Original Article

Correlation of Parathyroid Hormone Levels with Mineral Status in End-stage Renal Disease Patients

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Abstract

Parathyroid hormone (PTH) is the main regulator of calcium, phosphate, magnesium, sodium, and potassium homeostasis. Therefore, this study was conducted to evaluate the relationship between PTH and aforementioned minerals in end-stage renal disease (ESRD) patients. **Aim:** The aim of this study was to estimate serum intact parathormone (iPTH) and other biochemical parameters in ESRD patients and to find correlation between serum iPTH and biochemical parameters in the study group. **Results:** This cross-sectional study included 60 clinically diagnosed patients of ESRD of age (>18 years), either sex. Disordered mineral metabolism is common complications of ESRD patients. The mean value of calcium, phosphorus, and magnesium was 7.90 ± 1.16 mg/dL, 6.44 ± 1.72 mg/dL, and 2.57 ± 0.62 mg/dL, respectively, indicating hypocalcemia, hyperphosphatemia, and hypermagnesemia in ESRD patients. To compensate the deranged mineral status, increased levels of PTH were seen in ESRD patients with mean value of 173.93 ± 62.62 pg/mL. There was a statistically significant positive correlation found between PTH and S. creatinine ($P \leq 0.001$; $r = 0.596$), whereas the statistically significant negative correlation found between PTH and eGFR ($P \leq 0.001$; $r = -0.525$). A significant positive correlation found between PTH and phosphorous ($P = 0.003$; $r = 0.378$) and potassium ($P \leq 0.001$; $r = 0.421$). On the other hand, significant negative correlation found with calcium ($P \leq 0.001$; $r = -0.805$) and corrected calcium ($P = <0.001$; $r = -0.769$). But nonsignificant association was found with magnesium, sodium, and calcium × phosphorous ($P > 0.05$). **Conclusion:** It was concluded that PTH is playing crucial role in mineral metabolism; it should be frequently assessed in order to prevent any untoward mineral decompensation and to prevent complications like bone disease and extra skeletal calcification, and decrease cardiac disease risk in ESRD patients.

Keywords: End-stage renal disease, minerals, parathyroid hormone

Introduction

Chronic kidney disease (CKD) is a pathophysiological process with multiple etiologies, resulting in the inexorable attrition of nephron number and function and frequently leading to end-stage renal disease (ESRD). ESRD represents a clinical state or condition in which there has been an irreversible loss of endogenous renal function.[1] Diabetic and hypertensive nephropathy are the leading underlying etiologies of both CKD and ESRD.[2] Chronic renal failure (CRF) produces a number of abnormalities of calcium, magnesium, and phosphorus metabolism. Secondary hyperparathyroidism develops early in the course of chronic renal insufficiency, even at the glomerular filtration rate (GFR) of 50–80 mL/minute/1.73 m^2.[3] It is generally thought to result from hypocalcemia 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 parathyroid hormone (PTH) is increased, which, in turn, increases urinary excretion of serum phosphorus to maintain normal serum calcium and phosphorus level. Therefore, PTH is an important factor in the regulation of calcium, magnesim, and phosphorus metabolism. The key target organs of parathormone action are the kidneys and skeleton.[4] The intact parathormone (iPTH) peptide (MW ~ 9425 k.daltons) consists of 84 amino acids that are sequenced and designated according to reactivity. The N-terminal or amino-terminal 1-34 region of the iPTH molecule is biologically active. The middle and carboxy

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Quick Response Code:

Website: www.ijem.in

DOI: 10.4103/ijem.IJEM_279_18

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How to cite this article: Arora K, Goyal G, Soin D, Kumar S, Arora H, Garg C. Correlation of parathyroid hormone levels with mineral status in end-stage renal disease patients. Indian J Endocr Metab 2018;22:735-9.

terminal 35-84 region of the iPTH molecule is biologically inactive but possesses immunological reactivity.[5]

In view of all these considerations, this study was conducted to estimate the levels of PTH and to access its correlation with mineral status in ESRD patients.

Materials and Methods

This cross-sectional study was conducted in the Department of Biochemistry in collaboration with the Department of Medicine on total of 60 clinically diagnosed patients of ESRD of age (>18 years), either sex visiting the OPD or admitted in wards of Department of Medicine, Guru Gobind Singh Medical College and Hospital, Faridkot. Clinical data were taken, in which detailed history of patient regarding age and sex-related information was recorded, after taking the informed written consent from the patients.

Serum routine biochemistry was done on fully automated chemistry analyzer, Beckmann coulter AU480 based on Spectrophotometric method. PTH was measured by fully automated chemiluminescence machine (Immulite 1000 Seimens).

Statistical analysis was done using SPSS version 22. To see the relationship between the two variables, Karl Pearson's correlation coefficient was calculated and $P < 0.05$ was considered significant.

Results

The mean age of patients was 52.28 ± 16.25 years (range 18–85 years). Maximum number (45%) of patients was from the age group of 50–65 years followed by 26.67% in the age group of 34–49 years. There were 36 males and 24 females giving a male to female ratio of 1.5:1. Diabetes mellitus was present in 26.67% with the mean value of fasting plasma glucose 149.31 ± 66.95 mg/dL and 21.67% patients were hypertensive, whereas 30% patients had both diabetes and hypertension.

Mean value of routine biochemical parameters and their correlation with Parathyroid Hormone is given in Tables 1 and Table 2 respectively.

Table 1: Mean value of routine biochemical parameters in patients

Parameters	Mean±SD	Range
Fasting plasma glucose (mg/dl)	149.31±66.95	75.00-415.00
Blood urea (mg/dl)	104.48±64.69	34.00-310.00
S. creatinine (mg/dl)	7.48±2.93	3.00-20.00
Estimated glomerular filtration rate (ml/min/1.73 m^2)	9.96±2.92	4.00-15.00
Total serum protein (g/dl)	5.75±1.24	3.00-9.50
Serum albumin (g/dl)	3.11±0.76	1.80-5.40
Serum sodium (mEq/L)	138.00±7.67	119.00-156.00
Serum potassium (mEq/L))	4.81±1.06	2.50-7.00
Serum calcium (mg/dl)	7.90±1.16	6.00-12.00
Serum phosphorus (mg/dl)	6.44±1.72	3.40-14.20
Serum magnesium (mg/dl)	2.57±0.62	1.20-4.38
Calcium × phosphorus (mg^2/dl^2)	50.25±13.31	26.52-116.44
Corrected calcium (mg/dl)	8.61±1.40	5.58-13.76
Parathyroid hormone (pg/ml)	173.93±62.62	52.00-368.00

Corrected calcium was calculated from serum calcium and serum albumin by applying respective formula: Corrected calcium (mg/dL) = serum calcium + 0.8× (4-serum albumin g/dL)

Discussion

ESRD is associated with aberrations in the metabolism of minerals, such as calcium, phosphates, magnesium, sodium, and potassium. Various studies have identified PTH as the main regulator of calcium, phosphate, magnesium, sodium, and potassium homeostasis. Therefore, this study was conducted to evaluate the relationship between PTH and the aforementioned minerals in ESRD patients.

The maximum number (45%) of patients was from the age group of 50–65 years. Mean age of patients was 52.28 ± 16.25 years, which suggests that incidence of CKD increases with advanced age. Out of 60 patients included in this study, there were 36 males and 24 females giving a male to female ratio of 1.5:1.

Diniz *et al.* in 2012 observed in their study of 125 patients that the mean age was 57.4 ± 16.2 years with male to female ratio of 1.2:1.[6]

On exploring the data, the statistically significantly positive correlation found between PTH and S. creatinine ($P \leq 0.001$; $r = 0.596$) [Figure 1], whereas negative significant correlation found between PTH and eGFR ($P \leq 0.001$; $r = -0.525$) [Figure 2]. Nonsignificant correlation found between blood urea and PTH ($P > 0.05$).

Chowdary *et al.* in 2015 found that the mean value of PTH in CKD males was 295.66 ± 209.59 pg/mL, whereas that was 338.36 ± 287.79 pg/mL in females. Observed a significant rise in the PTH values with an increase in creatinine values and the increase in PTH is statistically higher in females ($P < 0.001$; $r = 0.121$) when compared with males ($P < 0.0001$; $r = 0.557$) in CKD patients.[7]

The mean value of potassium in this study was 4.81 ± 1.06 mEq/L. Also, it was found that the linear positive relationship between potassium and PTH observed in ESRD patients ($P = 0.001$; $r = 0.421$) [Figure 3].

The mean value of this study found serum calcium and serum phosphorous was 7.90 ± 1.16 and 6.44 ± 1.72 mg/dL, respectively. Furthermore, it was observed that serum PTH has linear negative correlation with serum calcium ($P \leq 0.001$; $r = -0.805$) [Figure 4], whereas linear positive correlation with serum phosphorous ($P = 0.003$, $r = 0.378$) [Figure 5].

Ionized calcium, generally 40% of total serum calcium level, is physiologically active, whereas the non-ionized calcium is bound to albumin or anions, such as citrate, bicarbonate,

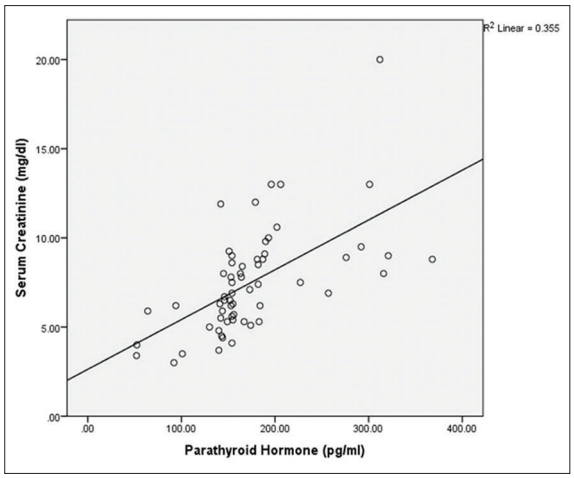

Figure 1: Scatter plot showing correlation of parathyroid hormone with S. creatinine ($P \leq 0.001$, $r = 0.596$)

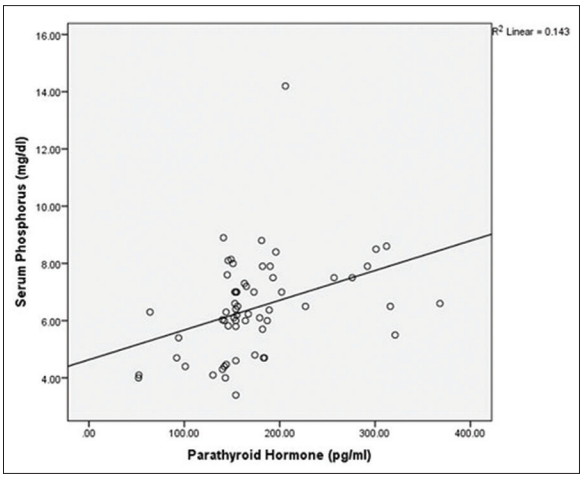

Figure 2: Scatter plot showing correlation of parathyroid hormone with glomerular filtration rate ($P \leq 0.001$, $r = -0.525$)

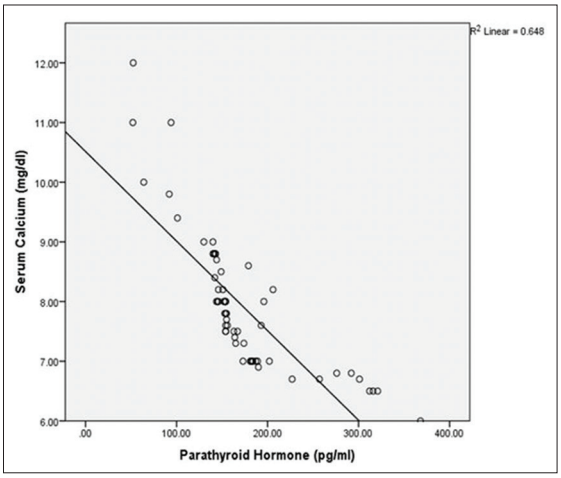

Figure 3: Scatter plot showing correlation of parathyroid hormone with potassium ($P = 0.001$, $r = 0.421$)

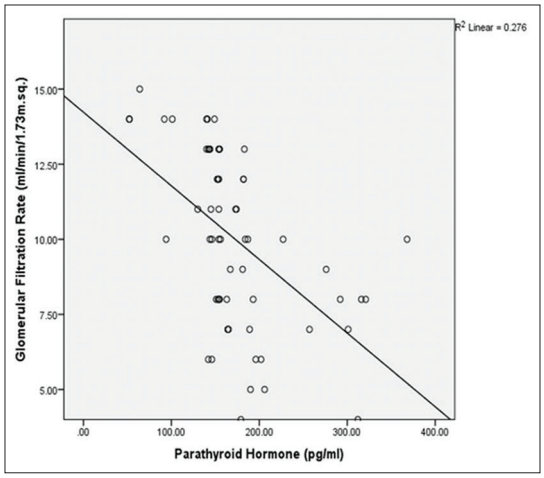

Figure 4: Scatter plot showing correlation of parathyroid hormone with calcium ($P \leq 0.001$, $r = -0.805$)

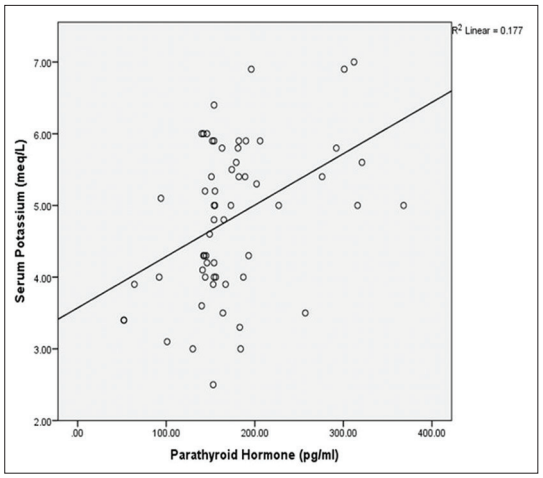

Figure 5: Scatter plot showing correlation of parathyroid hormone with phosphorous ($P = 0.003$, $r = 0.378$)

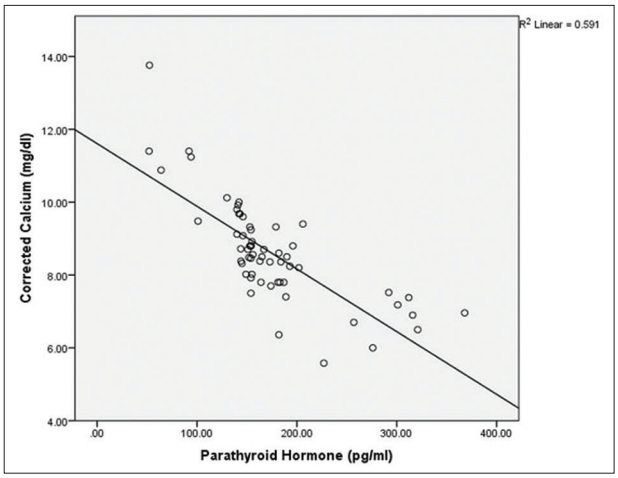

Figure 6: Scatter plot showing correlation of parathyroid hormone with corrected calcium ($P \leq 0.001$, $r = -0.769$)

and phosphorus. It is accepted that total calcium levels need to be adjusted for the level of albumin to better reflect the free calcium. In the presence of hypoalbuminemia, there is a relative increase in the ionized calcium relative to the total

Table 2: Correlation of parathyroid hormone with renal function test and estimated glomerular filtration rate

Parathyroid Hormone (pg/mL)	Parameter	*P*	Correlation coefficient	Significance
	Blood urea (mg/dL)	0.073	0.233	NS
	S. creatinine (mg/dL)	<0.001	0.596	HS
	Estimated glomerular filtration rate (mL/minute/1.73 m^2)	<0.001	−0.525	HS
	Serum calcium (mg/dL)	<0.001	−0.805	HS
	Serum phosphorus (mg/dL)	0.003	0.378	S
	Serum magnesium (mg/dL)	0.294	0.138	NS
	Serum sodium (meq/L)	0.855	−0.024	NS
	Serum potassium (meq/L)	0.001	0.421	S
	Calcium × phosphorus	0.847	−0.025	NS
	Corrected calcium (mg/dL)	<0.001	−0.769	HS

calcium, and thus total serum calcium may underestimate the physiologically active (ionized) serum calcium. A commonly utilized formula for estimating the ionized calcium from total calcium is to add 0.8 mg/dL for every 1 mg decrease in serum albumin below 4 mg/dL.[8]

So, in our study, the mean value of corrected calcium is 8.61 ± 1.40 mg/dL, and on comparing the data statistically, a significant negative correlation found between PTH and corrected calcium ($P \leq 0.001$; $r = -0.769$) [Figure 6].

In 2001, Ganesh *et al.* found that the mean value of serum creatinine was 11.4 ± 3.6 mg/dL. Mean value of serum calcium, serum phosphorous, calcium × phosphorous, and PTH levels was 9.4 ± 1.0, 6.2 ± 2.0, 57 ± 19, and 387 ± 783 pg/dL, respectively, in CKD patients.[9]

Malawadi *et al.* in 2014 found that the serum iPTH (331.68 ± 204.99 pg/mL) was significantly higher in more advanced renal failure (CRF stage 5), which confirms the relationship between severity of hyperparathyroidism and the degree of renal impairment. Serum iPTH is negatively correlated with creatinine clearance ($P \leq 0.001$; $r = -0.718$) and serum total calcium ($P < 0.001$; $r = -0.454$). However, the serum iPTH is positively correlated with inorganic phosphate ($P < 0.001$; $r = +0.621$), urea ($P < 0.001$; $r = +0.526$), and creatinine ($P < 0.001$; $r = +0.656$).[10]

In 2016, Vikrant *et al.* observed the following biochemical abnormalities: hypocalcemia (23.8%), hypercalcemia (5.4%), hypophosphatemia (2.8%), hyperphosphatemia (55.4%), raised alkaline phosphatase (56.9%), secondary hyperparathyroidism (82.7%), and hypoparathyroidism (1.5%). There was a significant positive correlation between iPTH with alkaline phosphatase ($P = 0.001$), creatinine ($P = 0.001$), and phosphorus ($P = 0.001$).[11]

The mean value of serum magnesium in this study found to be 2.57 ± 0.62 (mg/dL) that shows hypermagnesemia but nonsignificant correlation with PTH in ESRD patients ($P = 0.294$; $r = 0.138$).

But, our results are contradicting in this respective to study by Navarro *et al.* in 1999; they found patients with low PTH had a significantly higher serum Mg concentration than patients with adequate or high PTH. Moreover, regression analysis showed a negative linear correlation between serum PTH level and plasma Mg concentration ($P < 0.001$; $r = -0.6059$).[12]

The ratios of sodium/potassium, sodium/magnesium, sodium/calcium, calcium/potassium, calcium/magnesium, potassium/magnesium play important role as they indicate various decompensations in ESRD patients. Studies have been done to evaluate the role of secondary hyperparathyroidism in ESRD in altering these ratios.

Owiredu *et al.* also observed that there was a corresponding decrease in the serum concentration of PTH, for every mmol/L increase in the Ca2+/Mg2+ ratio ($P < 0.0001$; $r^2 = 0.33$), Na+/Mg2+ ratio ($P < 0.0001$; $r^2 = 0.26$) and K+/Mg2+ ($P < 0.0001$; $r = 0.19$). Furthermore, there was an inverse relationship between Na+/K+ ratio ($P < 0.0151$; $r^2 = 0.04$), Ca2+/K+ ratio ($P < 0.0001$; $r^2 = 0.28$), and PTH, whereas for every mmol/L, there was an increase Ca2+/Na+ ratio ($\beta = 0.0373$; $r^2 = 0.34$; $P < 0.0001$) and PTH.[13]

Our study shows significant negative correlation of PTH with sodium/potassium ($P = 0.004$; $r = 0.364$), calcium/potassium ($P \leq 0.001$; $r = 0.648$), sodium/calcium ($P \leq 0.001$, $r = 0.793$), and calcium/magnesium ($P \leq 0.001$; $r = -0.501$).

The understanding of mineral ratios is particularly interesting and probably offers more information than analyzing mineral levels alone. Electrolyte ratios have been linked to a number of endocrine abnormalities including thyroid and adrenal disturbances. Even though significant observations on the various electrolyte ratios were made in this study, further focused studies may be required to further elucidate the role of electrolyte ratios in the pathophysiology and prognosis of diseases associated with hormonal imbalances.[14]

So, the pathophysiology of secondary hyperparathyroidism may include. As kidney disease progresses, there is diminished filtration and excretion of phosphate resulting in hyperphosphatemia, a finding consistent with observations made in our and many more study. Initially, this is surmounted by an elevation in the serum level of PTH, which decreases proximal phosphate reabsorption. However, eventually there is hyperplasia and hypertrophy of the parathyroid gland as a result of this physiological compensation, setting the stage

for secondary hyperparathyroidism, and the vast array of metabolic, vascular, rheumatologic, and cardiac complications that are associated with its onset.[15]

Also hypocalcemia as it is a powerful stimulus for PTH secretion and for parathyroid growth, a finding consistent with observations was made in our study. The effects of calcium seem to be mediated by the calcium-sensing receptor, and there is decreased expression of the calcium-sensing receptor in the hyperplastic glands that are seen in kidney failure.

Furthermore, decreased levels of calcitriol also may contribute to parathyroid abnormalities. Calcitriol is major regulator of PTH secretion, and the vitamin D receptor is expressed in the parathyroid glands. Calcitriol decreases PTH secretion *in vivo* and *in vitro* as a result of an effect at the level of transcription of the PTH gene.

Skeletal resistance to the calcemic actions of PTH may also contribute to the development of hyperparathyroidism. Many factors likely are involved in this skeletal resistance, including phosphorus retention, possibly decreased levels of calcitriol downregulation of the PTH receptor.[16]

Conclusion

So, finally, the authors suggest that PTH linked with derangements in the metabolism of electrolytes like calcium, magnesium, phosphorus, and potassium in ESRD and contribute to a plethora of complications. PTH should be measured early in CKD and the necessary interventions concerning these electrolytes should be done to protect the CKD patients from any complications that will result in response to PTH excess.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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