Persistent Hyperparathyroidism Post- Kidney Transplantation: A Single Center Experience

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Abstract — Background and aim: Persistent hyperparathyroidism after renal transplantation, termed tertiary hyperparathyroidism, is not uncommon. We aimed to identify the prevalence of persistent hyperparathyroidism after successful kidney transplantation and to study the associated risk factors.

Methods: This is a cross-sectional study including 63 patients who underwent renal transplantation for the first time &for at least a year. Data was collected about demographic characteristics, duration of chronic kidney disease& dialysis therapy, history of hypertension, diabetes mellitus, coronary heart disease and use of medications including vitamin D. Levels of serum calcium and phosphate and renal function test were recorded prior and post- transplantation. Serum parathyroid hormone was tested only post- transplantation. The association of those variable with hyperparathyroidism was studied by Pearson's correlation. P≤0.05 was considered statistically significant.

Results: Hyperparathyroidism was found in 53 (84.10%) patients, there was a strong positive correlation of parathyroid hormone level and serum levels of calcium and phosphate with (p-value<0.001). While the correlation was negative of parathyroid hormone level and estimated glomerular filtration rate after transplantation. None of the variables apart from hypertension was strongly associated as a risk factor before transplantation for persistant hyperparathyroidism.

Conclusions: In this single center study; more than 80% of post-transplant patients with normal transplant function, have elevated levels of parathyroid hormone more than one year after transplantation. This may have a major impact on clinical treatment guidelines. However, no association was observed between pre-transplant age, duration of transplant, duration on dialysis as risk factors for persistent hyperparathyroidism.

 ${\it Index Terms} \ -- \ {\it Hyperparathyroidism}; \ {\it Calcium}; \ {\it Renal}; \\ {\it Transplantation}.$

I. INTRODUCTION

A. Epidemiology

Most patients with chronic kidney disease (CKD) develop some degree of secondary hyperparathyroidism (HPT) by the time they initiate renal replacement therapy (RRT). Kidney transplant recipients are vulnerable to persistent HPT and other disorders of mineral and bone metabolism associated with CKD [1].

Elevated post-transplantation PTH exceeding three months may be suggestive of persistent HPT. In patients with mild disease, secondary HPT resolves as a more normal glomerular filtration rate (GFR) is restored [2].

Published on July 20, 2020. Z. S. Abdulkazim, Baghdad Teaching Hospital, Iraq. M. K. Abdul Razak, University of Baghdad, Iraq. (corresponding e-mail: manal.aladhadh@meciq.edu.iq). However, persistent HPT is reported to occur in approximately 15 to 50 percent of patients following transplantation. Thus, Kidney Disease Outcomes Quality Initiative (KDOQI) guideline has suggested early and routine monitoring of PTH post-transplantation [3].

Authors differ on appropriate serum PTH levels after renal transplantation. Some diagnose persistent HPT when serum PTH levels are above 2.5 times the upper limit set for normal reference values [4].

The cause of persistent HPT is partly due to persistence of structural changes in the parathyroid glands, such as hyperplasia and adenoma formation, despite removal of the initial stimuli for HPT [5],[6].

In the transplant recipient, the clinical features are characterized by hypercalcemia and hypophosphatemia [7]. Factors additional to HPT that contribute to hypercalcemia and hypophosphatemia in transplant recipients include increased calcitriol production, resorption of soft-tissue calcium phosphate deposition, high-dose glucocorticoids, excess fibroblast growth factor (FGF-23) production by osteocytes [8], [9]. Most transplant physicians will allow up to 12 months post-transplantation for normalization of PTH. Past this point, a PTH level greater than two times normal (>130 pg/mL) is consistent with persistent post-transplantation HPT [10], [11].

B. Outcomes

- Persistent HPT has been associated with increased mortality [12-13]. In a multivariate analysis of 1614 transplant recipients identified from the Assessment of Lescol in Renal Transplantation (ALERT) trial, PTH values >65 pg/mL were associated with an increase in all-cause mortality (hazard ratio [HR] 1.46, 95% CI 1.12-1.92) [12].
- High PTH levels and hypercalcemia promote vascular calcifications, which are associated with an increased post-transplantation morbidity and mortality in kidney transplant patients [13].
- PTH concentrations >800 pg/mL have been associated with a >80% risk of graft failure. In an analysis of data from the ALERT trial, PTH >65 pg/mL was associated with an 85 percent increase in death-censored graft loss (HR 1.85, 95% CI 1.41-2.42) [14].
- Uncontrolled HPT and hypercalcemia are risk factors for post-transplantation bone disease, with an increased risk of fractures. In a study by (Wolf M et al, 2011) of 143 kidney transplant recipients, a PTH level >130 pg/mL at three months after transplantation was associated with a 7.5-fold increased risk of fracture over five years (HR 7.5, 95% CI 2.18-25.50) [15].

C. Management

• The optimal treatment of HPT prior to transplantation

may prevent persistent HPT and the approach varies among transplant centers. Almost all experts suggest subtotal parathyroidectomy for transplant candidates who have refractory HPT and moderate to severe symptoms (e.g. bone pain, fractures, muscle pain, weakness), particularly if transplantation is not imminent [16].

• Some transplant nephrologists do not perform parathyroidectomy prior to transplantation in asymptomatic patients, since HPT resolves in many, though not all, patients after transplantation [17].

KDIGO guidelines from 2017 provide recommendations on testing serum calcium, phosphate, PTH and alkaline phosphatase, and 25- hydroxyvitamin D levels in intervals according to the post-kidney transplant recipients' level of renal function. KDIGO also suggests treatment using vitamin D, calcitriol/ alfacalcidol and/or antiresorptive agents within the first 12 months of transplant [18].

II. AIM OF STUDY

We aimed to identify the prevalence of persistent hyperparathyroidism after successful kidney transplantation and to study the associated risk factors.

III. PATIENTS AND METHODS

A. Study design& sample

A cross sectional study on the kidney allograft recipients in the Iraqi center for kidney transplantation at Medical City in Baghdad wasdoneduring their follow up visits. Patients were reviewed by focused history taking about their demographic data, risk factors, past medical history of hypertension, diabetes mellitus& coronary artery disease, history of calculous kidney disease, the duration of CKD and dialysis& the duration of transplantation, their previous investigations and specific medical treatment that was given.

B. Inclusion criteria

- 1. Those patients who underwent renal transplantation for at least 12 months.
 - 2. Those who were transplanted for the first time.
 - 3. Those without graft rejection.

All data were collected on separated days for 3 months, 76 patients had been taken; 13 patients were excluded and 63 patients were included and investigated for level of PTH, Serum Calcium (S. Ca⁺²) which is corrected according to their corresponding serum albumin level, serum phosphate (S. PO4⁻³) and serum albumin level.

C. Measurements

The patients' data has been checked for various biochemical variables (PTH, S. Ca⁺² and S.PO₄ ⁻³) level. Pretransplantation level of PTH was not measured routinely for all candidates so unfortunately was not studied. Estimated GFR was measured using as shown below the Modification of Diet in Renal Disease equation (MDRD) [19].

eGFR=175×(creatinine in μ mol/L/88.4)^{-1.154}× × (age in yrs.)^{-0.203} ×(0.742 if female)×(1.21 if black)

For the purpose of this study, the lab references for serum PTH was (15-68.3) pg/ml using Abbott architect plus (Japan), j 1000 SR model. And for serum Ca^{+2} (8.5–10.5)

mg/dl, serum PO4⁻³ (2.48–4.34) mg/dl and serum albumin (3.5–5) g/dl using Abbott architect plus (Germany), C 4000 model. Both devices are automated.

D. Definitions

Hyperparathyroidism is defined as a generalized disorder of calcium, phosphate, and bone metabolism due to an increased secretion of PTH [20]. In this study PTH value more than 68.3pg/mLwas regarded high according to lab. reference range.

Secondary Hyperparathyroidism is defined as hyperparathyroidism that is caused by any condition associated with a chronic depression in the serum calcium level [21].

Tertiary Hyperparathyroidismis defined as a state of hyperparathyroidism in patient with CKD that is no longer responsive to medical therapy and requires surgery [20].

Hypertension is considered if the recorded systolic blood pressure ≥ 140 mmHg and or diastolic blood pressure ≥ 90 mmHg, or if the patient was on current antihypertensive therapy [22].

Diabetes mellitus is defined as the use of insulin or glucose-lowering medication on admission, or a diet for diabetes documented in medical history. The diagnosis of "undiagnosed DM" was made if patients with fasting glucose >7.0 mmol/L or random glucose >11.1 mmol/L together with an admission HbA1c >6.5% according to the latest American Diabetes Association (ADA) recommendations [23].

Coronary artery disease is defined as the presence of angiographically proven coronary artery stenosis, history of myocardial infarction or coronary artery bypass grafting operation and presence of current myocardial ischemia by ischemic changes indicated electrocardiography [24].

E. Statistical analysis

Statistical package for Social Sciences (SPSS version 20) was used for data analysis, and Microsoft Excel to generate graphs. Continuous variables were expressed as a mean± standard deviation (SD), while categorical variables were expressed as frequency and percentages. For bivariate analysis, the student's test (t-test) was used to compare means of continuous variables, and Pearson's Chi square to compare the categorical variables. Pearson's correlation test was used to evaluate the significant association between parathyroid hormone and covariates and a linear regression analysis was used to express the strength of association. The statistical tests were two-sided, and a P-value≤0.05 was considered statistically significant.

IV. RESULTS

A sample of 63 renal transplant patients with functioning graft were studied for persistent HPT after renal transplantation. None of the sample group had pre-transplant parathyroidectomy.

As illustrated in Table I, 42 (66.67%) were males, 48 (76.19%) were hypertensives, 19 (30.16%) were diabetics and 14 (22.22%) were having CAD. Mean duration of CKD was 3.75 ± 2.69 year with range (1-12y) while mean duration of dialysis was (2.86 ±1.97 year). Before transplantation; all

patients received oral calcium, 24 (38.1%) received oral vitamin D supplements and only 9 (14.29%) received sevelamer (a phosphate binding drug). Of total sample; only 7 (11.11%) had calculus kidney disease.

TABLE I: DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF THE

PATIENTS BEFORE TRANSPLANTATION		
Characteristics	Value	
Gender		
Male	42(66.67%)	
Female	21(33.33%)	
Duration of CKD [§] (years), Mean±SD [†]	3.75 ± 2.69	
Median (range)	3(1-12)	
Duration of dialysis (years), Mean±SD	2.86 ± 1.97	
Median (range)	2(1-10)	
Number of sessions/weeks, Mean±SD	2.63 ± 0.48	
Median (range)	3(2-3)	
Diabetes mellitus		
No	44(69.84%)	
Yes	19(30.16%)	
Hypertension		
No	15(23.81%)	
Yes	48(76.19%)	
Coronary artery disease		
No	49(77.78%)	
Yes	14(22.22%)	
Vitamin D treatment		
No	39(61.90%)	
Yes	24(38.1%)	
Sevelamer treatment		
No	54(85.71%)	
Yes	9(14.29%)	
Calculus kidney disease		
No	56(88.89%)	
Yes	7(11.11%)	

^{†:} Standard deviation, §: Chronic kidney disease.

As illustrated in Table II, mean duration of transplantation was $(3.73\pm2.64 \text{ year})$ with range of (1-9 year), mean level of serum PTH was $(203.1\pm30.55 \text{ pg/ml})$ with range of (7.5-1449.5). Mean serum Ca+2 was $(9.0\pm1.75 \text{ mg/dl})$ and mean serum phosphate was $(3.84\pm1.29 \text{ mg/dl})$.

TABLE II: DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF THE PATIENTS AFTER TRANSPI ANTATION

Characteristics	Value
Duration of transplantation (years)	
Mean±SD [†]	3.73 ± 2.64
Median (range)	3(1-9)
Serum corrected calcium (mg/dl)	
Mean±SD	9.0 ± 1.75
Median (range)	8.7(6.3-13.8)
Serum phosphate (mg/dl)	
Mean±SD	3.84 ± 1.29
Median (range)	3.65(1.7-8.5)
Serum parathyroid hormone (pg/ml)	
Mean±SD	203.1±30.55
Median (range)	134.8(7.5-1449.5)

^{†:} Standard deviation.

As illustrated in Table III, the patients included in the study had statistically significant reductions on their blood urea, and creatinine levels and significant increases in their eGFR levels (p-value<0.001) after transplantation, which indicates that they have a functioning graft at the time of the study.

TABLE III: COMPARISON OF PATIENTS' RENAL FUNCTION TESTS BEFORE AND AFTER TRANSPLANTATION

Characteristics	Time	Value	P-value
Blood urea (mg/dl), Mean±SD † Median (range)	Before	215.41±98.57 200(77-511)	0.001*
	After	42.92±18.87 38.5(11.7-108)	- <0.001*
Serum creatinine (mg/dl),	Before	9.97±3.48	
Mean±SD		9.2(4.9-19.5)	< 0.001*
Median (range)	After	1.2±0.41	_
		1.18(0.5-3.15)	
Estimated	Before	6.82±2.67	
GFR§(mL/min.1.73m ²)		6.34(2.48-13.16)	- <0.001*
Mean±SD	After	70.49±27.97	- <0.001
Median (range)		61.4(23.5-179.8)	

 $[\]dagger$: Standard deviation, $^{\$}$: Glomerular filtration rate, *: P-value <0.05 is statistically significant.

As illustrated in Fig. 1, out of 63 patients there was 53 patients (84.10%) with HPT compared to 10 patients (15.90%) without HPT.

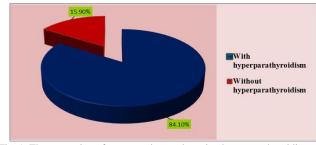


Fig. 1. The proportion of post- renal transplantation hyperparathyroidism.

Fig. 2 shows that in hyperparathyroid patients there was a statistically significant difference between hypercalcemic and normocalcemic patients with (p value < 0.001) and also between hypercalcemic and hypocalcemic patients with (p value<0.001). On the other hand, there was no statistically significant difference between normocalcemic and hypocalcemic patient with (p-value 0.768).

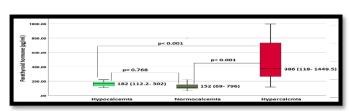


Fig. 2. Median serum level of parathyroid hormone according to serum calcium level.

As illustrated in Table VI, there was a negative correlation coefficient but statistically non-significant between PTH and the eGFR after transplantation.

It also shows a statistically significant positive correlation coefficient between PTH and both serum calcium and phosphate level after transplantation (P<0.001). There was a negative correlation coefficient but statistically non-significant between PTH and the patient's age at time of transplantation.

Fig. 3 represents a linear regression analysis between PTH level and S. Ca⁺², it shows that changes in S. Ca⁺² level after transplantation are caused by parathyroid hormone. The correlation was strong with a statistically significant difference with (p-value <0.001).

TABLE VI: PEARSON'S CORRELATION OF PARATHYROID HORMONE WITH DIFFERENT QUANTITATIVE VARIABLES BEFORE AND AFTER

TRANSPLANTATION				
Variable	Correlation	p-value		
	coefficient			
Estimated GFR [†] before	0.037	0.774		
transplantation				
Estimated GFR after	-0.140	0.275		
transplantation				
Calcium after	0.544	<0.001*		
transplantation				
Phosphate after	0.517	<0.001*		
transplantation				
Age at transplantation	-0.206	0.105		

[†] Glomerular filtration rate, *: P-value < 0.05 is statistically significant.

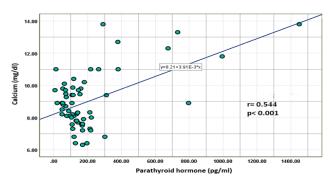


Fig. 3. Linear regression between parathyroid hormone level and serum calcium level.

As illustrated in Table V, all variables are divided into two sets according to their mean value. Before transplantation, there was a statistically significant association between hypertension and HPT with (p-value 0.034) but there was no statistically significant association between HPT and other variables (gender, duration of CKD, duration on dialysis, number of dialysis sessions per week, the eGFR, the presence of DM, the presence of CAD and the use of sevelamer or vitamin D replacement as risk factors for HPT before transplantation).

V. DISCUSSION

In this single center study; we have evaluated 63 patients with successful renal transplantation for persistent hyperparathyroidism and related risk factors. Tertiary hyperparathyroidism was found in 53 patients (84.10%) after transplantation. Mean level of PTH $(203.1\pm30.55 \text{ pg/ml})$ with range of (7.5-1449.5).

In another single-center experience [25], it was found that of 216 adult patients undergoing kidney transplantation, persistent HPT following transplantation was observed in 71 (32.9%) patients.

In our study; only 7(11.11%) patients had calculus kidney disease which is probably related to hypercalciuria. Persistent HPT may cause serious problems such as soft calcification, myopathy, hypertension, hypercalciuria. In particular, hypercalciuria not only causes renal tubular injury but also increases the risk of kidney stone, which is particularly deleterious in a kidney graft [26].

TABLE V: DISTRIBUTION OF RISK FACTORS FOR HYPERPARATHYROIDISM ACCORDING TO PARATHYROID HORMONE BEFORE TRANSPLANTATION

Variable	With	Without	p-
	Hyperparathyroidism	hyperparathyroidism	value
	No. 53 (84.10%)	No. 10 (15.90%)	
Gender			
Male	34(64.15%)	8(80%)	0.329
Female	19(35.85%)	2(20%)	
Duration of			
CKD [†] (years)			
≤4	36(67.92%)	9(90%)	0.156
>4	17(32.08%)	1(10%)	
Duration of			
dialysis (yrs.)			
≤3	37(69.81%)	6(60%)	0.541
>3	16(30.19%)	4(40%)	0.341
Sessions of			
dialysis / week			
≤2	20(37.74%)	3(30%)	0.641
>2	33(62.26%)	7(70%)	0.041
Diabetes			
mellitus			
No	39(73.58%)	5(50%)	0.136
Yes	14(26.42%)	5(50%)	
Hypertension			
No	10(18.87%)	5(50%)	0.034
Yes	43(81.68%)	5(50%)	
Coronary			
artery disease			
No	42(79.25%)	7(70%)	0.519
Yes	4(7.55%)	3(30%)	0.519
Vitamin D			
treatment			
No	31(58.49%)	8(80%)	0.199
Yes	22(41.51%)	2(20%)	
Sevelamer			
treatment			
No	45(84.91%)	9(90%)	0.673
Yes	8(15.09%)	1 (10%)	
Estimated			
GFR [‡] (ml/min)			
≤7	35(66.04%)	6 (60%)	0.713
>7	18(33.96%)	4 (40%)	0.713

[‡] Glomerular filtration rate, †: Chronic kidney disease

In a single center study in Australiadone by Amin TP, et al. [27], the prevalence of hypercalcemia was 15% out of 679 renal transplant patients.

In a study done in a Canadian transplant center by Muirhead N. et al. [5], the point prevalence of hypercalcemia was 16.6% at month 12, and point prevalence of serum (PTH)>10 pmol\L (reference range 1.6-7.5 pmol/L) was 47.6% at month 12. Estimated (GFR) was maintained throughout and was not different between patients with or without hypercalcemia or elevated PTH.

In another study done by Kandil E. et al. [17], 19 of 49 renal transplant patients had persistent HPT and underwent parathyroidectomy after kidney transplants.

In our study; patients were on dialysis for an average period of 2.86±1.97 year prior to transplantation and duration on dialysis before transplantation was not found as a risk factor for persistent HPT.

Similar result was found in the study done by Amin T. P. et al. [27] in which they found that PTH levels did not correlate with duration on dialysis prior to renal transplant.

While in the study done by Myles W. et al. [28], the identified independent predictors of HPT at month 3 after transplant (PTH>65 pg/mL) were greater dialysis vintage (odds ratio 1.44 per each year; 95% CI, 1.05-1.98; P=0.025), and pre-transplant treatment with vitamin D sterols, which was associated with significantly lower risk (odds ratio, 0.29; 95% CI, 0.10-0.87;P=0.028).

In another study done by Yamamoto T. et al. [29], data for 520 patients were analyzed and on multivariate analysis, long dialysis duration (p=0.009, hazard ratio (HR) 1.01) and post- transplant (<2 weeks) high calcium (Ca) (p<0.001, HR 25.04), were significantly identified as risk factors for tertiary HPT. Also, the level of PTH obtained during followup was correlated with the duration of dialysis.

In our study; there was a statistically significant positive correlation coefficient between PTH and both serum calcium and phosphate level after transplantation. So, the predominant cause for hypercalcemia is possibly pretransplantation hyperparathyroidism.

In our study, we found that all 63 patients patients received vitamin D post- transplantation while none of them received calcimemetic treatment and in our transplant center; we found no clear guideline regarding indications of its use. This may be related to its unavailability or because this type of treatment has few unwanted adverse reactions as it may cause significant decrease in PTH and hypocalcemia. Also, cessation of calcimimetic treatment leads to the return of serum calcium and PTH to pre-treatment levels, especially in patients with persistent HPT. In addition cinacalcet may exacerbate bone disease, although serum calcium normalizes [30].

In [25] study; it was found that cinacalcet use pretransplant was significantly associated with reduced posttransplant hyperparathyroidism (15% vs 4.7% respectively,

In our study; eGFR was not found as a risk factor for HPT before transplantation but there was a negative correlation between HPT and eGFR after transplantation which may explain the negative effect of HPT on renal function.

In a study done by Muirhead N. et al. [5], it was found that eGFR was not different between patients with or without elevated PTH.

Also; in a study done by Al-Moasseb Z. et al. [25], there was no association between PTH (3.62±4.16 mmol/L) or adjusted calcium levels (2.51±17 mmol/L) and eGFR at 1year post transplant ($r^2 = 0.23$).

In our study; there was a negative correlation coefficient between PTH and the patient's age at time of transplantation. This means that younger patients are more likely to have persistent HPT after transplantation.

On the contrary, in the study by Jahromi A. H. et al. [31], it was found that elderly patients had an increased risk of developing post-transplant hyperparathyroidism in the first year post transplant (P<0.05).

In our study; hypertension was significantly associated with HPT before transplantation. Our explanation is that hypertension in those patients was mainly caused by ESRD and it keeps being a risk factor for persistent HPT after transplantation. In addition, persistent HPT transplantation may cause serious complications and one of them is hypertension [4].

VI. CONCLUSION

In this single center study; our data indicate that more than 80% of post-renal transplant patients with normal transplant function, have elevated levels of PTH more than one year after transplantation. This may have a major impact on clinical treatment guidelines.

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