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A Study On The Prevalence And Risk Factors Of Post Renal Transplant Hyperparathyroidism: A Single Centre Experience

Arul Rajagopalan[1] , Shiva Kumar Ammayappan[*2], Kiruthika Somasundram[3], Gandhimohan Rajan[4]
[1]Professor and Head , [2,3]Assistant Professor, [4]Associate Professor,
Department of Nephrology,
[1,3,4]Coimbatore Medical College
[2]Tirunelveli Medical College.

***Corresponding Author:**
Dr. Shiva Kumar Ammayappan
56, Perumal nagar, Beemanagari,
Thirupathisaram, Kanyakumari-629901, Tamil Nadu, India

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Abstract

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Introduction

Chronic kidney disease results in an array of wide biochemical abnormalities. The spectrum of disorders include abnormal concentration of serum calcium, inorganic phosphate and magnesium, and disorders of parathyroid hormones (PTH), FGF-23(fibroblast growth factor-23) , and vitamin D metabolism. The overall clinical, biochemical and imaging abnormalities are broadly classified as a clinical entity or syndrome called chronic kidney disease-mineral and bone disorder (CKD-MBD)[1]. The parathyroid abnormalities in CKD include parathyroid gland hyperplasia, decreased expression of vitamin D receptors, decreased expression of calcium receptors and increased set point of calcium regulated parathyroid hormone secretion. Fortunately, renal transplantation results in improvement of CKD induced secondary hyperparathyroidism. However, recent studies[2,3] have reported a high incidence of post renal transplant hyperparathyroidism (PRTHP). Persistent PRTHP is associated with graft dysfunction, cardiovascular morbidity, bone loss, increased fracture risk, and poor quality of life[2]. There is no definite consensus on the level of parathyroid hormone to be defined as persistent PRTHP and the treatment protocol.

Material and methods

This cross-sectional study was conducted in a tertiary care centre, on patients who are on regular follow up and have completed at least 3 months after undergoing renal transplantation. The study was approved by the institution ethics committee and a proper informed consent was obtained. All patients with advanced graft dysfunction (eGFR<30 ml/min/1.73 m^2) and those on drugs, which may interfere with divalent cations (calcium supplements, vitamin D, Calcitriol, Cinacalcet) were excluded. A detailed history, physical examination including anthropometry and laboratory values were obtained. 25 hydroxy vitamin D levels and intact PTH was measured in serum by chemiluminescent immunoassay. In our study, serum intact PTH levels > 70 pg/ml was considered as hyperparathyroidism.

Descriptive statistics were used for quantitative data. Student's t-test was done to check the significance of quantitative data, whereas Chi- square test was done for qualitative data. The association between PTH and multiple independent factors was checked with Pearson correlation and multiple regression analysis. P<0.05 was considered as statistically significant.

Results

A total of 57 patients were studied, of whom 79% were males. The mean age was 36 years. The most common etiology of CKD in our population was chronic glomerulonephritis. The median transplant vintage was 58(32-84) months. The most common immunosuppression was prednisolone (98.2%). The incidence of hypertension and diabetes were 73.4% and 29.9 % respectively. The median parathyroid hormone level (PTH) was 161.5 (79.25-266.4) pg/ml. The prevalence of hyperparathyroidism was 70.78% (40 of 57 patients). Most of the patients who had hyperparathyroidism had a transplant vintage of more than 36 months (67.5%). All these patients were asymptomatic. The median vitamin D3 level was 32.86 (22.90-49.01) ng/ml. 35.1 % of the study population were vitamin D insufficient (vitamin D level 20-29 ng/ml) and 12.2 % were vitamin D deficient (vitamin D level <20 ng/ml). 15.7 % (9 of 57 patients) had serum calcium more than 10.5 mg/dl. The prevalence of hypophosphatemia (serum phosphate <3 mg/dl) was 40.3% (23 of 57 patients). The demographic data of the study population is shown in table 1. Table 2 depicts the comparison of various parameters between the normal PTH group and the hyperparathyroid group. Higher PTH levels were significantly associated with female gender, higher serum calcium and lower serum phosphorus levels. Significant correlation between serum PTH and serum phosphorus(p=0.04) and between serum PTH and serum calcium (p= 0.017) was observed. The levels of PTH level of the study population are depicted in the figure 1. Most of the patients had PTH in the range of 70-210 pg/ml.

Discussion

The prevalence of PRTHP in our study was high (70.78%), which may remain elevated for even upto 4 years. The characteristics of our study population is different from the global experience in terms of younger population and the native kidney disease being non diabetic kidney disease (chronic glomerulonephritis).

Studies from India have demonstrated a similar high prevalence of post-transplant hyperparathyroidism[3,4]. Our patients with PRTHP had significant high serum calcium and significant low phosphate. This is in contrast to another study[3] done in the same geographical population, where serum calcium and serum phosphate were not useful in the prediction of PRTHP. 9 out of the 40 hyperparathyroid patients had serum calcium more than 10.5 mg/dl. Similarly, 23 of 40 hyperparathyroid patients had hypophosphatemia.

Significant positive correlation was shown between serum calcium and PTH (Figure 2).

35.1% patients were vitamin D insufficient and 12.2 % patients were vitamin D deficient. The vitamin D of the hyperparathyroid group were slightly higher than no hyperparathyroid group, though not statistically significant.

The results are similar to other Indian studies, in which majority of post-transplant patients had vitamin D <30 ng/ml. The results are also in consensus with the general adult population, where the prevalence of vitamin D deficiency is 70-90%. Dietary deficiency and the lack of sunlight exposure in urban areas have been postulated as the possible explanation. Interestingly, in an Indian study[6] the prevalence of vitamin D deficiency which was 25% pre-transplant increased to 48% post -transplant.

Steroids may cause a calcium defect, which may have a negative impact on vitamin D. In addition, a state of secondary hyperparathyroidism causes increased clearance and inactivation of 25(OH)D3. The renal production of calcitriol increases in such a state, which in turn inhibits 25(OH)D3 through negative feedback. The possible explanation could be the loss of vitamin D binding globulins.

In turn, vitamin D deficiency stimulates the parathyroids via multiple pathways. It causes reduced PTH gene transcription repression, reduced density of vitamin D, and calcium -sensing receptors. These ultimately lead to the increased set point for PTH secretion[7].

There was a negative correlation of vitamin D with intact PTH in our study(Figure 3), which was similar to the study by Lobo et.al. However, in that study patients with PRTHP were normocalcemic with normal serum phosphate. The PTH levels in most of the patients improved after vitamin D supplementation.

One confounding factor in our study was the relatively low eGFR in patients with

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hyperparathyroidism, though it was not statistically significant.

Other measures to control PRTHP are cinacalcet and surgical parathyroidectomy. In a recent study[2], 32% PRTHP were treated with calcimimetics alone, and 6% of patients underwent surgical parathyroidectomy. However, both these interventions were used only after waiting for the PTH levels to improve till 1 year post transplant. Isakov and colleagues suggested that elevated PTH levels, as early as three months post-transplant confer a poor graft outcome. Therefore, early detection of PRTHP and early treatment may be considered, keeping in mind the long-term outcome of the graft. The consensus, as of now is to wait for one-year post-transplant for the serum PTH levels to normalize before proceeding for further intervention[10].

Higher pre-transplant PTH level are also associated with a higher chance of PRTHP. However, the pre transplant PTH levels were not done in our cohort.

Limitations

The drawbacks include the cross-sectional design, a lack of pre-transplant PTH and other data, and a small sample size.

Conclusions

The prevalence of post renal transplant hyperparathyroidism is not uncommon and it may persist for years after a successful graft outcome. The serum calcium and serum phosphate may be used as markers to monitor PRTHP. No significant difference was observed in the levels of vitamin D3 and alkaline phosphatase between patients with normal PTH level and patients with elevated PTH levels.

Early monitoring may help in diagnosing PRTHP early in the course and may help in timely intervention, thus ensuring a better long term graft survival.

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Table 1 – Demographic and laboratory data

Variable	Number
Total patients	57
Age (years)	36 years (29.5-43.5)
Gender (male:female)	45:12
Body mass index	23.5 kg/m^2(21.28-27.01)
Transplant vintage (months)	58 months (32-84)
Post-transplant immunosuppression (%)	
Corticosteroids	98.2%
Tacrolimus	79%
MMF	84.2%
Cyclosporine	8.8%
Azathioprine	14.1%
Everolimus/Sirolimus	7.1%
Prevalence of hypertension	41 (73.4%)
Prevalence of Diabetes	17 (29.9%)
Systolic BP (mm Hg)	130 (115-150)
Diastolic BP (mm Hg)	80 (80-90)
Blood Urea (mg/dl)	29 (21-34.5)
Serum creatinine (mg/dl)	1.5 (1.2-1.75)
Estimated GFR (ml/min)	58.6 (46.45-72.25)
Hemoglobin (g/dl)	12.8 (11.45-15)
Random blood sugar (mg/dl)	102 (86.5-132)
Serum calcium (mg/dl)	8.58 (7.88-9.43)
Serum phosphorus (mg/dl)	3.42 (2.72-4.18)
Serum albumin (gm/dl)	3.88 (3.705-4.1)
Serum 25 hydroxy vitamin D3 levels (ng/dl)	32.86 (22.905-49.01)
Plasma PTH (pg/ml)	161.5 (79.25-266.4)

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Table 2 – Comparison of normal with high parathormone groups

Parameter	Group I (PTH<70 pg/ml)	Group II (PTH>70 pg/ml)	P
PTH levels	62.24(52.5-68.05)	234.35(137.7-297.13)	
Patient number (%)	17 (28.82%)	40 (70.78%)	
Age (years)	36 (28-45)	35 (30.25-42.75)	0.0913
Gender (%)			
Male	13 (76.5%)	32 (80%)	0.275
Female	4(23.5%)	8 (20%)	0.001
Transplant vintage (months)	72 (26-112)	54 (32-81)	0.001
Body mass index (kg/m^2)	22 (19.53-26.155)	23.76 (21.43-27.49)	0.983
Systolic BP (mm Hg)	120 (115-130)	130 (112-150)	0.417
Diastolic BP (mm Hg)	80 (70-80)	80 (80-90)	0.075
Blood urea (mg/dl)	21 (18-31.5)	31.5 (26.25-35)	0.507
Serum creatinine (mg/dl)	1.3 (1-1.5)	1.5(1.3-2.1)	0.264
Estimated GFR (ml/min)	67.3 (57.2-91.35)	52.85 (41.23-65.03)	0.077
Random blood sugar (mg/dl)	96(71.5-131)	102.5(87-134.25)	0.071
Serum calcium(mg/dl)	8.48(7.91-8.8)	8.68(7.86-9.99)	0.017
Serum phosphorus (mg/dl)	4.26(4.07-4.35)	2.9(2.7-3.8)	0.05
Serum albumin (gm/dl)	4.04(3.84-4.13)	3.78(3.68-4.07)	0.255
25 hydroxy vitamin D3 levels(mg/dl)	29.1(22.74-60.125)	32.9(22.8-48.7)	0.287
Alkaline phosphatase (U/L)	160(138.3-172)	171.35(127.03-206.68)	0.635

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Figure 1- Histogram of serum PTH levels (pg/ml)

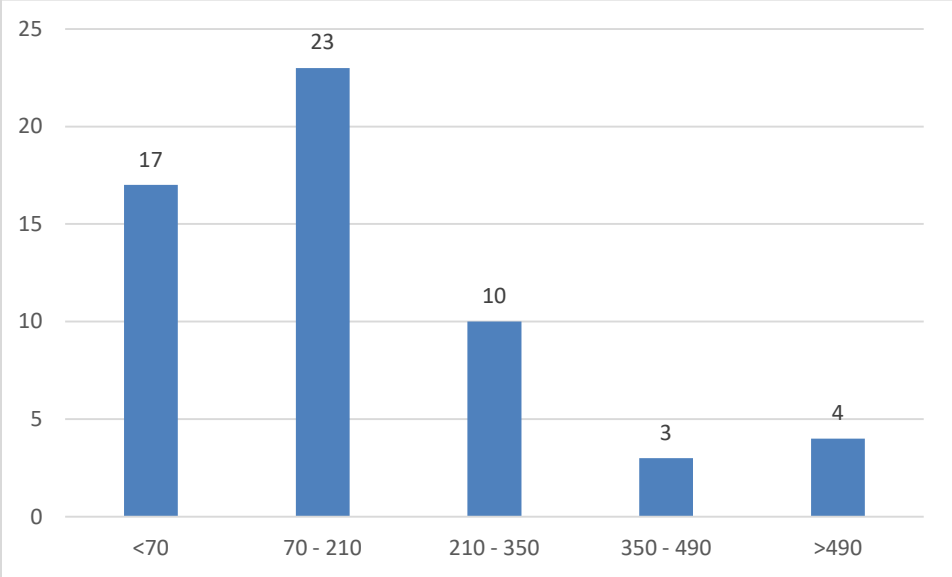

Figure 2- correlation between serum calcium and PTH level

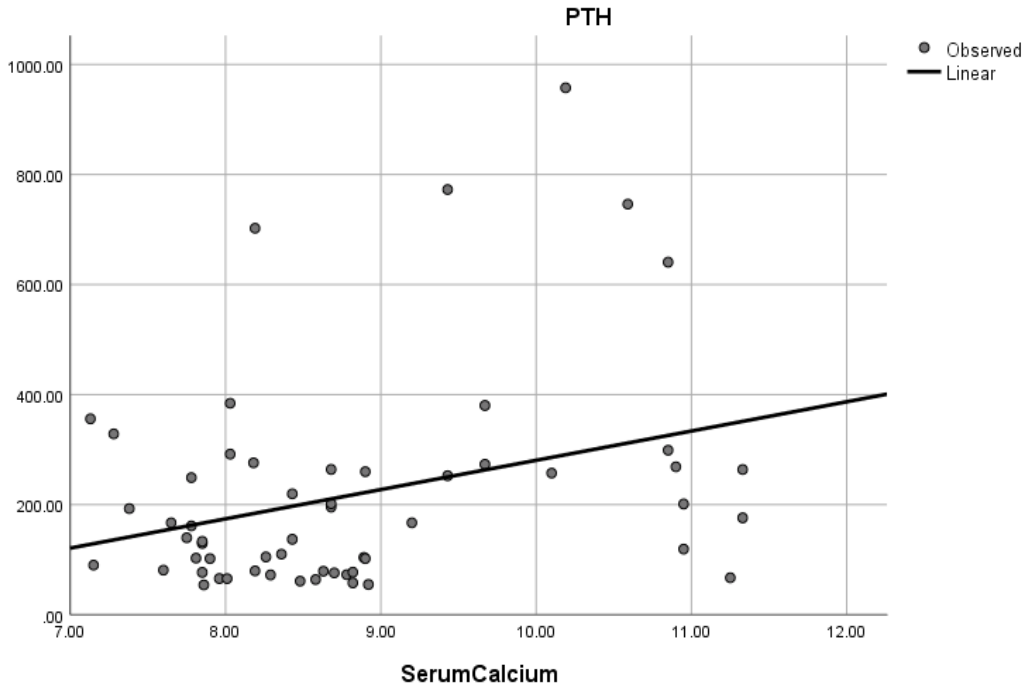

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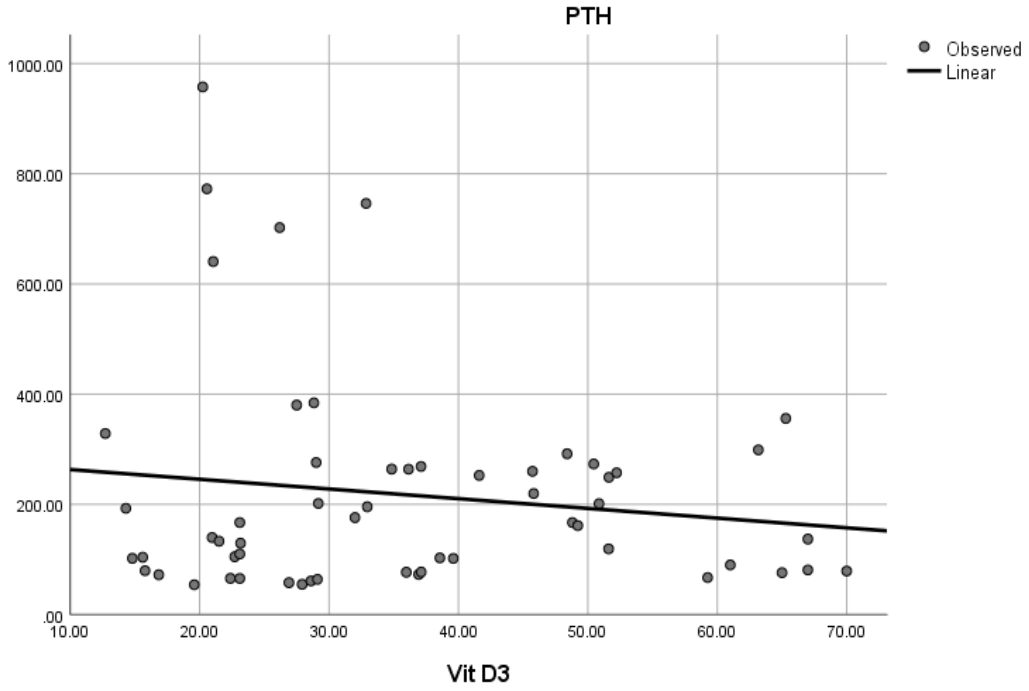
Figure 3 - correlation between vitamin D and PTH level



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