coll Cardiol*. 1996;27(2):285-90.
- Schmermund A, Denktas AE, Rumberger JA, Christian TF, Sheedy PF, Bailey KR, et al. Independent and incremental value of coronary artery calcium for predicting the extent of angiographic coronary artery disease: Comparison with cardiac risk factors and radionuclide perfusion imaging. *J Am Coll Cardiol*. 1999;34(3):777-86.
- Block GA, Hulbert-Shearon TE, Levin NW, Port FK. Association of serum phosphorus and calcium x phosphate product with mortality risk in chronic hemodialysis patients: a national study. *Am J Kidney Dis*. 1998;31(4):607-17.

20. Ganesh SK, Stack AG, Levin NW, Hulbert-Shearon T, Port FK. Association of elevated serum PO (4), Ca x PO (4) product, and parathyroid hormone with cardiac mortality risk in chronic hemodialysis patients. *J Am Soc Nephrol*. 2001;12(10):2131-8.
21. Stevens LA, Djurdjev O, Cardew S, Cameron EC, Levin A. Calcium, phosphate, and parathyroid hormone levels in combination and as a function of dialysis duration predict mortality: Evidence for the complexity of the association between mineral metabolism and outcomes. *J Am Soc Nephrol*. 2004;15(3):770-9.
22. Slinin Y, Foley RN, Collins AJ. Calcium, phosphorus, parathyroid hormone, and cardiovascular disease in hemodialysis patients: The USRDS waves 1, 3, and 4 study. *J Am Soc Nephrol*. 2005;16(6):1788-93.
23. Tonelli M, Sacks F, Pfeffer M, Gao Z, Curhan G. Relation between serum phosphate level and cardiovascular event rate in people with coronary disease. *Circulation*. 2005;112(17):2627-33.

Cite this article as: Kumar A, Singh P, Khan MI, Alam M. Role of serum phosphate level in cardiovascular events in non-CKD patients. *Int J Adv Med* 2019;6:1171-5.