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Research Article

A STUDY ON THE METABOLIC BONE PROFILE OF ADULT ONSET NEPHROTIC SYNDROME PATIENTS

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A R T I C L E I N F O

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Bone mineral density at 0, 3 and 6 months (BMD, BMD0, BMD3 and BMD6), Glucocorticoids (GC), Prednisolone(PRED),Tacrolimus (TAC), T score at 0, 3 and 6 months (T0, T3, T6)

A B S T R A C T

Background: Adult onset nephrotic syndrome patients following primary glomerular diseases receive one or more immunosuppressive agents. Glucocorticoids and Tacrolimus are the most commonly used agents in nephrotic syndrome.It is widely known that glucocorticoids induce and accelerate osteoporosis. High-dose glucocorticoids are administrated daily to patients in the acute phase of nephrotic syndrome in both adult and children. Tacrolimus,a calcineurin inhibitor, commonly used in the post renal transplant setting is being used as a steroid sparing agent in adult onset nephrotic syndromes.
Materials and Methods: A total of 46 patients of Adult onset nephrotic syndrome patients were studied.25 of them were on prednisolone regimen at1mg/Kg body weight/day, as per KDIGO guidelines and 21 were on Tacrolimus 0.075 mg/Kg/day in two divided doses regimen. Bone mineral density (BMD) was studied at the lumbar vertebral level (L1-L4) by BMD DEXA Scan at 0, 3 months and 6 months.
Results: Our study revealed the deleterious effect of glucocorticoids on the bone health of young individuals. Tacrolimus has also caused significant loss of BMD in the study subjects as has been shown in the post transplant settings in various studies.
Conclusion: It could be inferred that inspite of calcium and vitamin D supplementation high-dose glucocorticoids as well as Tacrolimus rapidly decrease patient's basal bone mineral density (BMD).

INTRODUCTION

Nephrotic syndrome in adults is defined as proteinuria more than 3.5 g/1.73 m^2 with hypoalbuminemia, edema and hyperlipidemia. It is a common chronic disorder characterised by alterations of permselectivity at the glomerular capillary wall, resulting in its inability to restrict the urinary protein loss. Nephrotic patients, 18 years onwards, are considered as candidates of adult onset nephrotic syndrome. Glucocorticoids are still the first line treatment for most primary glomerular diseases. Steroid sparing drugs like Tacrolimus, cyclosporine, mycophenolate mofetyl and rituximab are also used in different types of primary glomerular diseases. Steroid therapy affects particularly the axial skeleton and the proximal femur.

The earliest changes of steroid-induced bone loss can be detected in the lumbar spine (preferably lateral position) [1].Glucocorticoids induce a biphasic bone loss with a rapid initial phase of ~10–15% during the first few months and a slower phase of ~2–5% annually[2]. Steroids not only reduce the lifespan and promote the apoptosis of osteoblasts and osteoclasts but also decrease the recruitment of osteoblasts and osteoclasts from progenitor cells[1].

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During long-term (>3 month) use of steroids (>7.5 mg prednisone) bone loss occurs in 50% of patients, osteoporotic fractures in 25% of patients and osteonecrosis in some patients[2]. There have been studies in children of idiopathic nephrotic syndrome for clinical, biochemical and radiological evidence of metabolic bone disease but studies in adult onset nephrotic syndrome on therapy are lacking [3, 4]. Osteoporosis is a silent metabolic bone disease that increases risks for future fractures. At present, BMD, as measured by Dual Energy X-Ray Absorptiometry (DEXA) provides the measure of bone health in less than 40 year olds. The young-normal reading, known as the T-score, compares bone density to the optimal peak bone density of a healthy young adult (30 years old) of the same sex. The T-score determines fracture risk, which increases as bone mineral density falls below young-normal levels 5, 6. A Z-score compares your bone density to the average bone density of people your own age and gender.

WHO Definitions of Osteoporosis Based on Bone Density Levels

- Normal: Bone density is within 1 SD (+1 or -1) of the young adult mean.
- Low bone mass (osteopenia): Bone density is 1 to 2.5 SDs below the young adult mean (-1 to -2.5 SD).

- Osteoporosis: Bone density is 2.5 SDs or more below the young adult mean (less than -2.5 SD).
- Severe (established) osteoporosis: Bone density is more than 2.5 SDs below the young adult mean and one or more broken bones (osteoporotic fractures) has occurred [7].

Many well-controlled prospective studies with DEXA, particularly in the elderly women, indicate that the risk of fracture almost doubles for each SD reduction in BMD [7, 8]. Heaney Robert P stated that each drop of about 11% to 12% in bone density approximately doubles fracture risk [9]. Tacrolimus (FK506), a calcineurin inhibitor, was demonstrated to cause bone loss in experimental animals, however, in contrast, in liver transplant recipients, tacrolimus has been associated with a significant higher femoral neck BMD as compared with cyclosporine, after two years of transplantation [10, 11].

MATERIALS AND METHODS

All newly diagnosed adult onset nephrotic syndrome patients visiting Nephrology department in Institute of Postgraduate Medicine and Research, Kolkata were studied from February 2016 to December 2017.

Study Design: It was a single centre, hospital based prospective, observational study.

Study Population: The study population was drawn from all nephrotic syndrome patients attending the nephrology outpatients department of a tertiary care hospital, Institute of Postgraduate Medicine and Research, Kolkata.

Inclusion criteria: Patients of either sex with newly diagnosed adult onset nephrotic syndrome owing to primary glomerular disease diagnosed after renal biopsy.

Age: 18 years to 60 years

Exclusion criteria

1. Diabetic individuals
2. Secondary glomerular diseases
3. Past h/o treatment with steroids or other immune suppressives
4. H/O intake of medicines like Levo- thyroxine, bisphosphonates
5. Hyperthyroid patients
6. Post menopausal women
7. MDRD eGFR <60 ml/min to rule out CKD-MBD
8. Chronic obstructive pulmonary disease
9. Pregnancy
10. Refusal to undergo biopsy for diagnosis
11. Patients not requiring immunosuppresion at start of study post biopsy.

Study methodology: All nephrotic syndrome patients fulfilling our inclusion and exclusion criteria, attending the nephrology outpatients department of a tertiary care hospital, Institute of Postgraduate Medicine and Research, Kolkata, underwent full general physical examination, baseline investigations, coagulation profile, viral serologies and renal biopsy after informed consent for baseline biopsy and repeated BMD measurements and follow up visits. The biochemical markers including baseline renal and liver function tests, serum calcium corrected for hypoalbuminemia, vitamin D level and 24 hour urinary protein estimation were assessed at baseline, at 3 months and earlier as necessary.

Primary outcome: To study the BMD and T score by DEXA-BMD at the lumbar spine (L1-L4) in patients of primary glomerular diseases at 0, 3 months and 6 months after onset of therapy with steroids or tacrolimus.

Secondary outcome: Correlation of 24 hour urine protein with BMD at 3 months and correlation of cumulative prednisolone dose with BMD at 3 months.

All treatment naive patients were given Prednisolone or Tacrolimus alternately as per serial order of outpatients department number. The patients in the steroid group were initiated on oral prednisolone at a dose of 1 mg/kg/day (maximum dose 80 mg/day) as a single daily dose. Patients who did not achieve complete remission of proteinuria were continued on prednisolone for 16 weeks to declare primary steroid resistance. Those achieving complete remission were tapered over 6 months. The TAC group patients were initiated on oral TAC capsules at a dose of 0.075 mg/kg/day in two divided doses 12 h apart. A trough level of 5 to 8 nanogram/millilitre was maintained. It was continued for 12 months.Tacrolimus was stopped after 6 months if the patients did not achieve complete remission (<0.3G/day or <300milligram/gram) or 50% decline in proteinuria. All the patients in both groups received calcium and calcitriol combinations (500 mg elemental calcium with 250IU Vitamin D3) twice daily. Antihypertensive drugs like angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers or nondihydro- pyrolidine calcium channel blockers were given to maintain blood pressure levels if found hypertensive during the study period.

BMD at the lumbar vertebra level of L1-L4 was assessed at 0, 3 months and again at 6 months. BMD was assessed with LUNAR DPX DXA SYSTEM (SOFTWARE VERSION: 9.30) manufactured by GE Healthcare.

***Statistical Analysis*:** Statistical analysis was performed by Statistical Package for Social Science (SPSS) software 20.0.1 (SPSS Inc., Chicago, IL, USA) and GraphPad Prism version 5 (La Jolla California USA, www.graphpad.com). Data have been summarized as mean and standard deviation for numerical variables and count and percentages for categorical variables. Student's independent sample's t-test was applied to compare normally distributed numerical variables between groups; unpaired pro-portions were compared by Chi-square test or Fischer's exact test, as appropriate.

RESULTS

A total of 46 patients of Adult onset nephrotic syndrome patients were studied.25 of them were on prednisolone and 21 were on Tacrolimus.

Demographic profile

Table 1 Distribution of mean age, height, weight, calcium and vitamin D

	Number	Mean	SD	Minimum	Maximum	Median
Age(years)	46	30.5196	9.6529	20.0000	50.6000	26.2000
Height(centimeter)	46	158.4913	8.4956	140.0000	173.8000	158.3500
Weight(kilogram)	46	54.9783	9.9230	40.0000	81.0000	55.0000
Calcium (milligram/deciliter)	46	8.6343	.8462	6.2000	10.2000	8.8000
Vitamin D (nanogram/milliliter)	46	14.5476	7.4404	4.0000	40.9000	14.0500

Table 1 show that the mean age (mean± s.d.) of patients was 30.5196 ± 9.6529 years. The mean height (mean± s.d.) of patients was 158.4913 ± 8.495 cm. The mean weight (mean± s.d.) of patients was 54.9783 ± 9.9230 kg. The mean calcium (mean± s.d.) of patients was 8.6343 ± .8462. The mean vitamin D (mean± s.d.) of patients was 14.5476 ± 7.4404. 16 (34.8%) patients were female and 30(65.2%) patients were male.

There was no significant difference across gender groups (p =0.885).

Decrease in BMD with age was not statistically significant (p=0.088).

Distribution of mean vitamin D vs. drug was also not statistically significant (p=0.4223).

Primary outcome

Table 2 Distribution of mean BMD0, BMD3 and BMD6: DRUG

		Number	Mean	SD	Minimum	Maximum	Median	p-value
BMD0	PRED	25	1.0726	0.1675	0.7120	1.3420	1.1150	0.5526
Baseline	TAC	21	1.0453	0.1365	0.8480	1.3130	1.0130	
BMD3	PRED	25	0.8743	0.1606	0.5010	1.1890	0.8750	0.0681
3 months	TAC	20	0.9591	0.1377	0.7290	1.2120	0.9235	
BMD6	PRED	25	0.8730	0.1545	0.4980	1.1940	0.8640	0.0460
6months	TAC	21	0.9602	0.1290	0.7900	1.2100	0.8990	

BMD Unit: gram/square centimeter (g/cm^2)

Table 2 shows that in PRED, the mean BMD0 (mean± s.d.) of patients was 1.0726 ± .1675. In TAC, the mean BMD0 (mean± s.d.) of patients was 1.0453 ± .1365. Distribution of mean BMD0 vs. drug was not statistically significant (p=0.5526).

In PRED, the mean BMD3 (mean± s.d.) of patients was .8743 ± .1606. In TAC, the mean BMD3 (mean± s.d.) of patients was .9591 ± .1377. Distribution of mean BMD3 vs. drug was not statistically significant (p=0.0681).

In PRED, the mean BMD6 (mean± s.d.) of patients was .8730 ± .1545. In TAC, the mean BMD6 (mean± s.d.) of patients was .9602 ± .1290. Distribution of mean BMD6 vs. drug was statistically significant (p=0.0460).

The difference of BMD at the lumbar vertebra level of L1-L4 between the prednisolone and tacrolimus groups was statistically significant at 6 months of therapy. Prednisolone was more harmful to bone health than tacrolimus.

Table 3 Distribution of mean T0, T3 and T6: DRUG

		Number	Mean	SD	Minimum	Maximum	Median	p-value
T0	PRED	25	-0.4260	1.0013	-2.0000	1.3300	-0.4000	0.9754
Baseline	TAC	21	-0.4352	1.0123	-1.9000	1.4000	-0.7000	
T3	PRED	25	-2.1040	1.4267	-5.7000	0.1000	-2.4000	0.3355
3 months	TAC	21	-2.4810	1.1487	-4.6000	0.1000	-2.7000	
T6	PRED	25	-2.5724	1.3742	-5.8000	1.1000	-2.8000	0.0251
6 months	TAC	21	-1.7371	0.9963	-3.6000	0.1000	-1.5000	

Table 3 shows that in PRED, the mean T0 (mean± s.d.) of patients was -.4260 ± 1.0013. In TAC, the mean T0 (mean± s.d.) of patients was -.4352 ± 1.0123. Distribution of mean T0 vs. drug was not statistically significant (p=0.9754).

In PRED, the mean T3 (mean± s.d.) of patients was -2.1040 ± 1.4267. In TAC, the mean T3 (mean± s.d.) of patients was -2.4810 ± 1.1487. Distribution of mean T3 vs. drug was not statistically significant (p=0.3355).

In PRED, the mean T6 (mean± s.d.) of patients was -2.5724 ± 1.3742. In TAC, the mean T6 (mean± s.d.) of patients was -1.7371 ± .9963. Distribution of mean T6 vs. drug was statistically significant (p=0.0251).The difference of T score at the lumbar vertebra level of L1-L4 between the prednisolone and tacrolimus groups was statistically significant at 6 months of therapy.

Table 4 Distribution of patient's T Score at 3 months in the 2 groups

	DRUG		
T3(L1-L4)	PRED	TAC	TOTAL
Normal	8	2	10
Row%	80.0	20.0	100.0
Col %	32.0	9.5	21.7
Osteopenia	5	8	13
Row%	38.5	61.5	100.0
Col %	20.0	38.1	28.3
Osteoporosis	12	11	23
Row%	52.2	47.8	100.0
Col %	48.0	52.4	50.0
TOTAL	25	21	46
Row%	54.3	45.7	100.0
Col %	100.0	100.0	100.0

Table 4 shows that in PRED group, 8(32.0%) patients had normal T3 (L1-L4), 5(20.0%) patients had Osteopenia and 12(48.0%) patients had Osteoporosis. In TAC group, 2(9.5%) patients had normal T3 (L1-L4), 8(38.1%) patients had Osteopenia and 11(52.4%) patients had Osteoporosis. Association of T3 (L1-L4) vs. drug was not statistically significant (Chi-square value: 4.0183; p-value: 0.1341)

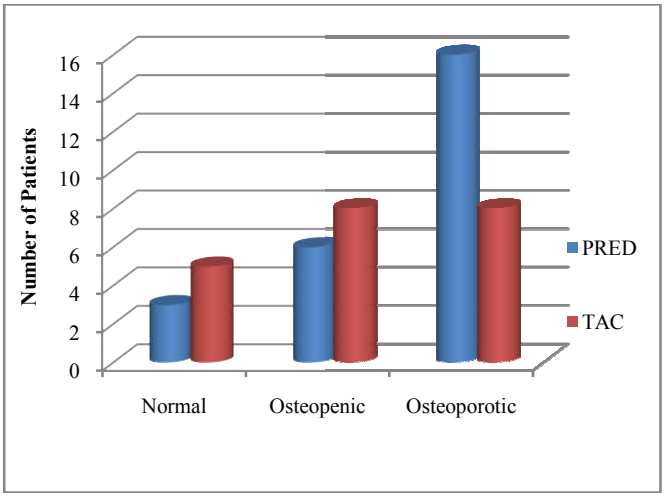

Fig 1 Distribution of patient's T Score at 6months in the 2 groups

Fig 1 shows that in PRED, 3(12.0%) patients had normal T6 (L1-L4), 6(24.0%) patients had Osteopenia and 16(64.0%) patients had Osteoporosis. In TAC, 5(23.8%) patients had normal T6 (L1-L4), 8(38.1%) patients had Osteopenia and 8(38.1%) patients had Osteoporosis.

Secondary outcomes

There was negative correlation (spearman rho) between cumulative prednisolone dose and BMD 3 at L1-L4 (p value =0.365).

There was negative correlation between 24 hour urine protein at baseline and BMD 3 at L1-L4 (p value=0.108).

DISCUSSION

In this study, the final sample size was 46. It included all those who completed the follow up. It was noted that most of the patients were of Minimal change disease (73.9%) followed by

patients having Focal segmental glomerulosclerosis (26.1%). Majority of the study subjects were in the 20-29 age bracket followed by the 30-39 years bracket. Males (65.2%) outnumbered females (34.8%).The minimum age was 20 and maximum 50.6 years. The mean age was 30.5 years. The mean BMD at the lumbar spine at baseline in the prednisolone group was 1.0726 and 1.0453 in the TAC group. The p value at baseline was 0.55 (not statistically significant). The mean BMD at the lumbar spine at 3 months was 0.8743 for the prednisolone group and 0.9591 for the TAC group. The difference was not statistically significant (p=0.0681). However the mean BMD at 6 months in the prednisolone group had decreased from 1.0726 to 0.8730 and mean BMD in the TAC group had decreased from 1.0453 to 0.9602.This difference between the two drug groups was statistically significant (p=0.0460). This result in the prednisolone group is concurrent to available literature which state that GC induced bone loss is maximum in the first 6 months.

The DEXA report may include a FRAX (fracture risk assessment tool) score for 40 to 90 year age group[12, 13, and 14]. In our study majority of patients were less than 40 years of age. FRAX was not applicable. The difference of T score at the lumbar vertebra level of L1-L4 between the prednisolone and tacrolimus groups was statistically significant at 6 months of therapy. Prednisolone group had a mean T score of -2.5724 which was in the osteoporotic range. Tacrolimus group had a mean T score of -1.7371 which was in the osteopenic range. Our study revealed the deleterious effect of glucocorticoids on the bone health of young individuals. Tacrolimus was also shown to cause significant loss of BMD in the study subjects as was shown in post transplant setting [12]. As all the patients were put on calcium and vitamin D supplementation at the onset, the hypocalcemia at 3 or 6 months was not noticed. Even after supplementation, the BMD at 3 and 6 months in the study subjects were significantly low. In our opinion, these patients should be initiated on antiresorptive therapy[15, 16]. The correlation between cumulative prednisolone dose and BMD, as well as 24 hour protein and BMD were not statistically significant. However there was a negative correlation between cumulative prednisolone dose and BMD. Currently, guidelines recommend oral bisphosphonate therapy as the first-line treatment, with adjuvant calcium and vitamin D. New evidence suggests greater BMD gains with zoledronic acid and teriparatide [17, 18]. These therapies may therefore provide important options particularly in high-risk patients with established Glucocorticoid Induced Osteoporosis. An extra mile in preventing glucocorticoid or tacrolimus induced osteoporosis might be addition of bisphosphonates to patients at baseline except in those with hypocalcemia. The limitation of our study was a small sample size. Repeated BMD measurements involved a cost factor too. A longer follow up of the patients with BMD measurements is required to demonstrate the longterm effects of these drugs on the bone health of such young individuals.

Treatment guidelines in adult onset primary nephrotic syndromes still heavily bank on steroids. Steroid sparing drugs like tacrolimus also are not totally safe for bone health. Studies of tacrolimus and bone health are common in post transplant setting. Studies investigating the effect of tacrolimus on bone health of young adults is rare. Drug related osteoporosis is often missed in young patients as they rarely complain unlike steroid induced cataracts as was experienced in our study. Adequate calcium and vitamin D intake is crucial to develop optimal peak bone mass and to preserve bone mass throughout life [19].

CONCLUSION

Osteoporosis occurs in all populations and at all ages and has significant physical, psychosocial, and financial consequences. More attention should be paid to skeletal health in persons with conditions associated with secondary osteoporosis. Regular exercise, especially resistance and high-impact activities, contribute to development of high peak bone mass.

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