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A Cross- Sectional Study on Assessment of Hyperparathyroidism in Patients with End-Stage of Renal Failure.

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Abstract

Background: Renal hyperparathyroidism is a common complex and challenging disorder of End-stage renal failure (ESRF) characterized by elevated parathyroid hormone levels as well as it develops early in the course of renal failure and is associated with increased risks of fractures, cardiovascular disease and death.

Material & Methods: This cross-sectional study was carried out in 120 patients of ESRF and 63 healthy controls. Serum creatinine,urea,uric acid ALP, calcium and blood electrolytes sodium and potassium were quantified , followed by statistical analysis and their correlation.

Result:. Out of 120 patients included in our study, there were 79 males and 41 females and the ratio was 2:1. It was observed that the value of serum iPTH is 645.62±468.8 pg/ml and others biochemical parameters like urea, creatinine, uric acid,sodium,potassium and alkaline phosphates except serum calcium were significantly higher in the case group as compared to the control group. It was also found that increase in serum iPTH, phosphorous and alkaline phosphatase value is statistically higher in females when compared to males in ESRF patients.

Conclusion: It was concluded that iPTH level is raised in End-stage Renal Failure Patients. Hyperparathyroidism is commonly seen is CKD (stage 4-5) patients where the parathyroid glands increase the parathyroid hormone production and secretion. It is found that Secondary Hyperparathyroidism is associated with mortality and morbidity in patients with advanced stage of CKD .

Keywords: End-stage renal failure, iPTH, secondary hyperparathyroidism

INTRODUCTION

End stage Renal Disease (ESRD) is life-threatening and is a worldwide public health problem. Unfortunately, a wide range of disorders and complications may develop because of the loss of kidney function among these patients which imposes a major social and economic burden for healthcare system [1,2]. The kidneys of patient with End-stage renal disease function below 10% of their normal ability, which may mean they are barely functioning or not functioning at all. The key causes of chronic kidney disease (CKD) include chronic glomerulonephritis, progressive nephritis, diabetes mellitus, chronic hypertension, long standing polycystic kidney and chronic pyelonephritis [3]. However, existing research indicates that in recent years, hypertension and diabetes are recognized as the two leading causes of End-stage kidney disease [4]. The worldwide prevalence of ESRD is 0.1% the incidence of patients with ESRD requiring renal replacement therapy (RRT) has remained fairly stable over the last decade, More than 80% of the patients with a glomerular filtration rate (GFR) below 20ml/min/1.73m^2, present with PTH levels above the upper limit of normal (PTH›6.8pmol/l) [5-7].

End-stage renal disease (ESRD) is the most common cause of secondary hyperparathyroidism (SHPT) [8,9]. In contrast to primary hyperparathyroidism, the hormonal disturbance in secondary and tertiary hyperparathyroidism is caused by an external stimulus.

The intact parathyroid hormone (iPTH MW~9425k Daltons) is an 84 amino acid polypeptide that increases serum calcium concentration by increasing calcium reabsorption in the thick ascending loop of nephron, increasing activated vitamin D (calcitriol) [10], production and indirectly increasing bone reabsorption. Secondary hyperparathyroidism (SHPT) causes common abnormalities of mineral metabolism in patients with chronic kidney disease (CKD) and is characterized by hyperplasia of parathyroid glands and increased plasma levels of parathyroid hormone (PTH).

It is well documented that disturbance in vitamin D, phosphorus, calcium and PTH metabolism contributes to bone disorders and cardiovascular complications of end stage renal diseases patients [11]. It is estimated that 30%-50% of stage 5 CKD patients have iPTH levels of ≥300pg/ml, as the kidneys fail, gross derangements in fluid and solute clearance occur [12].

MATERIAL AND METHODS:

The present study was conducted in the Department of Biochemistry and Nephrology of Shri Guru Ram Rai Institute of Medical and Health Sciences and Shri Mahant Indiresh Hospital, Dehradun. Before the start of the study, permission was granted from the Ethical Review Committee, of Institute and informed consent was obtained from all participants. A total of 120 patients of either sex [age ranged between 25-60 years] comprising of 79 males and 41 females and 63 controls were included in

this study. The samples were taken from the patients who visited OPD/IPD at SMI Hospital, Dehradun. Patients with history and physical findings of chronic renal failure disease and biochemical analysis suggestive of chronic renal disease were included in this study. Patients below the age of 25 years and with acute kidney injury (AKI) were excluded from this study.

Serum iPTH was done by using third generation VITROS 5600 Integrated immunodiagnostic system, which is based on competitive immunoassay technique.Serum urea, serum creatinine, serum uric acid, serum calcium,serum phosphorous were quantified by using VITROS 5600 Integrated system. Serum sodium and potassium were quantified by using HDC Lyte which is based on ion-selective electrode method.

Statistical Analysis

All data were analyzed using SPSS version 10 version software (SPSS). Differences in age between-group gender (male and female) ,cases,were examined by student t-test, mean, standard deviation, coefficient of variation and P-value.

RESULTS:

The present study was conducted in 120 patients with End-stage renal failure presenting to the OPD/IPD of SMI Hospital, Dehradun. The various biochemical investigations of these patients were assessed. In table 1 the mean of age group was 52 and 51 in the males and females in cases of End-stage renal failure respectively.

Table 2 is showing the level of serum urea, creatinine, uric acid, sodium, potassium, calcium, phosphorus, alkaline phosphatase, and iPTH in the patients of ESRF. Also Serum creatinine, urea, uric acid levels in ESRF patients were significantly raised as compared with control Serum iPTH,alkaline phophatase levels in ESRF patients were also highly significant.

Table 1: - Comparison of age (in years) between male and females of the study group.

Parameter	MALE CASES (79) MEAN±SD	FEMALE CASES (41) MEAN±SD
Age (in years)	52.82±15.09	51.8±11.25

Table 2: - Comparison of the various biochemical parameters Serum creatinine, urea, uric acid ,sodium, potassium,calcium,alkaline phophatase, iPTH between the study and control group.

Parameter	Study group (120) MEAN±SD	Control group (63) MEAN±SD	t-value	p-value	Significance
Creatinine(mg/dl)	7.36±6.60	0.79±0.25	7.8	<0.001	S
Urea(mg/dl)	125.6±49.6	23.79±11.82	16.0	<0.001	S
Uric acid (mg/dl)	6.63±1.89	5.37±1.90	4.27	<0.001	S
Sodium(mEq/L)	140.5±3.98	135.2±16.2	3.4	<0.01	S
Potassium(mEq/L)	4.8±0.79	4.0±0.64	6.9	<0.001	S
Phosphorous(mg/dl)	5.25±1.69	3.86±0.94	6.05	<0.001	S
Calcium(mg/dl)	7.81±1.39	8.84±0.66	5.55	<0.001	S
Alkaline phosphatase(U/L)	164.0±189.14	95.7±41.86	2.82	<0.01	S
iPTH (pg/ml)	645.62±468.8	94.2±55.4	9.29	<0.001	S

Table 3: -Comparison of serum Creatinine, serum Urea, serum Uric Acid and serum iPTH between male and female patients of ESRF

Parameter	Male(79) MEAN±SD	Female(41) MEAN±SD	t-value	p-value	Significance
Creatinine(mg/dl)	7.71±7.85	6.68±2.97	0.80	>0.05	NS
Urea(mg/dl)	128.74±49.54	119.53±49.9	0.96	>0.05	NS
Uric acid(mg/dl)	6.90±2.02	6.10±1.52	2.22	<0.01	S
iPTH (pg/ml)	603.83±451.61	726.12±496.11	1.36	>0.05	NS
Sodium(mEq/L)	140.45±4.20	140.6±3.58	0.25	>0.05	NS
Potassium(mEq/L)	4.84±0.83	4.8±0.72	0.26	>0.05	NS
Calcium(mg/dl)	7.82±1.37	7.78±1.44	0.14	>0.05	NS
phosphorus(mg/dl)	5.17±1.74	5.41±1.60	0.73	>0.05	NS
Alkaline phosphatase(U/L)	163.9±193.6	164.16±182.44	0.007	>0.05	NS

In table 3. Comparison of serum creatinine, serum urea, serum uric acid and serum iPTH between male and females of study group is shown. Mean serum creatinine and urea level is 7.71mg/dl vs 6.68mg/dl and 128.74mg/dl vs 199.45mg/dl in males & females respectively. Their level are high in male vs female but the difference is not significant. Similarly, Serum uric acid and iPTH level in male and female was 6.90mg/dl vs. 6.10mg/dl and 603.83pg/ml vs 726.83pg/ml respectively, which is slightly higher in males but the difference is not significant. No gender variation was observed in serum sodium, potassium, calcium, phosphorus and alkaline phosphatases levels in ESRF patients, as shown in the table 3.

DISCUSSION

This study was conducted at SMI Hospital in the Department of Biochemistry. We took 120 patients of End-stage Renal Failure who attended OPD/IPD of Nephrology Department. Serum urea, Serum creatinine, Serum uric acid, Serum I PTH, Serum electrolyte were estimated in these patients.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, sodium, and potassium homeostasis.

In our study it was found that there is a very high prevalence of Hyperparathyroidism secondary to kidney disease in the patients with stage 4 and 5 kidney failure. The maximum number of patients was between the age group of 40-70 years which was found to be 78.3%. Mean age of patients was 52.47±13.85 years, which suggests that incidence of ESRD increases with advanced age. Out of 120 patients included in this study, there were 79 males and 41 females and the ratio was 2:1.Diniz *et.al* in 2012 observed in their study of 125 patients that the mean age was 57.4±16.2 years with male and female the ratio was 1.2:1.

Kirti Arora *et.al* in 2018 found in their study of 60 patients that the mean age was 52.28±16.25years with male and female and the ratio between male and female was 1.5:1 [13].In our present study it was observed the value of serum iPTH is 645.62±468.8 pg/ml which was significantly higher in cases as compared to the control group.A previous study has suggested that elevation of PTH levels in patients with End-stage kidney disease increases cytoplasmic calcium concentration in vascular smooth muscle cells and thereby it promotes increases blood pressure. In turn, hypertension stimulates the secretion of PTH and promotes the progression of secondary hyperparathyroidism. This cycle accelerates the deterioration of renal insufficiency [14)]According to the K/DOQI (Kidney Disease Outcomes Quality Initiative) practice guidelines, it is suggested that plasma levels iPTH among ESRD patients undergoing maintenance dialysis should be maintained between 150-300pg/ml[15].

In present study, when mean value of iPTH levels was compared in males & females it was found that increase in PTH value is statistically higher in females when compared to males in ESRF patients. In 2015, similar results were seen in Chowdary *et.al* found that the mean value of PTH in CKD males and females observed a significant rise in the PTH values statistically higher in females ($P<0.001$) when compared with males ($P<0.0001$) in CKD patients [16]. A previous study suggested that the elevated estrogen and estrogen receptor levels up regulate the mRNA levels of PTH in parathyroid cell [17], which may explain the gender difference in the development of SHPT.

Malawadi *et.al* in 2014 found that the serum iPTH (331.68±204.99pg/ml) was significantly higher in more advanced renal failure (CKD stage 5), which confirms the relationship between severity of hyperparathyroidism and the degree of renal impairment([8].

The mean value of serum calcium in our study was found to be 7.81±1.39mg/dl. According to the Kidney Disease Outcomes Quality Initiative (KDOQI) recommendations for mineral metabolism, the standard serum calcium range is (8.4 to 9.5mg/dl). The serum calcium was below 8.4mg/dl in 64.16% (n=77) and above 9.5mg/dl in 0.84% (n=1) in ESRD patients. The most common cause of death in ESRF patients is cardiovascular disease that may be due to excess coronary artery calcification(19).

In this study the mean value of serum phosphate is 5.25±1.69mg/dl. The accepted normal range of serum phosphate is (3.5 to 5.5mg/dl) according to KDOQI guidelines for mineral metabolism. Serum phosphate was above 5.5mg/dl in 61.7% (n=74) and below 3.5 mg/dl in 2.5% (n=3) of ESRD patients.

In a previous study it was found that apart from other effects of PTH described earlier, the most potent effect is to increase serum calcium levels by enhancing renal tubular calcium reabsorption, stimulating net bone resorption and increasing the production of activated vitamin D (1,25(OH)2D3)[20]. Pocotte *et al.* 1991. Low levels of active vitamin D also directly result in PTH release and parathyroid cell proliferation [21].

Our results demonstrated that the hyperphosphatemia was an independent risk factor influencing the development of SPTH. Similar a previous study in 2011, Hruska KA *et.al* report that the blood phosphorus expression levels are one of the most important factors stimulating the synthesis and secretion of PTH in patients with CKD[22],with worsening renal function, the excretion of phosphorus from renal tubular decreases and blood phosphorus levels increases[23].

Voormolen *et.al* reported that elevated plasma phosphorus directly stimulates the synthesis and secretion of PTH in patients with stage 4-5 CKD. The effect of plasma phosphorus is independent of the level of plasma calcium or the activation of vitamin D [24] .

In our study it was observed the value of serum creatinine is 7.36±6.60mg/dl,which was significantly higher in cases as compared to control group. Serum creatinine levels are a commonly used index indirectly assessing the renal function of patients, and rising serum creatinine predicts the worsening of renal function [25].Previous reports have suggested that PTH elevation is negatively correlated with the reduction of the glomerular filtration rate [26]. The

results of my study demonstrated that PTH is negatively correlated with serum creatinine levels in patients with ESRF. Similarly in a study of Yudan Wei *et.al* reported negative correlation of PTH and serum creatinine with patients with advance CKD[27]. Urea is the major nitrogenous metabolic waste product of protein metabolism. Measurement of urea has been widely used as indicator of kidney function and it was observed that the value of serum urea is 125.6±49.6 mg/dl in our study, significantly higher in cases as compared to control group. Similar to the previous study serum urea value was higher in patients to advance CKD[28,29]. In our study, serum uric acid level in ESRD patients was significantly higher in cases than controls. Similar observation was seen in previous studies in 2015, Toyama *et.al* [30] that hyperuricemia results in the progression of renal dysfunctions.

In this study it was observed that he value of serum sodium and potassium are approximately similar to the other study. Result revealed increased serum potassium of almost equal concentration in female and male cases. Some effect of low potassium includes muscular weakness, cramping and fatigue. When kidneys fail, they can no longer remove excess potassium, so the level increases in the body. A high level of potassium in the blood is called Hyperkalemia which may occur in people with advanced stage of CKD [31, 32, 33].

The level of alkaline phosphatase in our study was higher than the normal range. Elevated ALP levels can be seen with worsening magnitude of bone turnover with the rate of elevation a reliable marker of severity of the high turnover osteodystrophy. Renal osteodystrophy arises as a consequence of bone remodeling dysregulation [34, 35].

CONCLUSION

Renal hyperparathyroidism develops early in renal failure, mainly as a consequence of lower levels of vitamin D, hypocalcemia, diminished excretion of phosphate and inability to activate vitamin D. RHPT is a continuum and diagnosis depends on demonstrating elevated levels of parathyroid hormone, PTH. Treatment consists of supplying vitamin D, reducing phosphate intake and treatment with active vitamin D analogs. It was concluded that iPTH level is raised in End-stage Renal Failure Patients. Hyperparathyroidism is commonly seen is CKD (stage 4-5) patients where the parathyroid glands increase the parathyroid hormone production and secretion. Secondary Hyperparathyroidism is associated with mortality and morbidity in patients with advanced stage of CKD.Hypocalcemia, Hyperphosphatemia, Hyponatraemia , and Hyperkalemia

were the most prevalent electrolyte imbalances in ESRD p atients. iPTH should be measured early in CKD and the necessary interventions concerning can be helpful, the electrolytes should be done for early diagnosis and protect the CKD patients from any complications that will result in response to PTH excess.

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REFERENCES

1. Ghaderian SB, Hayati F, Shayanpour S, Beladi Mousavi S. Diabetes and end-stage renal disease; a review article on new concepts. J Renal Inj Prev. 2015, 4(2), 28-33.
2. Beladi-Mousavi SS, Beladi-Mousavi M, Hayati F, Talebzadeh M. Effect of intranasal DDAVP in prevention of hypotension during hemodialysis. Nefrologia. 2012, 32, 89- 93.
3. Arora A.R; Kidney and lungs. Medical biochemistry, 1st edition, Jaypee publications, chapter 28,719-729.
4. Barsoum RS, chronic kidney disease in the development world. N Engl J Med 2006, 354, 997-9.
5. Moe SM. Vascular calcification and renal osteodystrophy relationship in chronic kidney disease. Eur J Clin Invest 2006, 36(Suppl 2), 51–62.
6. National Kidney Foundation. K/DOQI Clinical Practice Guidelines for bone metabolism and disease in chronic kidney disease. Am J Kidney Dis 2003, 1–201.
7. Craver L, Marco M, Martinez I et al. Mineral metabolism parameters throughout chronic kidney disease stages 1–5-achievement of K/DOQI target ranges. Nephrol Dial Transplant 2007, 22, 1171–1176.
8. Arnaud CD. Hyperparathyroidism and renal failure. Kidney Int.1973, 4, 89-95.
9. Silverberg SJ, Bilezikian JP. Evaluation and management of primary hyperparathyroidism. J Clin Endocrinol Metab 1996, 81, 2036–2040.
10. Cunningham J, Locatelli F and Rodriguez M: Secondary hyperparathyroidism: Pathogenesis, disease progression, and therapeutic options. Clin J Am Soc Nephrol 2011, 6, 913-921.
11. Panda DK, Miao D, Bolivar I, et al. Inactivation of the 25-hydroxyvitamin D 1alpha-hydroxylase and vitamin D receptor demonstrates independent and interdependent effects of calcium and vitamin D on skeletal and mineral homeostasis, J Biol CHEM 2004, vol 279.
12. Lach F. Secondary hyperparathyroidism in renal failure: The trade-off hypothesis revisited. Am J Kidney Dis 1995, 25, 663-79.
13. 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.
14. Ferrier KE, Muhlmann MH, Baguet JP, Cameron JD, Jennings GL, Dart AM and Kingwell BA: Intensive cholesterol reduction lowers blood pressure and large artery stiffness in isolated systolic hypertension. J Am Coll Cardiol 3, 1020-1025, 2002.
15. Group KDIGOC-MW. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). Kidney Int Suppl. 2009 S;1-130.
16. RD Chowdary, R Nellutla *et.al*; relation between parathyroid hormone and serum creatinine levels in chronic kidney disease patients:J Med Sci Res 2015, 3(1), 17-21.
17. Prince RL: Counterpoint: Estrogen effects on calcitropic hormones and calcium homeostasis. Endocr Rev 1994, 15, 301-309.
18. Malawadi BN, Suma MN *et.al*; secondary hyperparathyroidism in all the stages of chronic kidney disease in southern Indian population: Int J Pharm Pharm Sci 2014; Vol 6, Issue 4, 287-290.
19. Amiri M, Nasri H. Secondary Hyperparathyroidism in chronic kidney disease patients; current knowledge. J Parathyr Dis 2014, 2, 1-2.

20. R Brown *et.al*; hyperparathyroidism, platelet intracellular free calcium and hypertension in chronic renal failure; Kidney International 1993, 43(3), 700-705.
21. Pocotte, Gerald Ehrenstein *et.al*; regulation of parathyroid hormone secretion: Endocrine reviews 1991, 12(3), 291-301.
22. Hruska KA and Mathew S: The roles of the skeleton and phosphorus in the CKD mineral bone disorder. Adv Chronic Kidney Dis 2011, 18, 98-104.
23. Voormolen N, Noordzij M, Grootendorst DC, Beetz I, Sijpkens YW, van Manen JG, Boeschoten EW, Huisman RM, Krediet RT and Dekker FW; PREPARE study group: High plasma phosphate as a risk factor for decline in renal function and mortality in pre-dialysis patients. Nephrol Dial Transplant 2007, 22, 2909-2916.
24. L´opez, M. E. Rodr´ıguez-Ortiz, Y. Almad´en *et al*., "Direct and indirect effects of parathyroid hormone on circulating levels of fibroblast growth factor 23 in vivo," Kidney International , 2011, 80(5), 475–482.
25. Y. Imanishi, M. Inaba, K. Nakatsuka *et al.*, "FGF-23 in patients with end-stage renal disease on hemodialysis," Kidney International 2004, 65(5), 1943–1946.
26. S. Liu and L. D. Quarles, "How fibroblast growth factor 23 works," Journal of the American Society of Nephrology 2007, 18(6), 1637–1647.
27. V. Lavi-Moshayoff, G. Wasserman, T. Meir, J. Silver, and T. Naveh-Many, "PTH increases FGF23 gene expression and mediates the high-FGF23 levels of experimental kidney failure: a bone parathyroid feedback loop," American Journal of Physiology-Renal Physiology 2010, 299(4), 882–889.
28. Seethalakshmi C, Koteeswaran D, Chiranjeevi V. Correlation of serum and salivary biochemical parameters in end stage renal disease patients undergoing hemodialysis in pre and post- dialysis state. J Clin Diagn Res. 2014, 8(12), CC12–14.
29. Smith GL, Shlipak MG, Havranek EP, Foody JM, Masoudi FA, Rathore SS and Krumholz HM: Serum urea nitrogen, creatinine, and estimators of renal function: mortality in older patients with cardiovascular disease. Arch Intern Med 2006, 166, 1134-1142.
30. Tadashi Toyama, Kengo Furuichi, Miho Shimizu, Akinori Hara, Yasunori Iwata, Norihiko Sakai, Vlado Perkovic, Makoto Kobayashi, Toshiki Mano, Shuichi Kaneko, and Takashi Wada. PLoS One. 2015, 10(9), e0137449.
31. National Kidney Foundation: K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. Am J Kidney Dis 2003, 42 (4 Suppl 3), S1-S201..
32. Ahmed J and Weisberg LS. Hyperkalemia in dialysis patients. Semin Dial 2001, 14, 348-56.
33. Ming-fang Hsieh. Higher serum potassium level associated with late-stage chronic kidney disease. Chang Gung Med J 2011, 34, 418-25.
34. Eknoyan G, Levin A and Levin N. Bone metabolism and disease in chronic kidney disease. Am J Kidney Dis.2003, 42, 1-201.
35. Bala Waziri, Raquel Duarte, and Saraladevi Naicker.Chronic Kidney Disease–Mineral and Bone Disorder (CKD-MBD): Current Perspectives. Int J Nephrol Renovasc Dis. 2019, 12, 263–276.