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A Prospective Study of Post Renal Transplant Mineral Bone Disorder: A Single Center Experience.

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ABSTRACT

To evaluate sequential changes in biochemical bone parameters, parathyroid hormone (iPTH), and vitamin D levels over a period of 24 weeks after renal transplantation, we studied 52 patients (41 males, with a mean age of 31.98.) who underwent their first renal transplantation without a past history of parathyroid surgery or fractures. Serum calcium, phosphorus, albumin, Serum iPTH and vitamin D levels were measured before transplant, then at 2, 4, 12 and 24 weeks post transplantation. Serum calcium showed a significant increase from 2 to 12 weeks after transplantation, followed by a slight decline until 24 weeks. At the end of 12 and 24 weeks, 6 (11.53%) and 2 (3.8%) patients had hypercalcemia respectively. At the end of 12 weeks only 15.38% (8) patients had hypocalcemia and no patient had hypocalcemia at the end of 24 weeks. Serum phosphorus showed significant decline in the first 4 weeks post transplantation. At the end of 24 weeks 21.2% still had hypophosphatemia. iPTH levels declined rapidly in the first 4 weeks of post transplant period and there after decline slowly till the end of 24 weeks. Baseline iPTH and vitamin D3 levels did not correlate with persistent HPT. Hypovitaminosis D was seen in 16 (30.7%), 8 (15.3 %) and 11 (21.1%) patients at pretransplant, 12, and 24 weeks post transplant respectively. Unlike most studies in literature our patient population experienced lower prevalence of post transplant hypercalcemia, Hypovitaminosis D, and hyperparathyroidism which may have resulted from younger study population and shorter dialysis vintage.

Keywords: Hypercalcemia, Hyperparathyroidism, Hypophosphatemia, Kidney transplantation.

INTRODUCTION

The natural history of parathyroid function after successful renal transplantation (RT) and the factors predisposing to persistent hyperparathyroidism (HPT) are not well established. Despite significant improvement in renal function, nearly 80% of kidney allograft recipients demonstrate persistent HPT during the first post transplant year (1-4). Post transplant HPT is associated with hypercalemia and hypophosphatemia. Post-transplant hypercalcemia may predispose to complications such as calciphylaxis and renal failure (5, 6). The effects of post transplant hypophosphatemia are less clear; however, it has been suggested to affect bone mineralization (7). Knowledge of these data may be helpful in the development of algorithms for optimal surveillance and treatment of HPT after successful RT. The aim of this study was to assess the sequential changes in the biochemical bone parameters, the incidence of secondary HPT during the first 24 weeks after renal transplant.

MATERIALS AND METHODS

Study design and population

This single center prospective observational study was conducted in the Department of nephrology, Kilpauk medical college, Chennai, between April 2017 to and March 2019 and included all kidney transplant recipients during this time period.

Patients older than 18 years and with at least six months of post transplant follow-up were included in the study after obtaining informed consent. Both live and deceased kidney allograft recipients were included. Patients with normal, slow and delayed graft function were included.

Patients who were on active vitamin D3, calcium (Ca) salts, and bisphosphonates after transplantation, graft dysfunction on dialysis at six months post transplantation and those with a past history of parathyroid surgery, spine fracture were excluded.

Procedures, assays and calculations

Serum calcium, serum phosphorus, alkaline phosphatase, serum creatinine and albumin, serum iPTH and 25-hydroxyvitamin D3 levels were measured before transplantation and at 2, 4, 12 and 24 weeks post-transplantation. Serum iPTH and 25-hydroxyvitamin D levels were measured by the electro-chemiluminescence assay. Measured Ca levels were adjusted to albumin levels using Payne's equation: corrected Ca (cCa) = Ca +0.8× (4.0 - Alb (g/dL)) if serum albumin was <4 g/dL. GFR was estimated using CKD EPI equation.

Hypercalcemia was defined as corrected serum calcium levels >10.2 mg/dL, while levels < 8.4 mg/dL were defined as hypocalcemia. Similarly, hyperphosphatemia and hypophosphatemia were defined as serum phosphorus levels >4.5 mg/dL and levels <2.8 mg/dL, respectively. Values of iPTH levels >65 pg/mL were considered compatible with HPT, while levels <15 pg/mL were considered compatible with

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hypoparathyroidism. We considered 25- hydroxyvitamin D levels <30 ng/mL as vitamin D deficiency.

Statistical analysis

The collected data was entered in Microsoft Excel and analyzed using SPSS version 20.0. All the continuous variables are presented as mean and standard deviation. Categorical variables are presented as proportion (percentage). Repeated Measures ANOVA (Analysis Of Variance) was used to find the change in the parameters (albumin, calcium, phosphorous, vitamin D, IPTH, ALP, and Hb) during different time period of assessment (pretreatment, 2 weeks, 4 weeks, 12 weeks and 24 weeks post transplantation).

For all statistical significance analysis, p value <0.05 was taken as significance.

RESULTS

The 52 patients included in the study 41 (78.84%) were males and 11(21.1%) were females. The mean age of the participants was 31.98 ± 7.88. The most common cause of renal failure was chronic glomerulonephritis (CGN) in 39 (75%) patients, followed by diabetic nephropathy (DN) in 9 (17.3%) patients and chronic interstitial nephritis (CIN) in 7 (13.5%) patients. 51 (98%) patients were on renal replacement therapy prior to transplantation. 38 (73.07%) patients were on calcium based phosphate binder, 5 (9.6%) patients were on non-calcium-based phosphate binder (sevelamer carbonate). 6 (11.5%) patients received active vitamin D (calcitriol). None of them was on lanthanum and cinacalcet. The baseline demographic characteristics and laboratory values of the patients are summarized in Table 1.

Variables	Mean ± SD	Range
Age (years)	31.98±7.8	19-49
Duration of chronic kidney disease (years)	2.6±1.2	0.6-4
Duration on dialysis (months)	17.50±8.4	4-36
Serum calcium (mg/dL)	8.06±0.68	6.8-9.4
Serum phosphorus (mg/dL)	5.43±1.21	2.5-8.0
Serum alkaline phosphorus (IU/L)	122±41.2	56-198
Serum albumin (mg/dL)	3.2±0.42	2.1-3.9
iPTH (pg/mL)	372.5±206	59-895
25 (OH)D3 (ng/mL)	38.6±13.8	12-92

Table 1: Baseline characteristics.

Induction agent used was Basiliximab in 26(50%), ATG in 12(23.1%) and no induction was used in 14 (26.9%). All patients received corticosteroids, calcineurin inhibitors (tacrolimus) and antimetabolite (MMF) as maintenance immunosuppression therapy for six months.31 (59.6%) patients had NGF, 14 (26.9%) patients had DGF and 7 (13.5%) had SGF. A total of 16 (30.7%) experienced biopsy proven acute rejection, 11 (68%) patients had acute cell mediated rejection (ACR) and 5(32%) had acute antibody mediate rejection (ABMR).

Serum calcium showed a significant increase from 2 to 12 weeks after transplantation, followed by a slight decline until 24 weeks. At the end of 12 and 24 weeks, 6 (11.53%) and 2 (3.8%) patients had hypercalcemia respectively. At the end of 12 weeks only 15.38% (8) patients had hypocalcemia and no patient had hypocalcemia at the end of 24 weeks.

Serum phosphorus showed significant decline in the first 4 weeks post transplantation (Pi pretransplantation 5.438 ± 1.21 mg/dL, 4 weeks post transplant 3.8 ± 0.9 mg/dL). At the end of 24 weeks 21.2% still had hypophosphatemia.

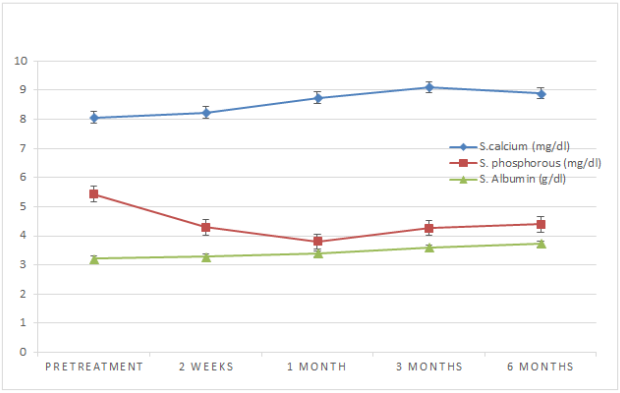

Figure 1: Sequential changes in important biochemical parameter

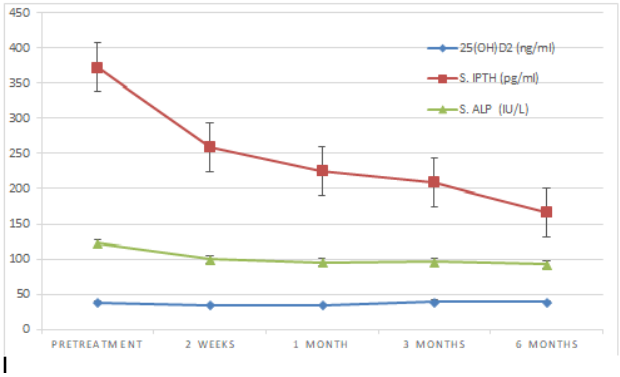

Figure 2: Sequential changes in important biochemical parameters.

The mean iPTH values were 372.57 ± 206.72, 225 ± 152.2, 166.53 ± 108.38 in the pretransplantion period, at 4 and 12 weeks post transplantation. iPTH levels declined rapidly in the first 4 weeks of post transplant period and there after decline slowly till the end of 24 weeks. Persistent HPT was seen in more patients with serum creatinine > 1.5 mg/dl. Baseline iPTH and vitamin D3 levels did not correlate with persistent HPT. Hypovitaminosis D was seen in 16 (30.7%), 8 (15.3 %) and 11 (21.1%) patients at pretransplant, 12, and 24 weeks post transplant respectively.

Patient group	Persistent hyperparathyroidism

	12 weeks (n = 9)	24 weeks (n = 4)
iPTH at baseline <150 pg/mL iPTH at baseline 150-300 pg/mL iPTH at baseline >300 pg/mL	0 3/17(17.64%) 6/30(20%)	0 2/17(11.7%) 2/30(6.66%)
Serum creatinine >1.5 mg/dL Serum creatinine <1.5 mg/dL	6/8 (75%) 2/44 (4.5%)	4/8 (50%) 0
Low Vit D3 Normal Vit D3	0 9/44 (20.4%)	0 4/41(9.75%)

Table 2: Factors correlating with persistent hyperparathyroidism.

DISCUSSION

This study is one of the few studies that have evaluated the natural history of CKD–MBD parameters in south India after kidney transplantation. Many studies have reported hypercalcemia to be a common complication after kidney transplantation. Hypercalcemia in early post transplant period may cause renal dysfunction by means of volume contraction and by reducing perfusion to the allograft by direct vasoconstriction (8). In our study the incidence of hypercalcemia was 9.6% and 3.8 % at 12 and 24 weeks post transplant respectively. Rathi et al. reported an incidence of 17.5% and 8% at 12 and 24 weeks respectively (9) . The incidence is lower than that reported in most studies, and may be a result of lower baseline serum calcium levels. Baseline serum calcium reported by Kawarazaki et al (12) and Rathi et al. (9) was 9.7 mg/dl and 8.7 mg/dl respectively which were significantly higher than our study population. However the peak serum calcium level was achieved after 2 months similar to Rathi et al. (9) and Christensen et al.(2).

Serum phosphorus showed significant decline in the first 4 weeks post transplantation. At the end of 24 weeks 21.2% still had hypophosphatemia. The factors responsible for the hypophosphatemia in the immediate post-transplant period are decreased phosphate reabsorption due to tubular defect and the phosphaturic effect of the persistent HPT. (10). Rathi et al (9) reported an incidence of 25% hypophosphatemia at the end of 24 weeks similar to our study.

Our patients experienced a rapid fall in iPTH levels during the first 4 weeks post transplant, there after the decline continued but at a slower rate. Only 17.3% (n = 9) and 7.69 % (n = 4) of patients had HPT at the end of 12 and 24 weeks respectively in our study. The prevalence reported in literature, is highly variable, ranging from 27–75 %(10, 11). In the study by Rathi el al. (9) about 42.7% patients at 12 weeks and 52% patients at 24 weeks had persistent HPT. Lower prevalence of HPT in our study may be a result of lower baseline iPTH levels, normal baseline vitamin D3 levels and shorter duration of dialysis in our study population. Moreover baseline iPTH and vitamin D3 levels did not correlate with HPT. However patients with incomplete normalization of renal function were more likely to experience HPT.

Although one might have expected more severe pretransplant hyperparathyroidism to be associated with more severe hyperparathyroidism after transplantation, by stratifying transplant recipients according to their baseline pretransplant PTH levels, we were able to show minor differences in PTH and other mineral metabolites after the initial 3 months after transplantation, and high rates of persistent hyperparathyroidism in both strata.(8) These results suggest that clinical surveillance for persistent hyperparathyroidism and hypercalcemia should not be reserved exclusively for individuals with high pretransplant PTH levels. We also observed reductions in markers of bone turnover in the early post transplant period, especially among recipients with high pretransplant PTH levels.

Limitations of our study include the small sample size, which does not allow us to generalize the results. Short dialysis vintage and younger patient population may be reason for lower incidence of post transplant HPT. Further studies with a larger sample size would allow inference with greater confidence. Additionally FGF 23 levels were not measured in our study.

CNCLUSION

Despite the improvement in the knowledge of the CKD-MBD and the enhanced armamentarium to manage these disorders in the pre-transplant period, persistent HPT and consequent hypercalcemia and hypophosphatemia remain significant problems in the short term in post-kidney transplant patients.

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