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Original Research Article.

Association of Parathyroid Hormone with Markers of Bone-Mineral Metabolism in Patients of Chronic Kidney Disease with Secondary Hyperparathyroidism

Bushra Fiza[1*], Jai Prakash[2], Suraj Godara[3], Maheep Sinha[4]

[1*]Associate Professor, [2]Demonstrator, [4]Professor & Head,
Department of Biochemistry, MGMCH, Jaipur, Rajasthan, India.
[3]Assistant Professor, Department of Nephrology, MGMCH, Jaipur, Rajasthan, India.

ABSTRACT

Background: Secondary hyperparathyroidism (SHPT) is one of the most obvious complications of chronic kidney disease (CKD). The pathogenesis of SHPT is complex and dependent on the imbalance of various biochemical markers of bone and mineral metabolism.

Aim: The present study was planned to evaluate the association of intact Parathyroid Hormone (iPTH) levels in CKD patients with bone-mineral metabolism markers.

Materials & Methods: Fifty diagnosed cases of CKD (stage 4 & 5), age up to 60 years were enrolled for the study. Fifty age and sex matched healthy individuals constituted the control group. Blood samples were collected using standard aseptic technique and subjected to analysis for serum Urea, Creatinine, uric acid, Calcium, Phosphorus, Alkaline phosphatase, 25(OH) Vitamin D and intact parathyroid hormone. Estimated Glomorular Filtration Rate was calculated by applying Cockeroft and Gault formula. Results obtained were compared between CKD patients and control group statistically by applying students' t-test. Pearson correlation for iPTH and other parameters were also evaluated.

Results: Besides deranged renal function, CKD patients exhibited hypovitaminosis D and hyperparathyroidism. The study also reported low levels of S Ca++, while S phosphorus and ALKP were significantly higher. iPTH demonstrated a significant negative correlation with S Ca++ (r = -0.418). A significant correlation was also observed between iPTH and S phosphorus(r =0.554) and ALKP (r=0.291).

Conclusion: Hyperparathyroidism is a common complication of end stage renal disease (ESRD). iPTH demonstrates strong association with S. Ca++, Phosphorus and ALKP, which are directly responsible for homeostasis of bone-mineral metabolism, in CKD patients. Monitoring of these markers in CKD patients shall be helpful in better management and in diminishing the occurrence of various comorbid conditions.

Key words: Chronic Kidney Disease, Hyperparathyroidism, Vitamin D, Hypovitaminosis, Bone- mineral disease.

***Correspondence to:**

Bushra Fiza
Department of Biochemistry,
Mahatma Gandhi Medical College & Hospital,
Jaipur, Rajasthan, India.

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INTRODUCTION

Chronic kidney disease (CKD) is represented as progressive impairment of renal function resulting in end-stage renal disease (ESRD) that may ultimately require renal replacement therapy. In recent years, CKD has emerged as a major health problem across the globe. As per the criteria defined by National Kidney Foundation, CKD can be classified on the basis of severity into 5 stages. Stage 1 refers to the earliest and mildest CKD stage whereas; Stage 5 indicates the most severe phase of CKD.[1] Stage 5 CKD is identified as a condition with glomerular filtration rate (GFR) as low as <15.0 ml/min/1.73 sq m^2 and is commonly addressed as ESRD.

Besides ESRD, CKD has been found to be associated with increased risk of cardiovascular disease. Increased prevalence of cardiovascular disease is one of the leading causes of increased morbidity and mortality among CKD patients. Most commonly CKD patients suffer from left ventricular hypertrophy and vascular calcification. CKD treatment is quite challenging not only due of its rapid progression but also because of the various secondary complications like hyperparathyroidism and hypovitaminosis D[3-5] which in turn may be responsible for development of cardiovascular complications as well as bone-mineral disorders. Hyperparathyroidism and hypovitaminosis D have been identified as independent risk factors for vascular calcification.

PTH is primarily involved in the homeostasis of bone metabolism. It regulates the level of calcium in the blood by balancing the release of calcium from bone, its absorption from intestine, and

excretion through urine. On the other hand, declining kidney function leads to deficiency of activated Vitamin D. This results in increased excretion of phosphorus. Consequently, the levels of calcium and other minerals involved in bone metabolism are affected and may lead to severe mineral disorders in extreme cases thereby adding to the misery of the patient.

The present study was planned to evaluate the association of S Calcium, Phosphorus Vitamin D and Alkaline phosphatase with Parathyroid hormone levels in CKD patients.

MATERIALS AND METHODS

The study was conducted on fifty diagnosed patients of CKD (stage 4 and 5), age up to 60 years, who visited the outpatient department of Nephrology, Mahatma Gandhi Hospital. Patients with acute renal failure, primary hyperparathyroidism and on vitamin D supplementation were excluded from the study. The study was conducted after seeking approval from the Institutional Ethics Committee. Fifty age and sex matched healthy subjects constituted the control group.

Blood samples of the enrolled patients were collected by venipuncture using standard aseptic techniques and analyzed for Serum Urea, Creatinine, Uric acid, Calcium Phosphorus and Alkaline Phosphatase (ALKP) using VITROS 4600 and OCD dry chemistry microslides. 25(OH) Vitamin D and intact PTH (iPTH) were estimated on VITROS ECI. All parameters were compared between the CKD patients and healthy subjects. The correlation of all estimated analytes with iPTH among CKD patients was assessed by applying Pearson's correlation.

Table 1: Distribution of variables between CKD patients and Control group

Variables	CKD patients (n=50)	Control Group (n=50)	P-value
Age (years)	38.98 ± 10.32	38.28 ± 13.72	NS
eGFR (ml/min)	14.31 ± 4.19	106.37 ± 13.01	0.000
S. Urea (mg/dl)	109.34 ± 48.26	26.32 ± 5.17	0.001
S. Creatinine (mg/dl)	8.56 ± 2.90	0.72 ± 0.13	0.000
S. Uric acid (mg/dl)	7.870 ± 2.570	4.218 ± 1.474	0.000
25(OH)VitaminD (ng/ml)	19.29 ± 10.77	39.368 ± 10.801	0.000
S. iPTH (pg/ml)	301.73 ± 218.17	41.19 ± 16.21	0.000
S. Calcium (mg/dl)	8.250 ± 1.300	8.924 ± 0.720	0.0131
S. Phosphorus (mg/dl)	6.014 ± 1.841	3.746 ± 0.898	0.000
Ca^{++} X PO_4^-	46.257 ± 13.620	33.736 ± 9.485	0.000
S. ALKP (U/L)	133.580 ± 83.227	97.260 ± 38.838	0.006

Table 2: Correlation of serum 25(OH) Vitamin D and other biochemical parameters with iPTH levels

Variables	Pearson Correlation Coefficient (r)	*p*-value
Calcium	-0.418	0.003**
Phosphorus	0.554	0.000***
Ca x p Product	0.335	0.017*
ALP	0.291	0.040*
eGFR	-0.503	0.000***

*p< 0.05; **p<0.01; ***p<0.001

RESULTS

All observations of the case and control groups were presented as mean ± SD and subjected to statistical analysis using SPSS 17 statistical program. Table 1 depicts the comparison of various indices between CKD patients and healthy controls. Mean age among the two groups was comparable (P=NS). Serum Urea, Creatinine and Uric acid were significantly higher whereas estimated Glomerular Filtration Rate (eGFR) was significantly lower among the CKD patients. Vitamin D levels were observed to be lower (P=0.000) in the CKD patients as compared to healthy subjects. On the other hand iPTH was significantly higher (P=0.000) in the above mentioned patients. Further, serum Calcium was observed to be lower (P=0.013) and serum phosphorus (P= 0.000) and ALKP (P= 0.006) were significantly higher in patients with CKD. The Ca X P product was also higher in the above patients. To assess the association between iPTH and other bone metabolism markers, Pearson's correlation was applied. The present study indicated a positive association of iPTH with Serum ALKP (Fig 4), phosphorus (Fig 2) and Ca X P product (Fig 3) (Table2). Serum Calcium, on the other hand exhibited a significantly negative correlation (Fig 1). As expected a significant correlation was also observed between eGFR and iPTH levels (Fig 5).

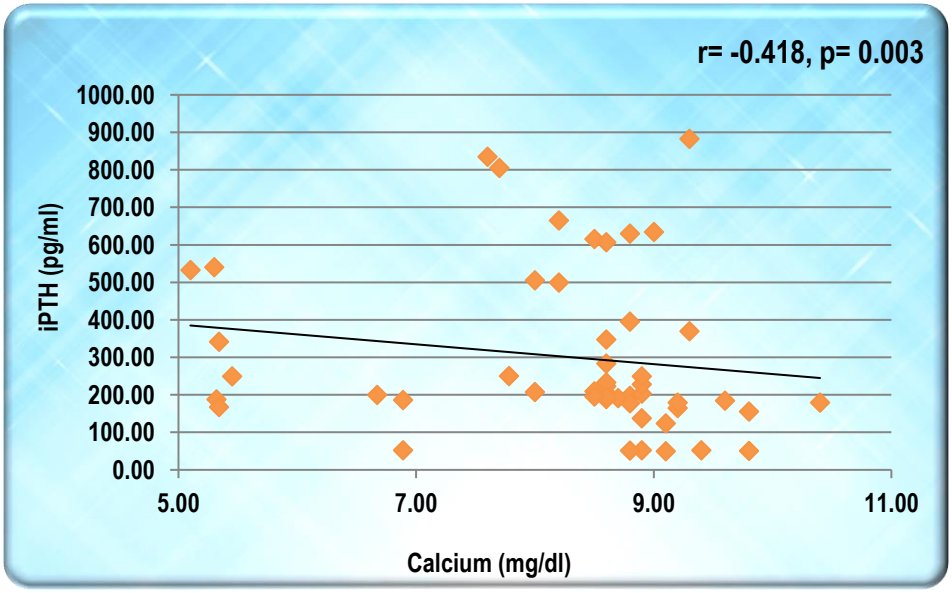

Figure 1: Correlation of serum calcium with iPTH levels

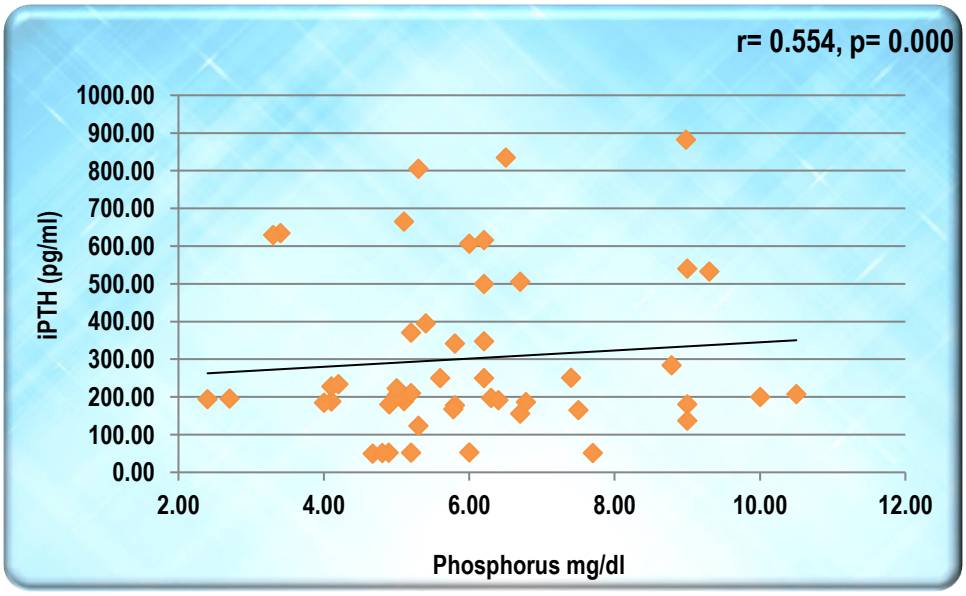

Figure 2: Correlation of serum phosphorus with iPTH levels

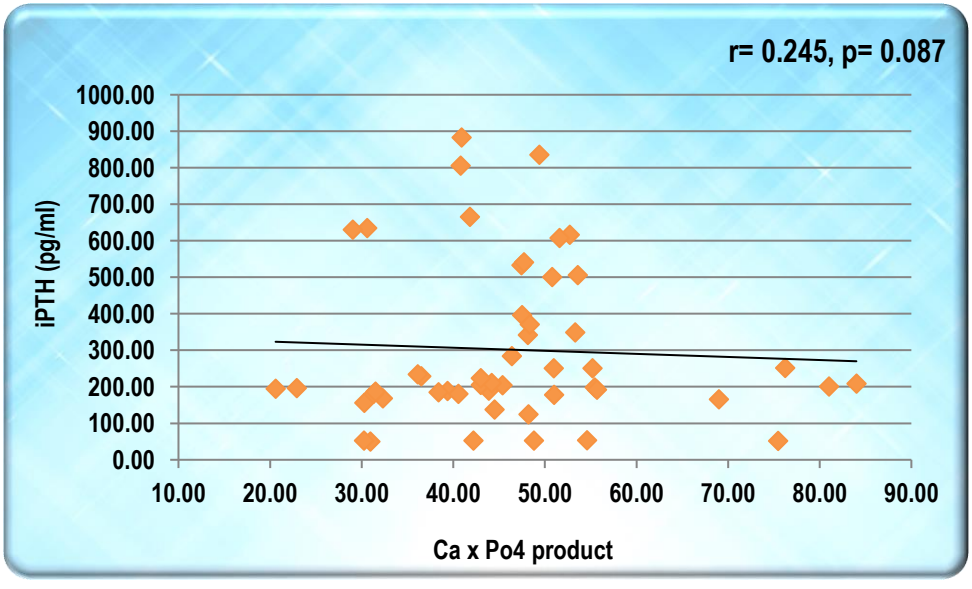

Figure 3: Correlation of Ca++ X P product with iPTH levels

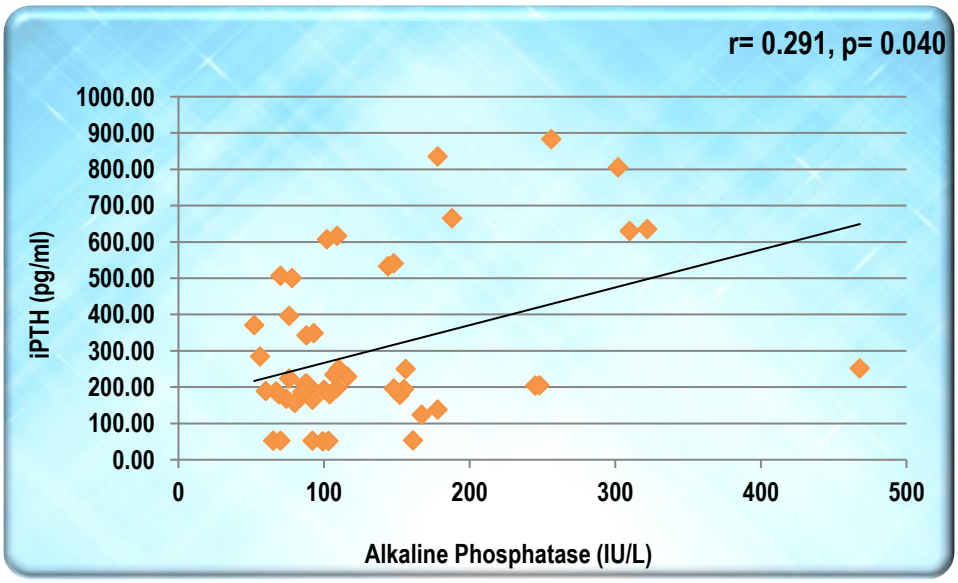

Figure 4: Correlation of Alkaline Phosphatase with iPTH levels

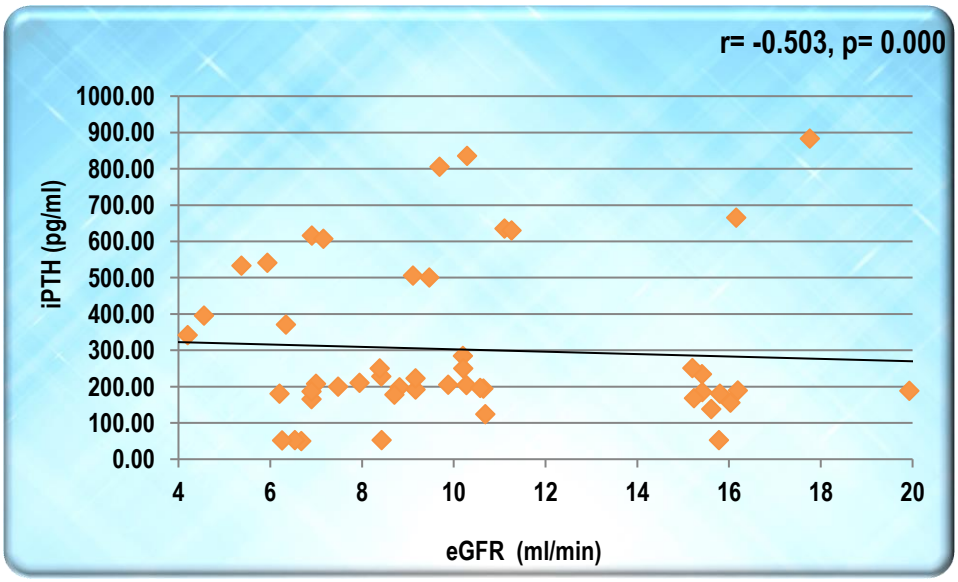

Figure 5: Correlation of eGFR with iPTH levels

DISCUSSION

The major complications of CKD include not only progression to ESRD, but also increased risk of cardiovascular diseases. Left ventricular hypertrophy and vascular calcification are also quite common among patients with CKD. Hyperparathyroidism[3] and hypovitaminosis D[4] are suggested to be independent risk factors for vascular calcification. In a previous study by the authors, Yogi et al, 2017[6], a highly significant positive correlation was demonstrated between S Vitamin D and iPTH levels (r = -0.614)

Out of fifty CKD patients, forty four patients (88%) had abnormal iPTH levels and only six (12%) of them had iPTH within normal range (7.5-53.5 pg/mL). The condition of SHPT results due to various biochemical changes, including deficiency of calcitriol, phosphorus retention, declining response of the calcium-sensing receptor (CaR) located in the parathyroid gland, and skeletal resistance towards the calcemic effect of PTH. With impairment of kidney function, phosphorus excretion decreases, which further results in rise of plasma phosphorus levels while plasma calcium and calcitriol levels decrease. Simultaneous reduction of calcitriol leads to a reduction in intestinal calcium absorption. All these factors contribute to the development of hypocalcemia and simultaneous increase in production of PTH.[7]

Secondary HPT manifests as either of the two types of renal osteodystrophy i.e. a high turnover state known as osteitis fibrosa, or, in combination with low bone turnover, known as mixed uremic osteodystrophy. The damage caused by osteitis fibrosa and mixed disease includes: marrow fibrosis that can lead to anemia of CKD; abnormal bone mineralization (osteomalacia); bone pain; myopathy and muscle weakness; spontaneous tendon rupture; pruritis; fractures; and vascular calcification.[6] Recent studies suggest that phosphorus retention may result in increase of fibroblast growth factor-23 (FGF-23) in the early course of CKD. This has further been found to suppress calcitriol synthesis, in turn leading to increased PTH.[8]

Aside from the negative skeletal effects of secondary HPT, soft tissue calcification can occur in other body tissues, including the skin and subcutaneous tissue, cornea and conjunctiva, muscle, lung, gastrointestinal tract, and cardiovascular system. Calcification of cardiac tissue can affect the myocardium, the conduction system, and valves, and thus may cause adverse

cardiovascular events.[9] In a recent study done by Tripathi V *et al* 2015[3]; found that CKD patients with high (≥400 pg/mL) iPTH have 8.93 times the risk of developing intimal thickness (IT) of ≥60 µm as compared with patients with low (<400 pg/mL) iPTH (P-value <0.05). The mean IT of the radial artery significantly correlated with the iPTH levels. Arterial disease is an important factor in uremic patients.

In the present study, mean serum calcium levels were significantly lower in CKD population as compared to healthy subjects ($p<0.01$), while serum inorganic phosphorus ($p<0.001$) and ca*p product ($p<0.001$) were statistically higher in CKD population. Our findings are supported by previous study of Malawadi BN et al 2014[10] and Rahman MH et al 2004[11]; where they have reported similar findings in kidney failure advances. Ganesh SK et al 2001[12]; hypothesized that elevated serum PO_4 may independently contribute to cardiac causes of death through enhanced vascular calcification of atherosclerotic plaques and increased myocardial calcification.

Higher serum phosphorus, Ca × PO_4 product, and calcium intake is further associated with increased coronary artery calcification. In addition to vascular calcification, elevated serum PO_4 may also contribute to vascular smooth muscle cell proliferation and compromise flow in the coronary microcirculation.[13,14]

Calcium, a divalent cation, and phosphorus, a monovalent anion, have a high binding affinity for each another. In serum, as the concentration of one or both ions increases, there is an increased risk for an ionic bond to form, creating an insoluble complex. This process may lead to extra skeletal calcification and potentially calciphylaxis or cardiac disease.[15] Additionally, the precipitation may decrease serum calcium concentrations, further stimulating PTH secretion. In fact, PTH production and secretion may be stimulated by hypocalcemia, hyperphosphatemia, and vitamin D deficiency.[16,17] Because PTH is chiefly responsible for preventing hypocalcemia, it stimulates osteoclasts to lyse bone, releasing calcium into the serum. Mean serum ALP levels were significantly higher in CKD patients (133.580±83.227 U/L) which may represent an adjunct marker of high bone turnover (Table1). In a study done by Kovesdy CP et al 2010[18] higher ALP level were associated with increased mortality irrespective of the statistical model. Alkaline phosphatase (ALP) is an enzyme measurable in most body fluids and usually originates from the liver or bone. In CKD patients without liver disease, ALP can be elevated in high-turnover bone disease.[19] Furthermore, elevated ALP may be causally involved in the cardiovascular calcification of CKD, making it a potentially important independent risk factor. Higher ALP has been shown to be associated with mortality and coronary artery calcification in CKD 5D (Regidor DL et al 2008) and in patients without CKD.[19,20]

CONCLUSION

Evaluation of correlation of various bone mineral metabolism markers with Serum iPTH levels among CKD patients in the present study indicate that eGFR, calcium, phosphorus and ALKP have strong association with iPTH levels. The balance of calcium, phosphorus, vitamin D, and iPTH is complex as well as interrelated. These factors, in fact, create obstruction to achieving and maintaining control of SHPT. The study therefore recommends that CKD patients must adhere to dietary restrictions, dialysis therapies, and complicated medication regimens. Close monitoring of these bone and mineral metabolism markers shall be helpful for the clinician to recommend proper medication and supplementation and hence will aid in averting the risk of secondary complications of CKD.

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