

## ORIGINAL ARTICLE

## HYPERPARATHYROIDISM IN PATIENTS WITH CHRONIC KIDNEY DISEASE

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**Background:** Chronic kidney disease (CKD) has a high mortality rate and is an inevitable consequence of many kidney diseases. This study assessed incidence of hyperparathyroidism in patients with CKD. **Methods:** This was a retrospective observational study. A total of 300 samples were screened, out of which 165 were selected which included 96 males and 67 females. The blood levels of iPTH, urea, creatinine, calcium, magnesium, phosphorus and albumin were analyzed using electrochemiluminescence technology (iECL) on Cobas e411 for iPTH and spectrophotometric technology on Cobas c501 for the rest of the parameters. **Results:** All the patients had abnormal renal function, out of which 29.7% had normal iPTH levels and 70.3% had elevated iPTH levels. Normal iPTH was seen in 19.4% males and 10.3% females, whereas in the elevated iPTH was seen in 40% males and 30.3% females. The *t*-test between normal and abnormal iPTH showed a significant correlation ( $p < 0.05$ ) between iPTH, urea, creatinine and albumin levels, whereas no significant correlation was seen with calcium, magnesium and phosphorus levels. **Conclusion:** There was a positive correlation between iPTH levels and levels of urea, creatinine, and albumin exhibiting increased iPTH levels in CKD patients suggesting underlying secondary hyperparathyroidism.

**Keywords:** Hyperparathyroidism, iPTH, Chronic Kidney Disease, CKD

Pak J Physiol 2017;13(2):49–51

### INTRODUCTION

Chronic kidney disease (CKD) is inevitable outcome of many diseases of the kidney, associated with a high mortality rate.<sup>1</sup> The prevalence of CKD has increased along with increasing prevalence of diabetes mellitus and hypertension.<sup>2,3</sup> CKD is associated with many metabolic disorders such as Vitamin D insufficiency and secondary hyperparathyroidism (SHPT) which induces increased morbidity and mortality.<sup>4–8</sup> Diabetes mellitus is the most common cause of CKD and there is an inverse correlation between intact parathyroid hormone levels and glycemic control in diabetic patients on hemodialysis.<sup>9</sup> A 5-stage classification of CKD has been provided by the National Kidney Foundation Kidney Disease Outcome Quality Initiative (NKF KDOQI) guidelines.<sup>10,11</sup> As the severity of CKD increases, irreversible molecular changes (hyperplasia) occur in the parathyroid glands that are considered to be one of causes of secondary hyperparathyroidism.<sup>12,13</sup> Consequently, when the glomerular filtration rate (GFR) falls, phosphorus clearance by the kidney decreases leading to hyperphosphataemia which stimulates PTH secretion.<sup>2,14,15</sup> The CKD associated with mineral and bone disorder (CKD-MBD) shows high levels of parathyroid hormone (PTH), high turnover bone disease and vascular calcification.<sup>16–18</sup> In CKD-MBD, clinically correcting abnormal PTH, phosphorus and calcium levels is the usual practice that reduces morbidity and mortality.<sup>19,20</sup>

The objective of this study was to study the parathyroid hormone levels in patients of chronic kidney

disease. This study assessed the frequency of hyperparathyroidism in patients with CKD by using metabolic parameters of urea, creatinine, calcium, phosphorus, magnesium, albumin, and intact parathyroid hormone (iPTH).

### MATERIAL AND METHODS

This retrospective observational study was carried out in the Department of Biochemistry, Laboratory Services, and Chemical Pathology, Liaquat National Hospital and Medical College from Jun to Nov 2016. A total of 300 samples were screened, out of which 165 samples were selected. These were further stratified according to gender.

All patients who were confirmed cases of CKD or those who had abnormal levels of urea and creatinine were included in the study. Age, gender and data of any other disease was collected and correlated. Patients with diseases other than CKD or those having primary hyperparathyroidism or on biotin therapy were excluded.

For iPTH, 2 ml of blood was collected in K<sub>3</sub>-EDTA (purple top), brought to the laboratory on ice and centrifuged immediately. Plasma was separated and stored at -20 °C. For urea, creatinine, calcium, phosphorus, magnesium and albumin, 4.5 ml of blood was collected in lithium heparin (green top) tubes and centrifuged. Plasma was stored at -20 °C. Dilutions and aliquots were prepared where needed.

Electrochemiluminescence (iECL) technology was used to analyze iPTH on Cobas e411 immunoassay analyzer (Roche Diagnostics, Basil). The reference

interval for iPTH used was 16–65 pg/ml for adults. Urea and creatinine were analyzed using spectrophotometric technology on Cobas c501 chemistry analyzer (Roche Diagnostics). The cut-off for urea and reference intervals of creatinine used were <50 mg/dl and 0.5–1.5 mg/dl respectively. Reference intervals for calcium, phosphorus, magnesium and albumin were 8.6–10.2 mg/dl, 2.5–4.5 mg/dl, 1.6–2.4 mg/dl and 0.2–6 g/dl respectively.

Data were analyzed using SPSS-18 through Student's *t*-test, paired and by using regression correlation analysis  $R^2$  among iPTH, urea and creatinine, and  $p < 0.05$  was considered statistically significant. Data were presented as Mean $\pm$ SD.

## RESULTS

There were a total of 49 (29.7%) patients with normal iPTH levels and abnormal renal function as seen by elevated levels of urea and creatinine. Out of these, 32 (19.4%) were males and 17 (10.3%) were females. The mean iPTH was 33.00 $\pm$ 17.08 and 34.18 $\pm$ 13.47 in males and females respectively. Creatinine was 3.18 $\pm$ 1.53 and 3.35 $\pm$ 1.72, calcium was 8.65 $\pm$ 2.39 and 8.74 $\pm$ 1.11, phosphorus was 4.53 $\pm$ 1.61 and 4.26 $\pm$ 1.59, magnesium was 2.26 $\pm$ 1.48 and 2.11 $\pm$ 0.43, and albumin levels were 2.79 $\pm$ 0.52 and 2.45 $\pm$ 0.54 in males and females respectively. Patients who had elevated iPTH with abnormal renal function were 116 (70.3%) with 66 (40%) males and 50 (30.3%) females. The mean iPTH

was 208.5 $\pm$ 153.21 in males and 255.34 $\pm$ 231.11 in females. The urea was 127.31 $\pm$ 63.74 and 125.6 $\pm$ 75.8, creatinine was 5.05 $\pm$ 3.59 and 4.5 $\pm$ 2.49, calcium was 8.16 $\pm$ 1.08 and 8.49 $\pm$ 0.84, phosphorus was 4.72 $\pm$ 1.77 and 5.04 $\pm$ 2.1, magnesium was 2.3 $\pm$ 0.55 and 2.26 $\pm$ 0.38 and albumin levels were 3.15 $\pm$ 0.67 and 2.95 $\pm$ 0.81 in males and females respectively.

The *t*-test between normal and abnormal iPTH levels was performed in males and there was found to be a significant correlation ( $p < 0.05$ ) between iPTH, urea, creatinine and albumin levels. There was no significant correlation with calcium, phosphorus and magnesium. The *t*-test in females showed significant correlation ( $p < 0.05$ ) between iPTH, creatinine and albumin levels and no significant correlation with urea, calcium, phosphorus and magnesium. The *t*-test performed between normal versus abnormal iPTH overall showed a positive correlation ( $p < 0.05$ ) between iPTH, urea, creatinine and albumin levels, with no significant correlation in calcium, phosphorus and magnesium levels. The *t*-test performed with normal and abnormal iPTH levels between males and females all showed no significant correlation.

When the iPTH was kept constant and two-tailed Chi-square comparisons were done with urea, creatinine, calcium, phosphorus, albumin and magnesium as variables, all the comparisons were non-significant.

**Table-1: Test parameters in patients with chronic kidney disease**

Parameters	Normal PTH with abnormal renal function		Abnormal PTH with abnormal renal function	
	Males (n=32) (Mean $\pm$ SD)	Females (n=17) (Mean $\pm$ SD)	Males (n=66) (Mean $\pm$ SD)	Females (n=50) (Mean $\pm$ SD)
Intact PTH	33.00 $\pm$ 17.08 <sup>a</sup>	34.18 $\pm$ 13.47 <sup>a</sup>	208.5 $\pm$ 153.21 <sup>a</sup>	255.34 $\pm$ 231.11 <sup>a</sup>
Urea	87.16 $\pm$ 34.79 <sup>b</sup>	98.23 $\pm$ 44.83	127.31 $\pm$ 63.74 <sup>b</sup>	125.6 $\pm$ 75.8
Creatinine	3.18 $\pm$ 1.53 <sup>b</sup>	3.35 $\pm$ 1.72 <sup>d</sup>	5.05 $\pm$ 3.59 <sup>b</sup>	4.5 $\pm$ 2.49 <sup>d</sup>
Calcium	8.65 $\pm$ 2.39	8.74 $\pm$ 1.11	8.16 $\pm$ 1.08	8.49 $\pm$ 0.84
Phosphorus	4.53 $\pm$ 1.61	4.26 $\pm$ 1.59	4.72 $\pm$ 1.77	5.04 $\pm$ 2.1
Magnesium	2.26 $\pm$ 1.48	2.11 $\pm$ 0.43	2.3 $\pm$ 0.55	2.26 $\pm$ 0.38
Albumin	2.79 $\pm$ 0.52 <sup>b</sup>	2.45 $\pm$ 0.54 <sup>c</sup>	3.15 $\pm$ 0.67 <sup>b</sup>	2.95 $\pm$ 0.81 <sup>c</sup>

a=  $p < 0.0001$ ; b=  $p < 0.001$ ; c=  $p < 0.02$ ; d=  $p < 0.04$

## DISCUSSION

In our study, the patients who had elevated iPTH had much higher levels of urea and creatinine as compared to those patients with normal levels of iPTH. Calcium levels were low normal in the normal iPTH group and noted to be lower in elevated iPTH group. Phosphorus was high normal in the normal iPTH group whereas it was significantly high in the elevated iPTH group. Magnesium and albumin levels were normal in both groups. There was no significant difference between the genders in both the groups.

The *t*-test analysis showed a significant correlation between iPTH levels and urea, creatinine and albumin levels showing that iPTH levels increase in CKD suggesting underlying hyperparathyroidism. The results are in agreement with earlier studies by Alam *et*

*al*<sup>21</sup> and Chowdary *et al*<sup>22</sup> which noted that longer the period of CKD, the higher can be the concentration of iPTH.

Previous studies reported discovery of calcium sensing receptors in the cell membranes of the parathyroid glands, which bind with extracellular calcium and inhibit PTH release.<sup>23,24</sup> When kidney function declines, phosphorus may build up in the blood, causing calcium levels in the blood to decline. This causes stimulation of the parathyroid gland and secondary hyperparathyroidism.<sup>22–24</sup> PTH causes calcium to move out from the bones and cause the bones to become brittle.<sup>22</sup> Hyperparathyroidism secondary to CKD shows abnormal mineral metabolism and complications which can lead to end stage renal disease, osteo-dystrophy and parathyroid hyperplasia.<sup>21</sup> The PTH baseline levels are also considered to be prognostic

factors in the evolution of renal function.<sup>25</sup> When hypocalcaemia becomes long-standing, due to chronic dialysis or with mal-absorption syndromes, there is parathyroid hyperplasia and excess of PTH production.<sup>13</sup> All four of the parathyroid glands become hyperplastic and function autonomously and this is called tertiary hyperparathyroidism.<sup>13</sup> Patients with secondary hyperparathyroidism may have hypocalcaemia or normocalcaemia and hyperphosphataemia, in addition to extremely elevated PTH and decreased Vitamin D levels.<sup>13</sup> Our data exhibited similarities with earlier reported studies.<sup>13,22–25</sup> Nonetheless, tertiary hyperparathyroidism shows elevated serum calcium and moderately elevated PTH levels with decreased Vitamin D, phosphate and elevated alkaline phosphatase levels.<sup>13</sup> Hence, such studies argued that there is positive correlation between elevated PTH and increased mortality in CKD patients.<sup>7,13</sup> Some studies also suggested PTH resistance or end-organ hyporesponsiveness to PTH in CKD patients, however the primary factors and mechanism currently under study.<sup>6</sup>

## CONCLUSION

The current study described a positive correlation between iPTH levels and metabolic parameters such as urea, creatinine, and albumin depicting association of high iPTH levels suggesting presence of secondary hyperparathyroidism in CKD patients.

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Received: 11 Apr 2017

Reviewed: 24 May 2017

Accepted: 2 Jun 2017