ORIGINAL ARTICLE CODEN: AAJMBG

Parathyroid hormone as early marker of derangements of mineral metabolism among patients in various stages of chronic kidney disease

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Received: 08th August 2022; ***Accepted:*** 30th November 2022; ***Published:*** 01st January 2023

Abstract: *Background:* 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 parathyroid hormone (PTH). *Objectives:* To correlate serum intact parathyroid hormone, urea, creatinine, calcium, phosphorus and alkaline phosphatase in various stages of CKD and to compare the same with the control group. To find the role of intact parathyroid hormone in the early diagnosis of mineral disturbances in CKD patients. *Methodology:* This study was carried out for a period of six months on confirmed cases of CKD visiting Nephrology OPD. Patients in various stages of CKD were included in the study. After informed consent blood samples were collected. *Results:* The mean level of PTH in cases is 136.80 ±92.70 where as in controls mean PTH level is 52.47 ±16.34 pg/mL. Statistically significant increase in levels of PTH were seen in patients than controls (P<0.001). *Conclusion:* A statistically significant increase in PTH levels from stage III of CKD was observed when calcium and phosphorus were still within reference range. Thus PTH levels can be used as a marker to identify the mineral disturbances in early stages of CKD.

Keywords: Parathyroid Hormone, Chronic Kidney Disease, Calcium, Phosphorus.

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). Beginning in CKD stage 3, the ability of the kidneys to appropriately excrete phosphorous load is diminished, leading to hyperphosphatemia. Kidneys fail to respond adequately to PTH, which normally promotes calcium reabsorption and phosphorus excretion. In addition, there is a down regulation of vitamin D receptor and resistance to the actions of PTH at tissue level causing secondary hyperparathyroidism. 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, extra osseous calcification, and death [1].

These changes probably begin early in the course of CKD, when Glomerular Filtration Rate (GFR) declines below 60 mL/min per 1.73 m2 [2]. Cardiovascular disease accounts for 70% of all deaths in patients with CKD, with an overall mortality of 20% per year in patients on dialysis [3]. Left Ventricular Hypertrophy (LVH) is the most prevalent cardiac complication observed in CKD patients and is often associated with

myocardial fibrosis, poor perfusion, and cell death. Hyperphosphatemia and hypercalcemia have been shown to promote calcification of the vasculature, myocardium, and cardiac valves. Vascular calcification, manifested in reduced vessel wall elasticity, increased intima media layer thickness is linked to LVH, and occurs with increased severity in dialysis patients versus non-CKD patients [4].

Vascular and soft-tissue calcifications are strong predicators of cardiovascular mortality among CKD patients. Clinical care guidelines suggest that, at least annual testing and subsequent treatment of disorders of bone and mineral metabolism is essential early in the course of CKD when GFR is still 60 ml/min per 1.73 m2. But various investigations suggest that less than 25% of patients reach the target levels for intact parathyroid hormone (PTH) measurement or control [5].

There is a rising incidence and prevalence of kidney failure with poor outcomes and high cost. The incidence of CKD is expected to rise annually by 5-8% [6]. The number of patients treated with dialysis or transplantation is projected to increase from almost 5, 00, 000 people in 2005 to 8, 00, 000 by 2020. A similar tendency is observed in Europe and United Kingdom. The estimated prevalence rates of chronic kidney disease in India are 800 and end-stage renal disease 200 per million inhabitants, respectively [7].

In South India, the main causes of CKD in decreasing order of prevalence are diabetic nephropathy (29.6%), chronic interstitial nephritis (20.4%), chronic glomerulonephritis (17.4%), and hypertensive nephropathy (11%) [8]. Unfortunately chronic kidney disease is “under diagnosed” and “under-treated” resulting in lost opportunities for prevention [9]. The Kidney Disease Outcomes Quality Initiative (KDOQI) of the National Kidney Foundation (NKF) defines “Chronic Kidney Disease as either kidney damage or a glomerular filtration rate (GFR) of less than 60 mL/min/1.73 m2 for 3 or more months” [10].

In 2002; KDOQI published its classification of the stages of chronic kidney disease, as follows: Stage 1: Kidney damage with normal or increased GFR (>90 mL/min/1.73 m2) Stage 2: Mild reduction in GFR (60-89 mL/min/1.73 m2) Stage 3: Moderate reduction in GFR (30-59 mL/min/1.73 m2) Stage 4: Severe reduction in GFR (15-29 mL/min/1.73 m2) Stage 5: Kidney failure (GFR < 15 mL/min/1.73 m2 or on dialysis). The KDOQI definition and classification of chronic kidney disease allow better communication among physicians and facilitate intervention at the different stages. Patients with chronic kidney disease stages 1-2 are generally asymptomatic; clinical manifestations typically appear in stages 3-5.

According to KDOQI guidelines, the risk factors for the development of CKD can be divided into Susceptibility factors [There is increased susceptibility to kidney damage seen in older age, family history of chronic kidney disease, reduction in kidney mass and low birth weight], Initiation factors [They directly initiate kidney damage like Diabetes, high blood pressure, autoimmune diseases, systemic infections, urinary tract infections, urinary stones, lower urinary tract obstruction and drug toxicity], Progression factor [They cause faster decline in kidney function after initiation of kidney damage they include higher level of proteinuria, higher blood pressure, poor glycaemic control in diabetes smoking],End-stage factors [These factors increase morbidity and mortality patients they include lower dialysis dose (Kt/V)], temporary vascular access, anaemia, low serum albumin level and late referra [11].

Diagnosis Kidney damage is usually ascertained by markers rather than by kidney biopsy. According to the KDOQI, persistent proteinuria is the principal marker of kidney damage [12]. An elevated albumin– creatinine ratio in urine samples is usually considered abnormal [13-14]. But, estimation of level of Glomerular filtration rate is the best measure of overall kidney functions both in health and disease [15]. The normal level of GFR varies according to age, sex and body mass. Normal GFR in young adults is approximately 120 to 130 mL/min per 1.73 m^2 and declines with age [16].

A GFR level less than 60 mL/min per 1.73 m2 represents loss of half or more of the adult

level of normal kidney function. Below this level, the prevalence of complications of chronic kidney disease increases.

Aim and Objectives:

1. To correlate serum intact parathyroid hormone, urea, creatinine, calcium, phosphorus and alkaline phosphatase in various stages of CKD and to compare the same with the control group.
2. To find the role of intact parathyroid hormone in the early diagnosis of mineral disturbances in CKD patients.

Material and Methods

This study was duration based case control study, carried out for a period of six months on clinically confirmed cases of CKD visiting Nephrology OPD and in patients at Trichy SRM Medical college Hospital & Research Centre, Trichy [formerly known as: Chennai Medical College Hospital & Research Centre]. It also included 50 healthy controls visiting for regular health check-up. Both, males and females were included in the study. Patients in various stages of CKD (Age above 18years) were included in the study and patients with autoimmune disorders, Post parathyroidectomy status patients were excluded from the study. After obtaining approval from ethical committee and a written informed consent from both cases and controls, samples were collected. The baseline data, clinical history of both cases and controls were taken.

The clinical findings, investigation report were entered on a predesigned proforma. Under strict aseptic precautions, 5ml of venous blood was collected after 8-10 hours of overnight fasting, from both cases and controls. Blood samples were collected in vaccutainer and kept at room temperature for 30-40 minutes for clotting and then centrifuged at 3000 revolutions per minute for 10 minutes. Serum samples were separated and collected in an Eppendorf tube and following investigations were carried out. Intact PTH – Electro chemiluminescence immunoassay (ECLIA) ,Serum calcium - Photometric test using arsenazo III, Phosphorus - Photometric UV test with endpoint determination, Blood urea - GLDH method : Fully Enzymatic method ,Serum creatinine - Modified Jaffe's Method, Alkaline Phosphatase - Kinetic photometric test.

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. The following assumptions on data are made; Assumptions:

1. Dependent variables should be normally distributed.
2. Samples drawn from the population should be random.
3. Cases of the samples should be independent.

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 [17-20]. Data were analysed using SPSS 20.0.; Microsoft word and Excel have been used to generate graphs, tables. Strongly significant (P value: $P \leq 0.01$), Moderately significant (P value: $0.01 < P \leq 0.05$),+ Suggestive significance (P value: $0.05 < P < 0.10$).

Results

In our study 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 years. The mean age in cases is 47.26 ±12.73 years, whereas in controls mean age is 43.83 ±15.12 years. Samples are gender matched and 70% of cases are males and 30% are females. In controls 62% are males and 38% are females.

The mean level of PTH in cases is 136.80 ±92.70 where as in controls mean PTH level is 52.47 ±16.34 pg/mL. Statistically significant increase in levels of PTH were

seen in patients than controls (P<0.001).52% of patients in CKD had urea levels above 46 mg/dL, none of the controls had urea levels above 46 mg/dL. 54% of cases had Creatinine levels >1.2mg/dL and none of the controls were in this range, 46% of case had Creatinine levels between 0.6-1.2 mg/dL and 48% of controls had the values in same range. 51.9% of cases had calcium levels between 8.5-10.2 mg/dL and 76% of controls had within the same range where as 48.1% of cases and only 24% of controls had levels <8.5 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.94% of patients had alkaline phosphatase levels between 56-153 IU/L where as 98% of controls had in the same range. 6% of cases had levels >153 IU/L and only 2% of controls had in the same range.

Table-1: Shows mean levels of PTH, Urea, Creatinine, Calcium, Phosphorus and Alkaline phosphatase levels in cases and controls

Biochemical parameters	Cases	Controls	P value
PTH pg/ml	136.80 ± 92.70	52.47 ± 16.34	< 0.001**
Urea mg/dl	76.60 ± 69.77	23.54 ± 7.46	< 0.001**
Creatinine mg/dl	4.11 ± 4.25	0.56 ± 0.10	< 0.001**
Calcium mg/dl	8.35 ± 1.07	8.98 ± 0.76	0.001**
Phosphorus mg/dl	4.40 ± 1.70	3.47 ± 0.62	0.001**
Alkaline phosphatase IU/L	90.92 ± 46.37	82. 91 ± 21.78	0.285

Table-2: Levels of PTH, Calcium and phosphorus of patients in various stages of CKD

Variables	Stages of CKD				
	Stage I	Stage II	Stage III	Stage IV	Stage V
PTH IU/L	67.72 ± 29.92	75.09 ± 33.38	96.47 ± 33.88	158.98± 115.1	211.13 ± 88.0
Calcium mg/dl	8.3± 1.01	8.48 ±01.12	7.43 ±1.46	8.5 ± 0.91	8.38 ± 1.01
Phosphorus mg/dl	3.25 ± 0.62	3.99 ± 0.76	5.55 ± 1.72	5 ± 2.8	4.66 ± 2.07

Table 1 showing the mean levels of PTH, Urea, Creatinine, Calcium, Phosphorus and Alkaline phosphatase levels in cases and controls. There were totally 50 cases; they were divided into various stages depending upon eGFR. 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 3 respectively. The levels of PTH, Calcium and phosphorus of patients in various stages of CKD was mentioned in table 2.

- *In stage I* CKD, we found that the levels of PTH, calcium and phosphorus were within reference range.
- *In stage II* CKD, the levels of PTH and phosphorus were slightly elevated; but within the reference range and calcium levels were also normal.
- *In stage III,* there is marginal elevation in PTH and phosphorus levels; and fall in calcium levels.
- *In stage IV* CKD, there is further elevation in PTH and phosphorus levels; and calcium levels come back to within range.
- *In stage V* CKD, there is significant increase in PTH levels, moderate increase in phosphorus levels and fall in calcium levels. The level of PTH, calcium and phosphorus are compared with various stages of CKD. Figure 1 shows the levels of PTH in various stages of CKD. Figure 2 shows the levels of calcium and phosphorus in various stages of CKD

Fig-1: Levels of PTH in various stages of CKD

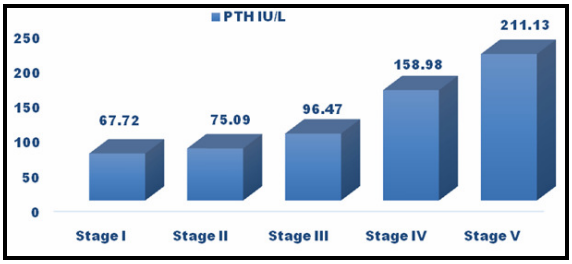
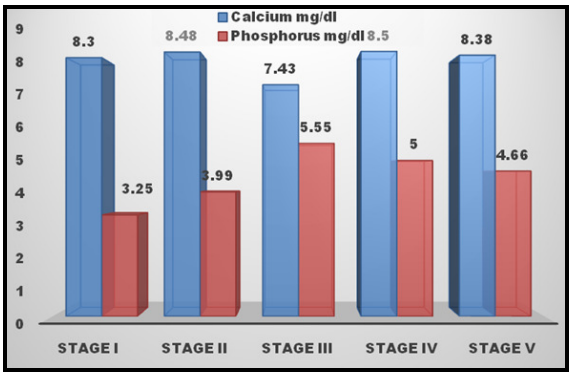


Fig-2: Shows the levels of calcium and phosphorus in various stages of CKD



Discussion

Many studies and literature have shown that CKD is associated with alterations in calcium and phosphorus metabolism leading to increased mortality and morbidity. These alterations would cause changes in PTH levels in almost all stages of disease. We have used this in our study to find out the usefulness of the Elevated PTH levels as an early marker of derangements in bone and mineral metabolism associated with CKD [21].

Nephrology guidelines also recommend targets and early treatment strategies to correct serum levels of phosphorus, calcium, and parathyroid hormone, because many data suggested there was a clear association between these potential risk biomarkers and vascular disease and death. Sonumerous drugs including phosphorus binders, vitamin D and calcimimetic agents have been specifically developed and promoted to decrease these complications. Pattern of Parathyroid hormone levels in CKD Recent observational studies have shown that even a slight elevation in PTH levels has been associated with an increased cardiovascular risk. It is also found that monitoring PTH levels from the early stages of CKD can prevent complications due to mineral disturbances.

Elevated serum phosphorus has been associated with the progression of secondary hyperparathyroidism and deposition of calcium in soft tissues. The long-term consequences associated with persistently elevated PTH levels in CKD include high-turnover bone disease, anemia, CVD, and mortality [2].

As a result, both NKF and Kidney Disease Improving Global Outcomes (KDIGO) guidelines recommend that PTH levels should be regularly monitored beginning in stage 3 CKD and that elevated levels should be treated with a combination of dietary phosphorus restriction and therapy with vitamin D and/or calcimimetic. In our study, we found a statistically significant increase in PTH level in cases as compared to controls ($p < 0.001$). The findings are similar to Block et al study, a significant increase in PTH levels was observed in CKD. They also identified high PTH levels as a significant correlate of all-cause mortality. They concluded that elevations in serum PTH might be associated with increased risk of death from cardiac causes [22].

Amann K et al studies also implicated parathyroid hormone as a permissive factor that promotes cardiac fibroblast activation and intermyocardiocytic fibrosis [23] Kalantar-Zadeh et al [24] studies also observed a significant increase in PTH levels in CKD. Phosphorus and Calcium in CKD: Elevated serum phosphorus has been related to vascular & coronary artery calcification and resulting cardiovascular morbidity and mortality. Among mineral abnormalities; hyperphosphatemia is most prevalent among patients with ESRD. We observed a statistically significant increase in serum phosphorus levels in cases as compared to controls ($p < 0.001$). Hyperphosphatemia and hypercalcemia have been shown to promote calcification of the vasculature, myocardium and cardiac valves [25].

Vascular calcification, manifested in reduced vessel wall elasticity, increased intima-media layer thickness and enhanced pulse-wave velocity, has been linked to LVH and occurs with increased severity in dialysis patients

versus non-CKD patients. Craver et al [26] studies observed a significant increase in phosphorus levels in patients who were in various stages of CKD ($p < 0.001$). He found that elevated PTH levels were associated with increased cardiovascular risk, loss of arterial elasticity and left ventricular hypertrophy.

Relevant mechanism could be direct action on vascular and cardiac cells, which express PTH receptors. J. Floege et al reported a significant increase in phosphorus levels and concluded that high level of phosphorus is a significant risk factor for mortality in CKD [27]. Goodman et al in a resent observational study highlighted the increased prevalence and extent of coronary artery calcification in young dialysis patients compared with normal controls [28].

Serum calcium levels are also involved in hyperparathyroidism progression but are more likely to play an important role in advanced stages, when they begin to decrease. Schwartz et al studies showed an association between higher levels of serum phosphorus and calcium-phosphorus product with an unfavourable renal outcome [29].

In their study higher serum phosphorus was associated with significantly higher risk for progression of CKD, even after adjustment for multiple potential confounders. The association of higher serum phosphorus with progressive CKD was more accentuated in patients with higher serum calcium. Thus supporting the hypothesis that tissue calcification may be the reason behind the complications. Tissue calcification is involved at the cellular and sub cellular levels, with hyperphosphatemia shown to be associated with increased expression of osteoblasts specific proteins in vascular smooth muscle cells (VSMCs) [30].

Reynolds et al showed that higher ambient serum calcium level led to more significant phosphorus-driven calcification of vascular smooth muscle in vitro [31]. Rise in urea and creatinine levels are seen, which are used to support the diagnosis of CKD. In our study, increase in alkaline phosphatase levels was observed in cases as compared to controls and the rise was of significant only in stage 5. High serum alkaline phosphatase is associated with increased mortality. An analysis of the Dialysis Outcomes and Practice Patterns Study (DOPPS) database found that elevated serum alkaline phosphatase levels in hemodialysis patients were associated with higher risk of hospitalization and death.

The potential mechanisms for this observation remain unclear. A study by Lee et al concluded that, alkaline phosphatase can promote vascular calcification by hydrolyzing pyrophosphate in the arterial wall [32] Sigrist et al conducted a longitudinal study and found elevated levels of alkaline phosphatase in stage IV and V of CKD, they found that higher levels of serum alkaline phosphatase were associated with progressive arterial calcification [33].

For early diagnosis, staging of CKD is required and was done by CKD-EPI equation and the levels of PTH, Calcium and Phosphorus of patients in various stages of CKD are as follows; In stage I CKD, we found that the levels of PTH, calcium and phosphorus were within reference range. In stage II CKD, the levels of PTH and phosphorus were slightly elevated, but within the reference range; and calcium levels were also normal. In stage III CKD, there is marginal elevation in PTH and phosphorus levels; and fall in calcium levels. In stage IV CKD, there is further elevation in PTH and phosphorus levels; and calcium levels come back to within range.In stage V CKD, there is significant increase in PTH levels; moderate increase in phosphorus levels and fall in calcium levels. The findings are concordant with National Kidney Foundation's Kidney Early Evaluation Program (KEEP) study [34].

They 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 isnormal in stage I and II; the levels fall in stage III and come back to normal range in stage IV and V. 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 [35].

Levin et al performed a cross-sectional analysis and found that calcium and phosphorus values did not become abnormal and were relatively stable until stage IV CKD [36]. In our study we observed an increase in phosphorus levels from Stage III of CKD. 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. Patel S et al, performed a cross-sectional study and observed that PTH levels increased with worsening of CKD [37].

A significant increase in PTH levels were also observed in our study which further increased with progression of CKD. Levin A et al performed a cohort study in patients with stage 4–5 CKD and found that the levels of PTH and phosphorus were associated with an increased risk of death and the progression of renal failure, whereas vitamin D therapy was associated with better survival [38]. Similar results indicating that secondary hyperparathyroidism is a risk factor associated with progression to dialysis or death have been obtained in cohort study conducted by Schumock CKD patients [39].

Conclusion

The aim of our study was to correlate serum intact parathyroid hormone, urea, creatinine, calcium, phosphorus, alkaline phosphatase in patients with CKD and to compare it with controls and to know the role of parathyroid hormone in early diagnosis of mineral disturbances. In our study, we found that statistically significant increase in the serum levels of intact parathyroid hormone, urea, creatinine, calcium and phosphorus, in patients with CKD as compared with controls. There was an increase in alkaline phosphatase level between cases and controls, but was not statistically significant.

A statistically significant increase in PTH levels from stage III of CKD was also observed when calcium and phosphorus were still within reference range. Thus PTH levels can be used as a marker to identify the mineral disturbances in early stages of CKD. Like in the standard guidelines which highlight the importance of measuring PTH early in the course of disease recommends an annual measurement of PTH once the diagnosis of CKD is made. If the PTH levels are measured and maintained within the target range, many complications can be prevented.

Limitations: The limitation of the study is the time and financial constraint to include the vitamin panels. Hence further studies are needed as prospective studies to monitor the complications of CKD with early diagnosis and correction of mineral derangements at the earliest.

Acknowledgments

Authors would like to sincerely appreciate the management and all staff in Department of General Medicine, Chennai Medical College Hospital and Research Centre, Trichy where this study was conducted.

Financial Support and sponsorship: Nil

Conflicts of interest: There are no conflicts of interest.

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Cite this article as: Rasheed Khan M, Thivyahprabha AG, Durga Sowmithri K and Ganesha Pandiyan M. Parathyroid hormone as early marker of derangements of mineral metabolism among patients in various stages of chronic kidney disease. *Al Ameen J Med Sci* 2023; 16(1): 18-26.

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