



Original Research Article

Secondary hyperparathyroidism in patients with chronic kidney disease: A case control study

Jyothi A Natikar^{1,*}, A Shailaja¹

¹Dept. of Biochemistry, Vydehi Institute of Medical Sciences & Research Center, Bangalore, Karnataka, India



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ABSTRACT

Introduction: Secondary hyperparathyroidism is a major complication of Chronic kidney disease resulting from disturbances in the regulation of Parathyroid hormone, calcium, phosphorus and vitamin D. Adding to the burden of CKD elevated Parathyroid hormone levels are responsible for the long-term consequences like renal osteodystrophy, vascular calcifications and also contributes to cardiovascular morbidity and mortality among end-stage renal disease patients. Hence, this study was conducted to correlate the levels of PTH in patients with CKD in comparison to normal healthy controls.

Materials and Methods: 54 patients diagnosed as CKD and 46 healthy controls are included in the study. Serum levels of Urea, creatinine & PTH measured in both cases and controls.

Results : Statistically significant increase in PTH levels were observed in cases as compared to controls ($p < 0.001$).

Conclusion: An increase in PTH levels is seen as the disease progressed. Thus, periodic measurement of PTH is recommended in all patients with CKD in order to reduce complications.

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1. Introduction

CKD is a highly prevalent health issue across the world, with a prevalence rate of 11-13%.¹ This is a direct consequence of chronic diseases like diabetes and hypertension. Approximately 40% patients with diabetes develop nephropathy and diabetic patients alone account for 12 million people with CKD.² The estimated prevalence rates of chronic kidney disease in India are 800 per million population and incidence of end-stage renal disease is 200 per million population.³

Over production of PTH secondary to reduced renal functions is called secondary hyperparathyroidism. Secondary hyperparathyroidism is characterised by elevated serum parathyroid levels and alteration of calcium and phosphorus homeostasis. The deficiency of activated vitamin D and an increase in phosphorus excretion by the remaining functional nephrons together stimulate excess

PTH synthesis and secretion.² Abnormalities in mineral metabolism occur early in the course of CKD and are responsible for complication like osteodystrophy. In recent years, it is found that these changes are responsible for cardiovascular complications.⁴

Early diagnosis of secondary hyperparathyroidism is crucial in the management of patients with CKD. The National kidney foundation & Kidney disease outcome quality initiative (KDOQI) have given various guidelines for maintaining the target levels of PTH, Calcium and phosphorus in various stages of CKD. The guidelines also highlight the importance of measuring the PTH levels, it recommends an annual measurement of PTH once the diagnosis of CKD is made. If the levels are maintained within the target range then the various complications can be prevented by adequate treatment.⁵

Thus this study was conducted to correlate the changes in PTH levels in patients with CKD in comparison to controls.

* Corresponding author.

E-mail address: drjyothiarvind@gmail.com (J. A. Natikar).

2. Materials and Methods

The study was done at Vydehi Institute of Medical Sciences and Research Centre, Bangalore, Karnataka. After obtaining the Institutional Ethics committee clearance the study was started. An informed consent was taken from all participants for the study.

54 patients diagnosed with CKD, who were in various stages of the disease, were investigated. The exclusion criteria are known cases of autoimmune disorders, paediatric patients and patients with congenital renal disorders. The base line demographic data, clinical history, family history and personal history were obtained from each patient.

46 healthy individuals attending routine health checkup and healthy staff members were included in the study as controls.

Venous blood sample is collected in vacutainers. Samples were immediately placed on ice and after transport to the laboratory, were centrifuged at 3000 rpm for 10 minutes. Serum was separated and analyzed as per recommended protocols.^{6,7}

2.1. Methodology

2.1.1. Measurement of creatinine

CR-S reagent is used to measure the creatinine concentration by a modified rate Jaffé method in Beckman Coulter UniCel Dx C 600 System using controls AQUA CAL 1 and 2.⁸

2.1.2. Measurement of urea

Urea reagent of an enzymatic urease method was used in UV fixed rate method.⁹ Beckman Coulter UniCel Dx C 600 System using controls AQUA CAL 1, 2 and 3.

2.1.3. Measurement of PTH

The Intact PTH assay is a two-site immune enzymatic sandwich assay measured in Beckman Coulter Access 2.¹⁰

The 54 patients diagnosed with CKD were divided into various stages of disease depending on their creatinine levels and age using MDRD formula.

The MDRD formula is: $186 \times \text{plasma creatinine}^{-1.154} \times \text{age}^{-0.203}$ ($\times 0.742$ if female).¹¹

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 dialysis).

There were 6 patients in Stage 1, 18 in Stage 2, 5 in Stage 3, 6 in Stage 4 and 19 in Stage 5.

2.2. Statistical analysis

Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean \pm SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5 % level of significance. Chi-square/ Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups.¹²⁻¹⁴

2.3. Significant VALUES

+ Suggestive significance (P value: $0.05 < P < 0.10$).

* Moderately significant (P value: $0.01 < P \leq 0.05$).

** Strongly significant (P value : $P \leq 0.01$)

2.4. Statistical software

The Statistical software's like SPSS 15.0 were used for the analysis of the data and Microsoft word and Excel have been used to compile, generate graphs, tables.

3. Results

The mean age of patients with CKD is 47.26 ± 12.73 years. Maximum patients were in the age group of 51-60 years. In healthy controls the mean age was 43.83 ± 15.12 years. Samples are age matched with $P = 0.220$. Among the cases 72% were males and 28% were females. In healthy controls 59% were males and 42% were females. Samples are gender matched with $P = 0.155$.

Among the patients studied 39% of patients were in stage 5 followed by 37% in stage 2, 9% of patients were in stage 4 followed by 8% in stage 1 and 3.

The normal range for creatinine is between 0.6-1.2mg/dl, urea is 18-46 mg/dl & of PTH is 16-66 pg/ml.

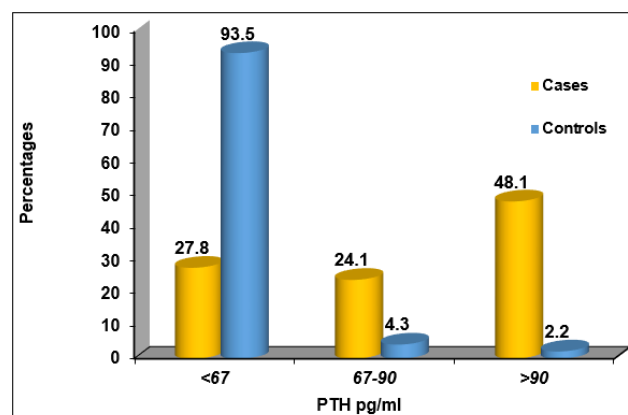


Fig. 1: Distribution of PTH pg/ml in two groups of patients studied

PTH levels were measured in cases and controls. The normal value of PTH is 16-66 pg/ml. 27.8% of patients had

Table 1: Comparison of mean levels of various bio chemical parameters in cases and controls

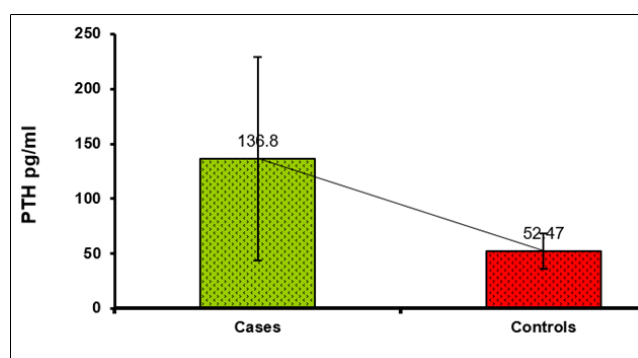
Biochemical parameters	Cases	Controls	P value
PTH pg/ml	136.80±92.70	52.47±16.34	<0.001**
Urea mg/dl	76.60±69.77	23.54±7.46	<0.001**
Creatinine mg/dl	4.11±4.25	0.56±0.10	<0.001**

Table 2: Distribution of PTH pg/ml in two groups of patients studied

PTH pg/ml	Cases		Controls	
	No	%	No	%
<67	15	27.8	43	93.5
67-90	13	24.1	2	4.3
>90	26	48.1	1	2.2
Total	54	100.0	46	100.0
Mean ± SD	136.80±92.70		52.47±16.34	

values >67 pg/ml, 24% of patients had values in between 67-90 pg/ml and 48% had >90 pg/ml.

Among the controls 93.5% had values <67 pg/dl and 4% had values between 67-90 and only 2% had levels >90 pg/ml.

**Fig. 2:** Mean PTH levels in cases and controls

The mean levels of PTH in cases are 136.80±92.70 and controls is 52.47±16.34 pg/ml. There is a statistically significant increase in PTH levels in cases as compared to controls p value is <0.001.

Statistically significant increase in urea levels was seen in cases as compared to controls (p<0.001). The mean level in cases is 76.60±69.77 and control is 23.54±7.46(p<0.001).

Statistically significant increase in creatinine levels was seen in cases as compared to controls (p<0.001). The mean level in cases is 4.11±4.25 and control is 0.56±0.10(p<0.001).

The levels of PTH is compared in patients in various stages of CKD. As the disease progressed, there was progressive increase in PTH levels. The mean level of PTH in stage I was 67.72±29.92, 75.09±33.38 in stage II, 96.47±33.88 in stage III and 158.98±115.1 in stage IV and 211.13±88.0 in stage V respectively.

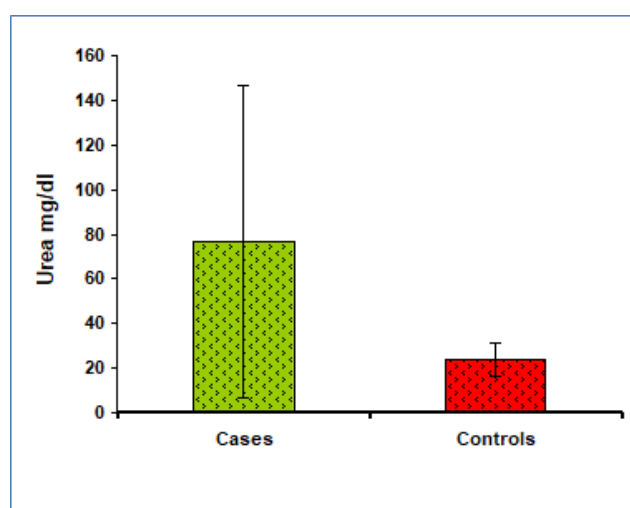
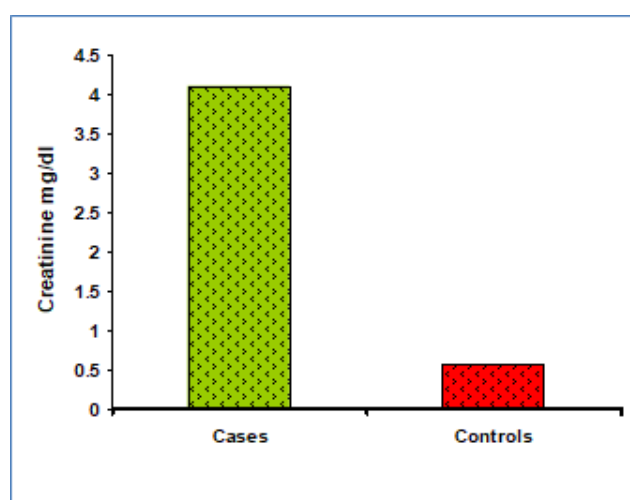
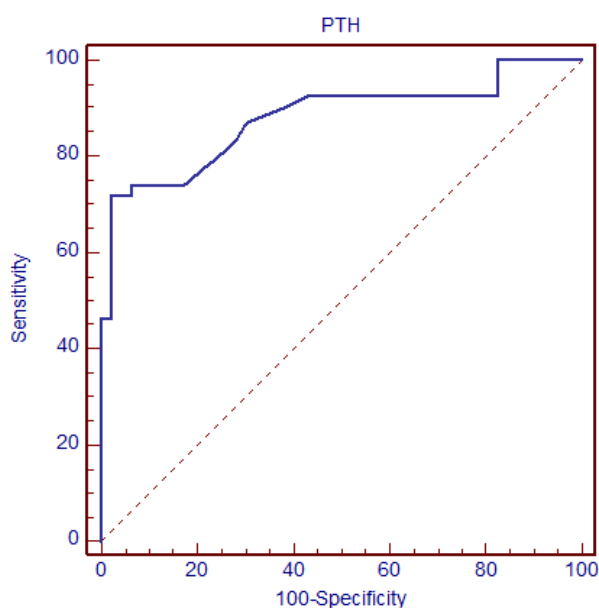
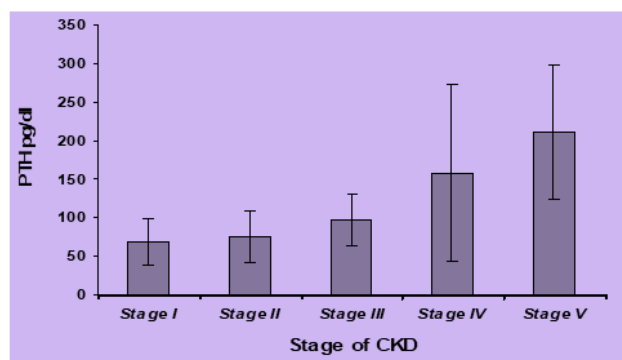
**Fig. 3:** Mean Urea levels in cases and controls**Fig. 4:** Mean Creatinine levels in cases and controls

Table 3: ROC curve analysis to determine diagnostic potential of PTH

Cut-off	Sensitivity	Specificity	LR+	LR-	AUC	P value
>67	72.22	97.83	33.22	0.28	0.879	0.034*
>90	50.00	97.83	23.00	0.51	-	-

Table 4: Comparison of PTH levels according to CKD stage

Variables	Stage I	Stage II	Stage of CKD Stage III	Stage IV	Stage V	P value
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**

**Fig. 5:** ROC curve for PTH**Fig. 6:** Comparison of PTH levels according to CKD stage

4. Discussion

Decreased renal function interferes with the kidneys' ability to maintain fluid and electrolyte homeostasis. Plasma concentrations of creatinine and urea, which are highly dependent on glomerular filtration, begin a nonlinear rise as GFR diminishes.¹⁵

The decrease in functioning renal mass results in hypocalcaemia, hyperphosphatemia and reduced calcitriol levels which stimulate PTH secretion and synthesis and promote parathyroid gland hyperplasia leading to secondary hyperparathyroidism.

The damaged kidney is unable to excrete phosphorus load or can convert vitamin D into its active metabolite calcitriol, leading to a compensatory secondary hyperparathyroidism.¹⁶ In addition, an elevation in Fibroblast growth factor 23 levels is also apparent early in the course of CKD.¹⁷ These mineral and endocrine functions disrupted in CKD are critically important in the regulation of bone remodelling. As a result, bone abnormalities like altered remodelling and loss of bone volumes are common in patients with CKD stages 3-5.¹⁸ Derangements in mineral metabolism are also associated with cardiovascular disease and all-cause mortality.^{19,20} In individuals on dialysis, cardiovascular mortality rates are 10- to 500-times higher than in the general population.²¹

Multiple cross-sectional studies in dialysis patients have found that disordered mineral metabolism, including hyperphosphatemia and hyperparathyroidism, increases the risk of cardiovascular and all-cause mortality.²² One mechanism by which abnormal mineral metabolism may increase.

Cardiovascular risk is by inducing or accelerating arterial and valvular calcification.²³

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 calcimimetics.²⁴

Recent observational studies have shown that even slight elevation in PTH levels are associated with an increased cardiovascular risk. LVH is the most prevalent cardiac complication observed in CKD patients and is often

associated with myocardial fibrosis, poor perfusion, and cell death.^{25,26}

In a cross sectional study, Saleh et al. found PTH to be an independent predictor of LVH among patients in the upper PTH percentiles.²⁷

Nasri et al analyzed the influence of PTH on myocardial function. In their cross-sectional study in hemodialysis patients, they determined that excess PTH played a significant role in the development of LVH and reduced left ventricular ejection fraction.²⁸

The relationship between elevated PTH and LVH was further explored in a retrospective study by Goto et al. determined that parathyroidectomy in CKD patients with advanced SHPT led to a significant improvement of left ventricular ejection fraction and function.²⁹

It is also found that monitoring PTH levels from the early stages of CKD can prevent complications due to mineral disturbances vascular and soft-tissue calcifications are due to hyperphosphatemia are the strong predictors of cardiovascular mortality among CKD patients.³⁰

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, where 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.³¹ Amann K et al. Studies implicated parathyroid hormone as a permissive factor that promotes cardiac fibroblast activation and inter-myocardial fibrosis.³² Kalantar-Zadeh et al. studies also observed a significantly increase in PTH levels in CKD.³³

Patel S et al., performed a cross-sectional study and observed that PTH levels increased with worsening of CKD.³⁴ Similar findings were seen in our study, where a significant increase in PTH levels were observed which further increased with progression of CKD.

5. Conclusion

Secondary hyperparathyroidism is commonly prevalent in CKD and must be treated at the earliest, in order to prevent the associated morbidity and mortality. The target levels of PTH as described by KIDGO must be maintained in order to avoid complications. Reducing serum parathyroid levels is an important goal for improving quality of life and preventing adverse health outcomes in such patients.

6. Source of Funding

None.

7. Conflicts of Interest

None.

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Author biography

Jyothi A Natarikar Assistant Professor

A Shailaja Professor, Lab Director, Central Diagnostic Laboratory

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