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EVALUATION OF THE EFFECTS OF BIOCHEMICAL MARKERS LIKE CALCIUM, PHOSPHORUS AND PARATHORMONE IN PREDICTING THE COMPLICATIONS & MORTALITY IN CHRONIC KIDNEY DISEASE

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Abstract

Introduction: Chronic kidney disease (CKD) is an international public health problem affecting about 5–10% of the population. As kidney function declines, there is a progressive deterioration in mineral homeostasis with disruption of normal serum concentrations of phosphorus, calcium and changes in circulating levels of hormones like parathyroid hormone (PTH) and Vitamin D_3.

Hyperparathyroidism plays a vital role in the excess morbidity and mortality in chronic kidney disease. As a result; patients are at increased risk of bone disease, extraosseous calcification, and death.

Aims and Objectives: To estimate the serum Calcium, Phosphorus, Parathyroid Hormone levels in patients with CKD and to compare them with healthy individuals. To know the association between Calcium, phosphorus and PTH in CKD patients.

Material & Methods: 50 cases of CKD and 50 controls were included in the study. Serum calcium, phosphorus and PTH were measured in both cases and controls.

Statistically significant increases in levels of all parameters were seen in cases as compared to controls.

Conclusion: The levels of PTH, calcium & phosphorus are used as surrogate markers of disease progression. Abnormalities can occur subtly, usually without any symptoms, and may progress to cause more complications if not detected early. The ultimate goals of treating secondary hyperparathyroidism are to normalize mineral metabolism, prevent bone disease, and prevent extra skeletal manifestations of the altered biochemical processes.

Various CKD Guidelines recommend targets and early treatment strategies to correct serum levels of phosphorus, calcium, and PTH levels.

Keywords: CKD – Chronic kidney disease, PTH – Parathyroid hormone, ESRD – End stage renal disease, Glomerular filtration rate -GFR

Introduction

Chronic kidney disease constitutes a public health problem that is estimated to affect more than 10% of the global population and the prevalence of which has increased in recent years.[1]

CKD is a pathophysiological process with multiple aetiologies, resulting in the inexorable attrition of number & functions of nephron and frequently leading to ESRD. It represents a condition in which there has been an irreversible loss of endogenous renal function.[2]

CKD is a state of imbalance of several important physiologic regulatory mechanisms, among them mineral balance, acid– base balance, nutritional balance, and energy balance, resulting in accelerated cardiovascular disease (CVD) and mortality.

Mineral disturbances and secondary hyperparathyroidism develop early in the course of disease, even when the GFR is 50–80 mL/minute/1.73 m^2. [3]

The most important complication of CKD is cardiovascular disease, which is the primary cause of death in these patients.

The derangement in minerals seen is CKD, is a systemic disorder which is characterized by abnormal calcium, phosphorous, PTH, and vitamin D metabolism. Along with affecting the skeletal system, it also causes cardiovascular and soft tissue calcifications. [4]. These biochemical abnormalities are the early indicators for identification of mineral bone disease in CKD.

The bone mineral metabolism abnormalities start during first stages of CKD as renal function decreases, so it is recommended that attending physicians should monitor and control biochemical parameters early in the development of CKD. [5]

Secondary hyperparathyroidism develops due to hypocalcaemia caused as a result of phosphate retention and deficient vitamin D synthesis. In response to an increase in serum phosphorus concentration, production of vitamin D is decreased and secretion of PTH is increased. This in turn, increases urinary excretion of serum phosphorus to maintain normal serum calcium and phosphorus level. Thus, PTH plays a central role in metabolism of minerals within the body. [6]

Aims and Objectives:

To estimate the serum Calcium, Phosphorus, PTH levels in patients with CKD and to compare them with healthy individuals. To know the association between Calcium, phosphorus and PTH in CKD patients.

Materials and Methods:

The study was conducted at Vydehi Institute of Medical Sciences and Research Centre, Bangalore, Karnataka. CKD patients visiting Nephrology clinics were included in the study. All patients between 20-60 years were included in the study. Patients with congenital renal disorders were excluded. A written informed consent was taken from all patients.

The personal details of patients were documented. Clinical history, personal & family history was taken in detail from each patient. Normal Healthy individuals were included as controls in the study. Blood samples were collected in vacutainers and transported to the laboratory and analysed. [7]

The investigations like Serum urea, creatinine, Calcium, Phosphorus and PTH levels were analysed in Beckman coulter Unicell DXC 600 and Access 2 immunoassay system. Controls were used from Bio Rad.

Methodology:

Serum Urea was measured by enzymatic Conductivity rate method, serum Creatinine was measured by modified rate Jaffé method, serum intact PTH levels were measured by CLIA and serum Calcium and phosphorus were measured by ISE indirect method. [8-12]

Statistical Analysis:

Statistical Methods: Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean ± SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5 % level of significance. Analysis of variance (ANOVA) has been used to find the significance of study parameters between three or more groups of patients, Student test (two tailed, independent) has been used to find the significance of study parameters on continuous scale between two groups Inter group analysis) on metric parameters. Leven1s test for homogeneity of variance has been performed to assess the homogeneity of variance. Chi-square/Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups.

Significant figures

** Strongly significant (P value: P≤0.01)
* Moderately significant (P value: 0.01<P ≤ 0.05)
+ Suggestive significance (P value: 0.05<P<0.10)

Statistical software: The Statistical software namely SPSS 15.0 was used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables etc**.** (13-14)

RESULTS:

For our study, the following results were obtained.Samples were matched according to their age. Maximum number of patients, 32% were in the age group of 51-60 years, followed by 24% patients in 31-40 yrs. The mean age in patients is 47.26 ±12.73 years, whereas in controls age is 43.83 ±15.12 years.

Samples are gender matched. 70% of cases are males and 30% are females. In controls 62% are males and 38% are females. Among the study population, 66% were diabetic and 63% were hypertensive.

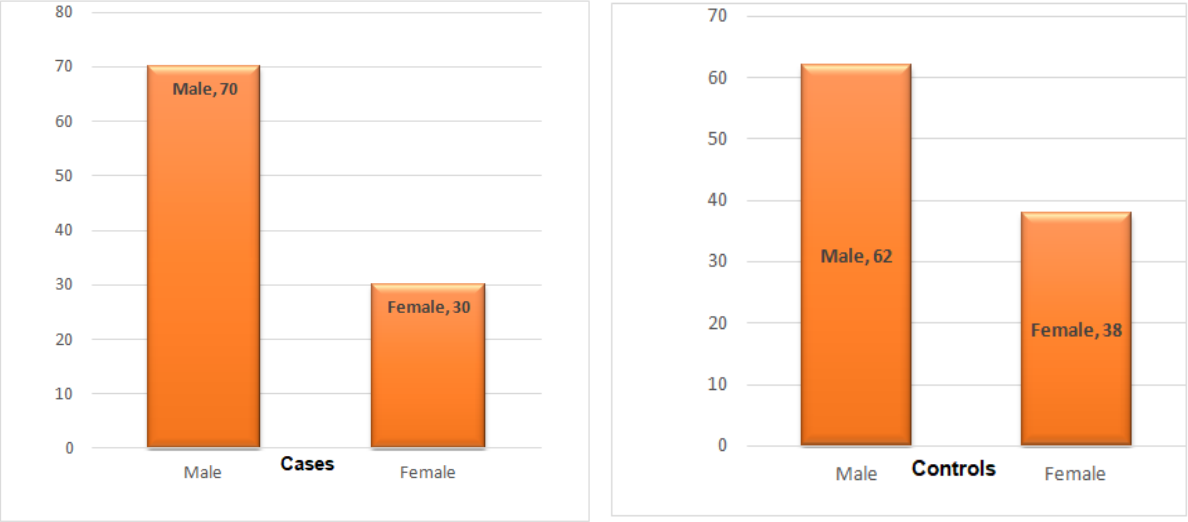

Figure 1: Gender distribution in cases and controls studied

Distribution of PTH in two groups studied

PTH levels were compared in both cases and controls. The mean level of PTH in cases is 142.80 ±92.70, where as in controls mean PTH level is 50.49 ±18.35 pg/ml. The Reference range for PTH is 67-90 pg/ml. 44% of cases had values above 90 pg/ml, whereas only 2% of controls had levels above 90 pg/ml. There was a statistically significant increase in PTH levels in cases as compared to controls. (P<0.001).

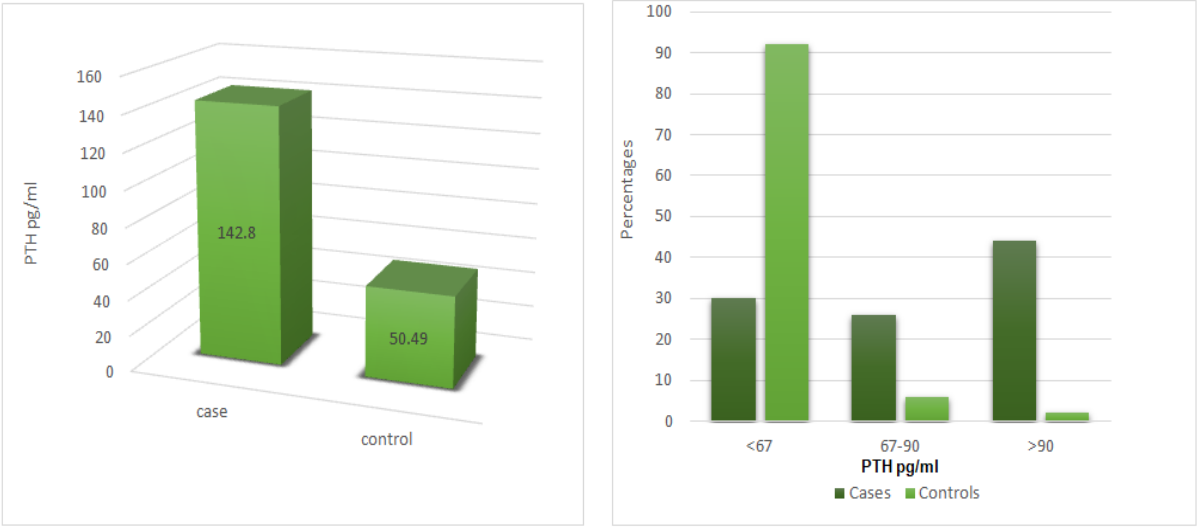

Figure 2: Mean PTH levels in cases and controls

The mean levels of **PTH** in cases are 142.80 ±92.70 and controls is 50.49 ±18.35 pg/ml. There is a statistically significant increase in PTH levels in cases as compared to controls p value is <0.001**.

Distribution of Calcium in two groups studied

Calcium levels were compared in cases and controls. The normal range of calcium is 8.5-10.2 mg/dl. 51.9% of cases and 76% of controls had calcium levels within normal range. Whereas 48.1% of cases had levels <8.5 mg/dl as compared to 24% of controls.

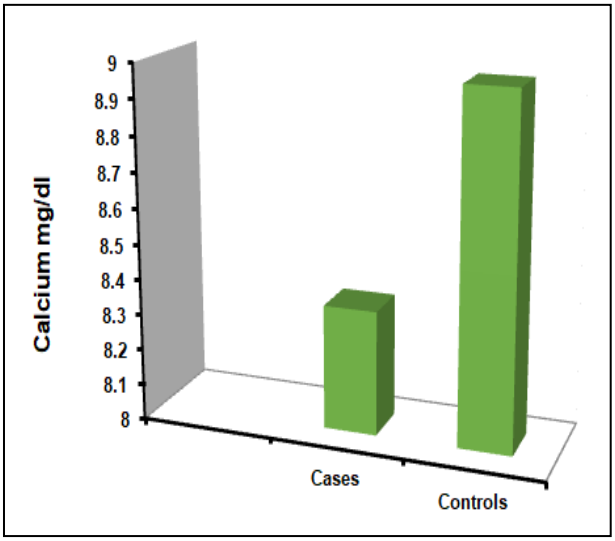

Figure 3: Mean Calcium levels in Cases and controls.

There was decrease in levels of **calcium** in cases as compared to controls and this was statistically significant. The mean level of calcium in cases is 8.35±1.07 and control is 8.98±0.98 (p= 0.001**).

Distribution of Phosphorus in two groups studied

Phosphorus levels were measured in cases and controls. The normal levels of Phosphorus is 2.5-4.5 mg/dl. 62% of cases had Phosphorus levels between 2.5-4.5mg/dl and 98% of controls.20% of cases had levels between 4.6-5.5 mg/dl only 2% of controls had in same range.18% of patients had levels >5.5 mg/dl and none of controls had in this range.

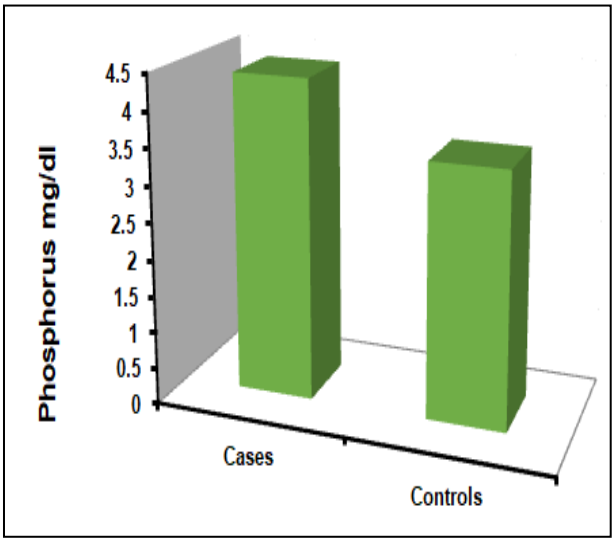

Figure 4: Mean Phosphorus levels in Cases and controls

Increase in levels of **phosphorus** was observed in cases as compared to controls which was statistically significant. .The mean level of phosphorus in cases is 4.40±1.70 and control is 3.47±0.62 (p<0.001**).

Distribution of cases in various stages of CKD

There were totally 50 cases; they were divided into various stages depending upon GFR. 38% of patients were in CKD stage 5 followed by 36% in stage 2, 10% patients in stage 4 and 8% of patients were present in stage 1 and stage 3 respectively.

Table 6: The levels of PTH, Calcium and phosphorus of patients in various stages of CKD are as follows:

Variables	Stage of CKD					P value
	Stage I	Stage II	Stage III	Stage IV	Stage V	
Calcium mg/dl	8.3±1.01	8.48±1.12	7.43±1.46	8.54±0.91	8.38±1.01	0.500
Phosphorus mg/dl	3.25±0.62	3.99±0.76	5.55±1.72	5±2.8	4.66±2.07	0.209
Ca*PO4 product	26.66±3.86	33.41±5.7	40.09±9.05	42.28±24.42	38.9±16.28	0.281
PTH pg/ml	67.72±29.92	75.09±33.38	96.47±33.88	158.98±115.1	211.13±88.0	<0.001**

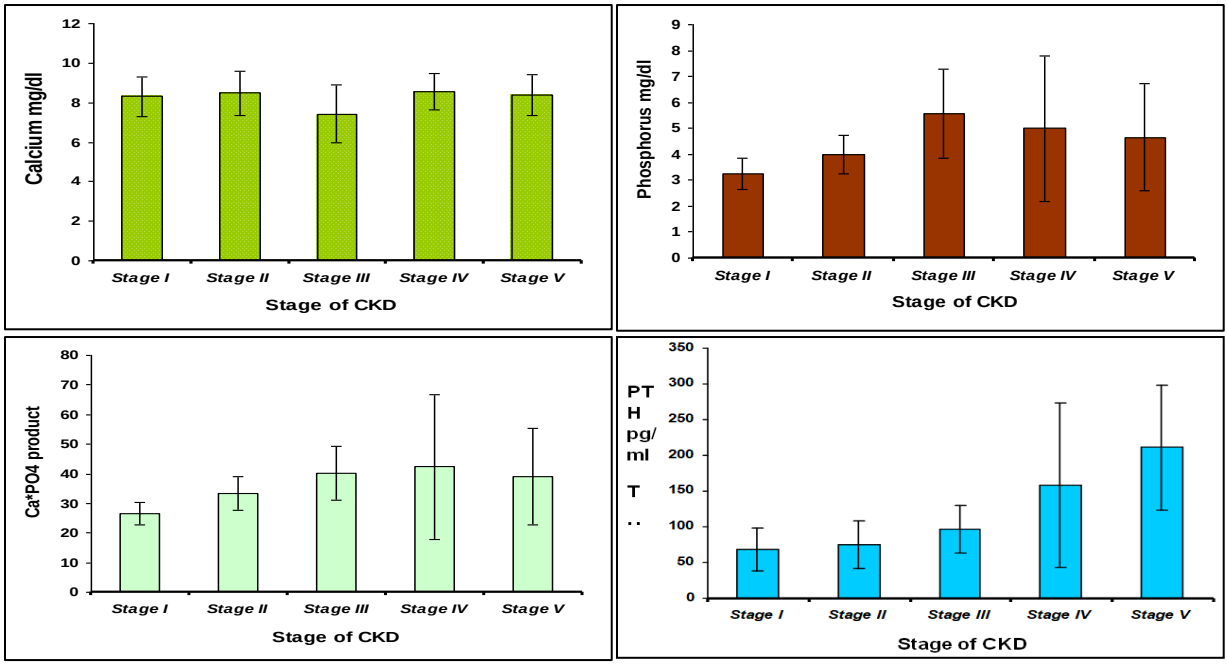

Figure 6: Values of PTH, Ca, and P in different CKD stages

Discussion:

The serum levels of PTH were significantly increased in cases as compared to controls. The mean level of PTH in cases is 142.80 ±92.70 and controls is 50.49 ±18.35 pg/ml ($p<0.001$). Statistically significant increase in levels of calcium was seen in cases as compared to controls. The mean level of calcium in cases is 8.35±1.07 and control is 8.98±0.98 ($p<0.001$). Increase in levels of phosphorus was observed in cases as compared to controls which was statistically significant. .The mean level of phosphorus in cases is 4.40±1.70 and control is 3.47±0.62 ($p<0.001$).

A large, prospective, multicentre, cohort study conducted by Noordzij et al, involving 1629 hemodialysis and peritoneal dialysis patients showed a significant increase in hazard ratio (HR) of 1.57 (1.07–2.30) in patients with the highest quartile of phosphate using both baseline and time-dependent values. (15)

Similarly, Block et al study done on 40,538 patients on maintenance hemodialysis reported an increased risk of death with increasing levels of phosphate. (16)

A triad of high calcium, elevated phosphate levels and high or low PTH levels was associated with increased mortality in MHD patients. (17)

In our study we observed an increase in phosphorus levels from Stage III of CKD.

Bellasi et al. observed an association between serum phosphate [>=4.3 mg/dL] and the risk of starting dialysis or dying. (18) Higher serum phosphate concentrations within the normal range were also associated with a more rapid decline in renal function and a progression to ESRD. (19)

In patients with CVD, serum phosphate 3.5 mg/dL or higher was associated with an increased risk of death compared to serum phosphate lower than 3.5 mg/dL (20).

A recent controlled trial has shown that calcimimetic drugs also effectively decrease PTH levels in patients with stage 3–4 CKD, but their use is limited by hypocalcemia and increased plasma phosphorus levels (21)

In our study we found a statistically significant increase in PTH level in cases as compared to

controls ($p<0.001$). Similar findings were observed in a large community-based cohort of 3,570 subjects with normal renal function and serum calcium levels found that those whose PTH levels were higher (iPTH >62 pg/ml) were significantly more likely to have coronary heart disease than those whose levels were within normal limits (22)

PTH can act directly on the cardiovascular system as specific PTH receptors have been identified on cardiomyocytes, and it has been shown that their activation increases intracellular calcium levels as well as the strength and frequency of cardiac contractions (23).

In addition to their known effects on bone and kidney, high PTH levels have also been implicated in a plethora of untoward effects on cardiovascular function and structure, including metabolic lipid abnormalities, impaired insulin sensitivity, hypertension, cardiac hypertrophy and fibrosis, myocardial calcium deposition, valvular calcification, and vascular stiffness and calcification (24).

Until recently, it was thought that hyperphosphatemia was the earliest sign of SHPT and bone metabolism disorders. However, when patients reach Stage 3 CKD, it is highly probable that none of the routine biochemical parameters assessed will be abnormal. In fact, the PTH level is often increased before clinical hyperphosphatemia occurs.

National Kidney Foundation's Kidney Early Evaluation Program (KEEP) study observed a statistically significant increase in PTH, calcium & phosphorus levels in various stages of CKD. They found a significant decrease in levels of calcium from stage III to stage IV whereas; in stage V it is again raised. Similar findings were observed in our study where, the levels of calcium is normal in stage I and II, the levels fall in stage III and come back to normal range in stage IV and V. (25)

Kates DM et al, studies evaluated the relationships among serum phosphate, calcium, PTH, and 1, 25-dihydroxyvitamin D in CKD patients who were in various stages of disease and demonstrated a similar finding. The study also suggested that phosphate may directly enhance PTH secretion in this setting (26).

Conclusion

Nephrology Guidelines recommend targets and early treatment strategies to correct serum levels of phosphorus, calcium, and PTH levels.

The levels of PTH, calcium & phosphorus are used as surrogate markers of disease progression. The ultimate goals of treating secondary hyperparathyroidism are to normalize mineral metabolism, prevent bone disease, and prevent extra skeletal manifestations of the altered biochemical processes. So numerous drugs including phosphorus binders, vitamin D and calcimimetic agents have been specifically developed and promoted to decrease these complications.

References

1. Coresh J, Astor BC, Greene T, Eknoyan G, Levey AS. Prevalence of chronic kidney disease and decreased kidney function in the adult US population: Third National Health and Nutrition Examination Survey. Am J Kidney Dis. 2003 Jan; 41(1):1-12.
2. Coresh J, Selvin E, Stevens LA, et al. Prevalence of chronic kidney disease in the United States. JAMA. 2007;298(17):2038–2047. doi:10.1001/jama.298.17.2038
3. Jha V, Garcia-Garcia G, Iseki K, et al. Chronic kidney disease: global dimension and

perspectives. Lancet. 2013;382(9888):260–272. doi:10.1016/S0140-6736(13)60687-X.

4. Mizobuchi M, Towler D, Slatopolsky E J. Vascular calcification: the killer of patients with chronic kidney disease. Am Soc Nephrol. 2009 Jul; 20(7):1453-64.
5. Furuhashi T, Moroi M, Joki N, Hase H, Masai H, Kunimasa T, Nakazato R, Fukuda H, Sugi K. The impact of chronic kidney disease as a predictor of major cardiac events in patients with no evidence of coronary artery disease. J Cardiol. 2010 May; 55(3):328-36.
6. Levin A, Bakris GL, Molitch M, Smulders M, Tian J, Williams LA. Prevalence of abnormal serum vitamin D, PTH, calcium, and phosphorus in patients with chronic kidney disease: Results of the study to evaluate early kidney disease. Kidney Int 2007;71:31-8
7. Tietz, N. W.Specimen Collection and Processing and Sources of Biological Variation. Textbook of Clinical. Textbook of Clinical chemistry. 2nd Edition .Philadelphia, W.B.Saunders;1994.
8. Paulson G, Ray R, Sternberg J .A Rate-Sensing Approach to Urea Measurement. Clin. Chem.1971; 17:644
9. Henry, J. B., Clinical Diagnosis and Management by Laboratory Methods, 18th Edition, W. B. Saunders Company, Philadelphia, PA (1991).
10. Souberbielle JC, Friedlander G, Cormier C. Practical considerations in PTH testing. Clin Chim Acta.2006;366:81-89.
11. Anker P, Wieland E, Ammand D,et al. Neutral Carrier Based Ion-Selective Electrode for the Determination of Total Calcium in Blood Serum Anal. Chem.1981; 53: 4.
12. Determination of Serum Inorganic Phosphorus. Dryer R, L Routh.Clin. Chem.1963;4:191
13. Bernard R. Fundamentals of Biostatistics. 5th Edition. Duxbury, 2000:80-240.
14. Suresh K.P. and Chandrasekhar. Sample Size estimation and Power analysis for Clinical research studies. Journal Human Reproduction Science, 2012, 5(1), 7-13.
15. Noordzij M, Korevaar JC, Boeschoten EW, et al. The Kidney Disease Outcomes Quality Initiative (K/DOQI) guideline for bone metabolism and disease in CKD: association with mortality in dialysis patients. *Am J Kidney Dis*. 2005;**46**(5):925–932
16. Block GA, Klassen PS, Lazarus JM, et al. Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. *J Am Soc Nephrol*. 2004;**15**(8):2208–2218
17. 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):607–617.
18. Bellasi A, Mandreoli M, Baldrati L, Corradini M, Di Nicolo P, Malmusi G, Santoro A: Chronic kidney disease progression and outcome according to serum phosphorus in mild-to-moderate kidney dysfunction. Clin J Am Soc Nephrol. 2011, 6 (4): 883-891. 10.2215/CJN.07810910.
19. Voormolen N, Noordzij M, Grootendorst DC, Beetz I, Sijpkens YW, van Manen JG, Boeschoten EW, Huisman RM, Krediet RT, Dekker FW, et al: High plasma phosphate as a risk factor for decline in renal function and mortality in pre-dialysis patients. Nephrol Dial Transplant. 2007, 22 (10): 2909-2916. 10.1093/ndt/gfm286.
20. Tonelli M, Sacks F, Pfeffer M, Gao Z, Curhan G: Cholesterol, Recurrent Events Trial I: Relation between serum phosphate level and cardiovascular event rate in people with coronary disease. Circulation. 2005, 112 (17): 2627-2633. 10.1161/CIRCULATIONAHA.105.553198.
21. Chonchol M, Locatelli F, Abboud HE, Charytan C, de Francisco AL, Jolly S, Kaplan M, Roger SD, Sarkar S, Albizem MB, Mix TC, Kubo Y, Block GA: A randomized, double-blind, placebo-controlled study to assess the efficacy and safety of cinacalcet HCl in participants with CKD not receiving dialysis. Am J Kidney Dis 2009;53:197–207.
22. Kamycheva E, Sundsfjord J, Jorde R: Serum parathyroid hormone levels predict coronary heart disease: the Tromsø Study. Eur J Cardiovasc Prev Rehabil 2004;11:69–74.
23. Schluter KD, Piper HM: Cardiovascular actions of parathyroid hormone and parathyroid hormone-related peptide. Cardiovascular Res 1998;37:34–41.
24. Rostand SG, Drueke TB: Parathyroid hormone, vitamin D, and cardiovascular disease in chronic renal failure. Kidney Int 1999;56:383–392
25. Levin A, Bakris GL, Molitch M et al. Prevalence of abnormal serum vitamin D, PTH, calcium, and phosphorus in patients with chronic kidney disease: results of the study to evaluate early kidney disease. Kidney Int.2006;71(1):31-8.
26. Kates DM, Sherrard DJ, Andress DL. Evidence that serum phosphate is independently associated with serum PTH in patients with chronic renal failure. Am J Kidney Dis.1997;30(6):809-13.