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Pre and Post Renal Transplant Bone Disease: A Prospective Study.

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Abstract: ***Introduction****:Renal transplants have been performed over 40 years, and there is now long-term data about the bone disease in these patients. Although many aspects of Renal osteodystrophy improve, the bone density and strength may worsen due the adverse effects of immunosuppression.* ***Material & Methods****: A total of 45 patients who underwent first renal transplantation at our institute over 2 year period (January 2005 to December 2006) were recruited in the study.All the above patients were followed from 3 months before till 6 months after renal transplantation. All patients were subjected to lumbo sacral dual energy x ray absorptiometry (DEXA SCAN) one month before and 6 months after renal transplantation along with para thyroid hormone assay.****Results****: In 77 % of patients the cause of end stage renal disease was Chronic glomerulo nephritis and chronic interstitial nephritis constituted 23% . There is a trend towards osteoporosis (25.6%) and osteopenia (25.6%) post renal transplant and normal bone mineral density was found only in 48.8% of patients. Low turnover bone disease was the predominant bone disease in the post renal transplant state.High cumulative steroid dose of more than 4 grams was associated with osteoporosis and osteopenia.****Conclusions****: Metabolic bone disease is common in pre and post-transplant states.Only 49% had normal bone mineral density by DEXA post-transplant.Remaining 51% had osteopenia or osteoporosis probably due to high doses of gluco corticoid use & persistence of hyper parathyroidism.*

Keywords*: renal transplant, clinical, biochemical, skeletal abnormalities*

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I. Introduction

Renal transplants have been performed over 40 years, and there is now long-term data about the bone disease in these patients. Although many aspects of Renal osteodystrophy improve, the bone density and strength may worsen due the adverse effects of immunosuppression. Symptomatic fractures are reported in 4 to 11% of patients, with average first fracture 2 to 5 years after transplantation.43 Bone density decreases in patients after renal transplantation, although there is some variation in reported rates of loss. This may reflect the underlying variability in types of renal osteodystrophy that exist prior to transplantation. Ongoing studies suggest that the rate of loss is greatest in the first year, but after several years the rate of loss is about 1-2%/year [1].

Bone biopsies frequently show abnormalities after kidney transplantation. The findings are variable, which is not surprising because there is such a wide spectrum of abnormalities before transplantation. Bone formation and resorption are often very high before transplantation. Thus, these rates may decrease after transplantation and still be higher than normal[2]. The osteoid surface is higher in those taking cyclosporine. Osteomalacia is not generally encountered after transplantation, even in cases of hypophosphataemia[3]. The bone density may reflect differences in bone histology; in mixed or hyperparathryoid disease the spine BMD z-score was -0.3, in Adynamic disease is was -0.4, and in those with normal histology it was +0.8.

Hyperparathyroidism usually improves after transplantation, since the new kidney can excrete phosphate and produce 1, 25-dihydroxyvitamin D in appropriate amounts. About 1/3 of patients develop hypercalcemia after a transplant; this persists in 7% and requires parathyroid surgery in about 2% 37 .The PTH may continue to gradually decreasefor 7 years after surgery. Higher pre-transplant PTH and longer time on dialysis predict higher post-Transplant PTH. The persistence of high PTH is related to the size of the parathyroid glands. Each parathyroid cell continues to secrete a basal level of PTH, and even with maximal metabolic inhibition, the total PTH secretion may be too high. This problem may resolve after several years, but some patients with hypercalcemia require partial parathyroidectomy.

The late-term increase in PTH may be related to corticosteroids, which may cause secondary hyperparathyroidism[3]. Osteitis fibrosis may persist in the bone, but in other cases it may resolve. Radiographic studies of hyperparathyroidism also may improve after transplantation. In some of the larger studies PTH levels are directly correlated to decreases in bone density.

Literature pertaining to post renal transplant bone disease from our country is sparse. Hence the present prospective study was undertaken involving biochemical and radiological parameters (Calcium, Phosphorus and ALP, PTH, DEXA).

The Objectiveof the study was to evaluate clinical, biochemical and skeletal abnormalities in live related renal transplant patients before and after renal transplantation

II. Material And Methods:

A total of 45 patients who underwent first renal transplantation at our institute over 2 year period (January 2005 to December 2006) were recruited in the study. All patients who were on prolonged steroid intake with significant steroid side effects, those with prolonged intake of drugs that interfere with bone metabolism like OCP, sex hormones etc. were excluded from the study.

All the above patients were followed from 3 months before till 6 months after renal transplantation. A detailed history regarding symptoms of bone disease, past history of bone disease, duration of hemo dialysis and treatment was taken. At enrollment all patients were subjected to routine biochemical investigations like renal function tests, serum albumin, serum calcium, phosphorus and alkaline phosphatase. X ray lumbo sacral spine and X ray hands were taken to look for any evidence for renal osteo dystrophy. Every month serum calcium, phosphorus, ALP, serum albumin was done in all patients pre and post transplant. Serum calcium was corrected for corresponding albumin levels. To calculate the cumulative dose of prednisone, the dose of methyl prednisolone was converted to an equivalent dose of prednisone by multiplying it by 1.25 [4].

Serum intact para thyroid hormone assay was done in all patients by Electro chemiluminiscence assay one month before and 6 months after renal transplantation.

All patients were subjected to lumbo sacral dual energy x ray absorptiometry (DEXA SCAN) one month before and 6 months after renal transplantation along with para thyroid hormone assay.

Fasting blood samples were obtained for serum creatinine, calcium, and phosphate and serum alkaline phosphatase assays.Creatinine assay was done by Kinetic alkaline picrate method; calcium was estimated by using Cresolphtaleincomplexone and phosphate by Ammonium molybdate and were measured by standard automated techniques.Serum alkaline phosphatase assay was done by Para nitro phenol method (normal range 10-13 KAU/L). Albumin assay was done by Bromo cresol green method and all measurements were done by standard automated techniques

PTH assay:

Intact PTH was measured using the QuiCk-IntraOperative intact PTH assay (Nicholas Institute Diagnostics).This immune chemiluminiscence assay uses two goat polyclonal antibodies against PTH, one coated on a polystyrene bead and another labeled with an acridinium ester. Blood is first drawn from the patient and transferred to an EDTA- containing Vacutainer tube (3mL) and gently mixed.Aliquots of 700µL of blood are pipetted in to two micro centrifuge tubes and centrifuged for 30 seconds 3000g. Plasma (200µL) is then pipetted into duplicate 12 x 75-mm glass tubes, and100µL of the acridinium-labeled signal antibody and the capture antibody-coated polystyrene bead are added. Tubes are incubated at 450 C for 7min while shaking at 400rpm in heater-shaker apparatus (Quick Pak Kinetic Enhancer).After incubation; beads are washed three times with 2mL of saline. Beads are transferred to clean12 x 75 tubes and counted for 2 seconds in a single-tube luminometer (QuiCk-PakQuantifier).The total time to perform this assay ,including specimen processing, is12 to14min.Approximately 1hour is required in the laboratory to perform instrument performance checks, to generate the calibration curve, and to assay quality-control material.

DEXA:

DEXA scan was done using GE lunar prodigy advance bone densitometer one month prior and 6 months after renal transplantation. On the day of the scan patient should not take calcium supplement.. For the test, a patient lies down on an examining table, and the scanner rapidly directs x-ray energy from two different sources towards the bone being examined in an alternating fashion at a set frequency. The mineral density of the patient's bone weakens or prolongs the transmission of these two sources of x-ray energy through a filter onto a counter in a degree related to the bone mass present. The greater the bone mineral density, the greater the signal pick on the photon counter. The use of the two different x-ray energy sources rather than traditional radioisotope studies greatly enhances the precision and accuracy of the measurements. Vertebral bone density values represented the average of four vertebrae, L1 to L4.

6 patients expired with in the first 6 months after renal transplantation. And these were excluded from the study. So a total of 39 patients were analyzed in the study. All patients were analyzed for Type of bone disease, Pre and post-transplant bone mineral density, Factors influencing bone mineral density and Para thyroid hormone levels. Patients wereclassified into low, high, turnover bone disease on the basis of clinical manifestations, biochemical and hormonal parameters. . All the patients were divided into 3 groups as normal, osteopenia, osteoporosis on the basis of T scores on DEXA scan. Pre renal transplant and post renal transplant Biochemistry, DEXA values, Para thyroid hormone levels, Type of bone disease were compared. Correlation between steroid dose and Bone mineral density were done. Results were analyzed with SPSS Windows version 10.0.

III. Results

A total of 45 patients who underwent renal transplantation at our institute over 2 year period (January 2005 to December 2006) were included and were followed from 3 months before till 6 months after renal transplantation.Six patients expired with in the first 6 months after renal transplantation and these were excluded from the study. So a total of 39 patients were analyzed in the study, out of whom 37 were males and 2 females with mean age being 28.2 years (16-42 years). Bone pains were the most common clinical presentation in pre and post-transplant states followed by myopathy.

Donor characteristics: Majority of donors were females with mother (in 22 cases) being the most common. Mean age of thedonor was 46 + 7.7 years.

Basic disease: In 77 % of patients the cause of end stage renal disease was Chronic glomerulo nephritis and chronic interstitial nephritis constituted 23% . One patient has multi cystic kidney disease and Reflux nephropathy was seen in one.

Treatment:Pre renal transplant- Pre transplant all patients received hemodialysis with average of 12 hours per week . Mean Duration before renal transplantation was 4.7 + 0.9 Months with average number of hemodialysis being 41.

Dialysate calcium: 3.5 meq/l and Dialysate calcium in patients with hypercalcemia 2.5 meq/l

Treatment before renal transplantation:Calcium acetate 1500 mg/day (1.5 to 3 gms / day) Calcitriol: 0.25 – 0.5 µg /day.

Post renal transplant:The patients were on one of the following 3 immuno suppressive protocols post renal transplant .

1.Cyclosporine, Azathioprine and Steroids

2.Tacrolimus,Azathioprine and Steroids

3.Mycophenolate mofetil and Steroids

All patients received methyl prednisolone 1 gram immediate post-transplant over 3 days followed by oral steroids 0.5mg/kg day . Five patients developed acute rejection and received 3 additional doses of Methyl prednisolone 1 gram each .

Cumulative dose of steroid in patients without acute rejection: 3.82 gms (3-4.5gms) Cumulative dose of steroid in patients with acute rejection:7.79gms(6.75-.35gms)

Table 1: Biochemical parameters pre and post-transplant

	Pre transplant	**Post-transplant**	**p value**
Mean corrected calcium (mg/dl)	7 .32 ± 0.53	8.53 ± 0.61	0.0427
Mean phosphorus(mg/dl)	5.88 ± 1.20	4.99 ±1.25	0.038
Mean SAP(KAU/l)	19 ± 7	12 ± 8.8	0.297
Mean Ca x P product (mg^2 / dl^2)	54.36 ± 9.91	42.56 ± 9.99	0.060
Mean PTH(pg/ml)	165	91	0.862

Bone mineral density: There is a trend towards osteoporosis (25.6%) and osteopenia (25.6%) post renal transplant and normal bone mineral density was found only in 48.8% of patients.

Parathyroid hormone levels: Pre transplant mean PTH was 165 + 90 pg/ml and post transplant mean PTH was 91+ 43 pg/ml. Only 50% had normal PTH at 6 months post renal transplant . 5% of patients had PTH level of more than 4 times normal.

Type of bone disease:Though bone biopsy was not done , on the basis of clinical features and biochemical parameters bone disease was arbitrarily divided into low, high turnover bone disease. 35 % of patients had high turnover bone disease and 25% had low turnover bone disease pre transplant. Low turnover bone disease was the predominant bone disease in the post renal transplant state.

Table 2: Type of bone disease

	PRE TRANSPLANT	POST TRANSPLANT	p value
NORMAL	15(38.46%)	20(5.28%)	0.012
HTBD	14(35.89%)	2(5.12%)	0.033
LTBD	10(25.64%)	17(43.58%)	< 0.001

With regards to relation between steroid dose and bone mineral density post renal transplant, High cumulative steroid dose of more than 4 grams was associated with osteoporosis and osteopenia.

Table 3: Relation between steroid dose and bone mineral density post renal transplant

STEROID DOSE	Osteopenia	Osteoporosis	Normal
< 4 grams (4)	1	0	3
4-6 grams (30)	9	5	16
> 6grams (5)	0	5	0

And with regards to relation between Native kidney disease and bone mineral density pre transplant, Osteopenia and osteoporosis were commoner in chronic interstitial disease (33% & 22% respectively) than chronic glomerulonephritis.

IV. Discussion

In our study all subjects received allografts from live related donors. The study population consisted of predominantly males. Mean age of the patient was 28.2 + 7.2 years. Majority of donors were mothers with mean age of 46 + 7.7 years.

In our study chronic glomerulo nephritis (CGN) was the predominant cause of ESRD followed by chronic interstitial nephritis (CIN). Osteopenia and osteoporosis were more common in CIN than CGN patients with significant worsening of osteopenia in post renal transplant state. Abnormal BMD was present in 20 % of CGN and 55% of CIN patients in pre renal transplant state.

Bone pains (30 %) were the predominant clinical manifestation in our study in pre renal transplant state. Myopathy was seen in 20% and pruritus in 8%. None of the patient had fractures pre transplant. This was similar to study by Elisa et al [5] in which 50%patients had bone pains, 30% had myopathy, 2% had pruritus and none developed fractures or deformities.

There was a significant improvement in the clinical features post renal transplant with 50% showing improvement in symptoms. One patient however developed avascular necrosis in the post renal transplant state probably related to high dose of steroids given for acute rejection and presence of low turnover bone disease in the pre transplant state.

All patients received calcium carbonate and vitamin D pre transplant .Calcium supplementation and vitamin D were not given post renal transplant. Mean duration of dialysis was 4.7 months in our study which was less when compared to study by Elisa et al [5].

Mean cumulative dose of steroid was 4.337 grams (3 - 8.35grams) .It was 5.208grams (3.470 – 17,210) in Elisa et al study 54. Cumulative dose of steroid in patients without acute rejection was 3.82 gms (3 - 4.5gms) and in patients with acute rejection was 7.79 grams (6.75 - 8.35gms). All patients who developed acute rejection had osteoporosis post-transplant. This is probably due to high dose steroids used for treating acute rejection. This high dose steroids is also responsible for persistence of low turnover bone disease in post-transplant state

Mean corrected serum calcium was low and mean serum phosphorus and i PTH were high in the pre renal transplant state. 56% of patients were hypocalcemic and 64 % patients were hyper phosphatemic in the pre transplant state. Mean PTH pre transplant was 165 pg / ml. There was a significant improvement in the post-transplant biochemistry with 74% showing normal serum calcium and 79% showing normal serum phosphorus.

Profound hypophosphatemia may develop in the first few months (3-6) after renal transplantation and in patients with excellent graft function up to 25% may develop it [6,7,8,9]. Most common causes are persistent secondary hyper parathyroidism, vitaminD deficiency, glucocorticoid use and phosphaturia. But only 2.5 % patients developed post renal transplant hypo phosphatemia in our study unlike in other studies.

In our study 38.76% of patients had normal PTH, 28% had 0 -2 times normal, and 32 % had more than twice normal PTH pre renal transplant. PTH levels uniformly decreases post renal transplant as shown in various studies but actual PTH remains elevated despite absolute decline [10,11,12] .Our study revealed 50% patients had normal PTH, 34 % has 0-2 times normal and 16% had more than twice normal PTH post renal transplant. Even though there is persistence of hyperparathyroidism in 50% of patients post renal transplant, only 15% had increase in PTH levels above pre transplant values. There is decrease in absolute level of PTH post-transplant but PTH remained above normal physiological range in all patients similar to other studies [5, 10, 11].

Low BMD at hip, spine, distal radius is common in patients with CKD. Female gender, prolonged duration of hemo dialysis, high PTH, lower BMI and previous renal transplantations are associated with this. After renal transplantation it is shown that recipients lose BMD rapidly in the first 6 months. Females lose bone mass from lumbar spine and males from femoral neck [13]. Gluco corticoids and cyclosporine are implicated but role of later is controversial [14]. At 3 months Almond et al [15] noted 3.93 % decrease in femoral neck BMD and 6.8 % decrease in lumbar spine BMD in male renal allograft recipients.

Our study revealed 72 % patients had normal BMD by DEXA pre renal transplant while 23 % had osteopenia and 5% had osteoporosis .There was a trend toward increase in osteopenia and osteoporosis post renal transplant with 25% showing osteopenia and another 25% showing osteoporosis.High cumulative steroid dose was the main culprit. 50 % of patients with osteoporosis received 4-6 grams of steroids.There is no significant correlation between BMD and PTH levels. In general patients with osteoporosis tends to have mean high PTH.

Even though bone biopsy was not done in our study we divided our patients into low turnover and high turnover bone diseases based on clinical features, biochemical and serum intact parathyroid hormone levels.

Elisa et al [5] studied 20 patients 3 months prior to and 6 months after renal transplantation with bone histo morphometry and their results showed LTBD in 60 % of patients, HTBD in 10 %, Mixed bone disease in 15%, Insignificant mild disease in 15 % prior to renal transplantation .Forty five percent of pre transplant LTBD patients showed improvement in bone turn over. This is most likely related to improvements in calcitropic hormones. Fifty five percent (55 %) of LTBD patients had persistence of LTBD Post renal transplantation. All patients with mild disease, 30 % of mixed bone disease and 50% of HTBD patients converted to low turnover bone disease. This may be due to high doses of gluco corticoids.

In our study 25 % had LTBD and 35 % had HTBD in pre transplant state. Predominant bone disease post-transplant was LTBD (43.58%). There was persistence of LTBD in 80%, 35 % of HTBD are converted to LTBD and 25 % of normal patients developed LTBD.14.28% of HTBD patients had persistence of HTBD, 35 % converted to LTBD post renal transplant.

Schreiber PW et al[16] observed that vitamin D levels did not differ significantly between peri-transplant (median 32.5nmol/l) and 6 months post-transplant (median 41.9nmol/l; P = 0.272). Six months post-transplant median 1, 25-(OH)2 vitamin D levels increased by >300% (from 9.1 to 36.5ng/l; P<0.001) and median intact parathyroid hormone levels decreased by 68.4% (from 208.7 to 66.0 ng/l; P<0.001). Median β-Crosslaps (CTx) and total procollagen type 1 amino-terminal propeptide (P1NP) decreased by 65.1% (from 1.32 to 0.46ng/ml; P<0.001) and 60.6% (from 158.2 to 62.3ng/ml; P<0.001), respectively.

A review literature by Stuart M et al[17] found that parathyroidhormone levels decreased significantly during thefirst 3 months after transplant but typically stabilized at elevatedvalues after 1 year. Calcium tended to increase aftertransplant and then stabilize at the higher end of the normalrange within 2 months. Phosphorus decreased rapidly towithin or below normal levels after surgery and hypophosphatemia,if present, resolved within 2 months. Low levels of1,25(OH) 2 vitamin D typically did not reach normal values

V. Conclusion

Metabolic bone disease is common in pre and post-transplant states.Most patients had hypocalcaemia and hyper phosphatemia pre transplant, which tended to normalize by 6 months post-transplant.Post-transplant hypophosphatemia was not a significant problem and seen only in 2.5% of patients. Calcium phosphorus product an important marker for vascular calcification was not significantly elevated in our patients. Half of patients had persistent high PTH post-transplant at 6 months.Only 49% had normal bone mineral density by DEXA post-transplant.Remaining 51% had osteopenia or osteoporosis probably due to high doses of gluco corticoid use & persistence of hyper parathyroidism.Predominant bone disease post-transplant was low turnover bone disease.

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