European Journal of Molecular and Clinical Medicine

ISSN: 2515-8260 Volume 09, Issue 06, 2022

ROLE OF BETA BLOCKERS AND ASSOCIATED FRACTURE RISK IN INDIAN SUBJECTS WITH PRIMARY OSTEOPOROSIS

Dr. B. Shobharani,[1*] Dr. P. Swathi[2]

[1*]Assistant Professor, Department of Biochemistry, Sri Venkateswara Medical College, Tirupati, Andhra Pradesh

[2]Assistant professor, Department of Biochemistry, Sri Venkateswara Medical College, Tirupati, Andhra Pradesh

Corresponding Author:

Dr. B. *Shobharani,* Sri Venkateswara Medical College, Tirupati, Andhra Pradesh

Date Of Submission- 3-3-2022
Date Of Acceptance- May 2022
Date Of Publication In June 2022

Type of study: original research paper

Conflicts of interest: Nil

ABSTRACT

Background: Osteoporosis leads to an increase in bone fragility with a decrease in bone mass. Literature data reports a decreased risk of fracture and a higher bone mineral density in subjects on beta blockers. However, few literature studies reported no effect of non-selective or selective beta blockers on fracture risk in osteoporosis subjects.
Aim: The present study aimed to assess the effect of non-selective and selective beta-blockers on fracture risk in Indian subjects with osteoporosis.
Methods: 120 subjects with osteoporosis from both genders were divided into 3 groups using cardio-selective beta-blocker (CSBB), NSBB (non-selective beta-blocker) group, and a control group. In all the subjects, bone turnover markers, BMD (bone mineral density), FR (fracture risk), and T-scores were assessed and results were formulated.
Results: After 6 months of assessment, it was seen that mean T-scores had a significant difference between the three groups. Bone mineral density was significantly higher in NSBB (non-selective beta-blockers) receiving group compared to the control group. Fracture risk was statistically lesser in CSBB and NSBB groups. Also, in comparison to the control group, lesser bone turnover markers were seen in both NSBB and CSBB groups.
Conclusion: CSBB and NSBB can help in improving bone mineral density with decrease bone turnover markers and fracture risk in subjects with osteoporosis. NSBB has a more

ISSN: 2515-8260 Volume 09, Issue 06, 2022

pronounced effect on reducing fracture risk at all three studied locations. Also, a significant reduction in bone turnover markers was seen particularly in s-CTX compared to the CSBB group.

Keywords: Beta-blockers, bone fracture, Bone mineral density, Bone turnover markers, Fracture risk

INTRODUCTION

Osteoporosis is a bone disorder affecting a large population globally and is defined by increased bone tissue destruction and reduced bone mineral density. Based on WHO criteria, osteoporosis is diagnosed with a BMD (bone mineral density) T-score of 2.5 standard deviations or more below peak bone mass. In the elderly, osteoporosis is seen in two forms namely Type I (postmenopausal) and type II as senile due to aging. Fractures due to osteoporosis are one of the most dangerous effects of the disease, causing severe damage and increasing chances of mortality. Also, a high financial burden is posed by osteoporosis and associated fractures with adequate materials and expert personnel which cause an additional unacceptable burden. Hence, it is vital to identify various risk factors associated with osteoporosis making it a focus in the research area.[1]

Common and major risk factors associated with osteoporosis are coronary artery diseases, low estrogen levels, diabetes, gender, age, and hypertension along with smoking history and taking drinks with high caffeine. Hypertension and osteoporosis are age-related disorders caused by interactions in genetic and environmental variables with hypertension being a substantial risk factor for osteoporosis. However, literature reports conflicting results on the link between hypertension and osteoporosis. Hypertension is reported to harm BMD (bone mineral density).[2]

A study done on a largely female population showed a link between raised blood pressure and femoral neck bone loss. Calcium loss related to hypertension has also been reported to cause hip fractures. Other literature data reported no link between low bone mass and high blood pressure. Subjects with osteopenia and osteoporosis have been found to have equal bone mineral density with or without hypertension.[3]

Hypertension is usually treated with beta-blockers which are adrenergic receptor antagonists and reduces blood pressure by releasing renin from the kidney and inhibiting heart adrenergic receptor channels. Beta-blockers have also recently been reported to affect fracture healing and bone metabolism. Adrenergic receptors have been presented by osteoblast-like cells which is not a usual finding. M-CSF (colony-stimulating factors) and RANKL (receptor activator of nuclear factor kappa-B ligand) are needed for the development of osteoclast, and activation of adrenoreceptors initiates the osteoclastogenesis.[4]

In subjects on beta blockers, a 30% increase in bone mineral density and reduced fracture risk is seen for the whole body, hips, and spine. Another study suggested for osteoporosis treatment, leptin signaling in the hypothalamus can stimulate a sympathetic positive tone which can target leptin and its signaling pathways by beta blockers. Following this hypothesis, osteoporosis enhancement can be done with beta blockers focusing on leptin and its signaling route in the hypothalamus.[5] The existing literature data is scarce for the interaction of osteoporosis and beta blockers. Hence, the present study was done to assess the

ISSN: 2515-8260 Volume 09, Issue 06, 2022

effect of non-selective and selective beta-blockers (non-selective or selective) on fracture risk in Indian subjects with primary osteoporosis.

MATERIALS AND METHODS

The present research study included 120 subjects, both males and females with a confirmed diagnosis of primary osteoporosis. The study population was recruited from hospital of Sri Venkateswara Medical College, Tirupati, Andhra Pradesh within the defined study period.

The inclusion criteria for the study were subjects with BMD T-scores of 2.5 or more and standard deviation below peak bone mass, male and female subjects, subjects of age 50 years or more, female osteoporotic subjects, both hypertensive and normotensive subjects, and subjects willing to participate in the study. The exclusion criteria were subjects not willing to participate and give consent, subjects on medications increasing osteoporosis as antidepressants, corticosteroids, and anti-anxiety drugs, and subjects on medicine improving osteoporosis as statins, nitrates, ACE inhibitors, and angiotensin receptor blockers. After explaining the detailed study design, informed consent was taken from all the study subjects in both written and verbal format.

After final inclusion, detailed history was recorded for all the subjects followed by an examination. The demographics included BMI, height, weight, gender, and age along with medical history and medical history. Associated risk factors were also assessed such as smoking and alcohol intake. For all the subjects, Fracture risk for the next five years was assessed by evaluating change (enhancement) in fracture risk with Fracture index, and a known BMD calculator was assessed along with an increase in T-scores and BMD using dual-energy x-ray absorptiometry. Prior fragility fractures were grouped into 3 categories namely hip, non-vertebral, and clinical vertebral fragility fractures.

Also, the study assessed reduction change in urine f DPD (urine-free deoxypyridinoline) using ELISA, reduction change in urine NTX (urine cross-linked N-terminal telopeptides of type 1 collagen) using ELISA, and reduction change in blood CTX (blood level of the C-telopeptide fragment of type 1 collagen) using ELISA.

All the study subjects were advised 70 mg once weekly of Alendronate, 1mcg vitamin D3 daily, and 500 mg once daily calcium supplements to preserve bone density. The included subjects were randomly divided into 3 groups. Group I had control subjects (n=40) who were given conventional osteoporosis treatment and were released after 6 months of completing treatment. Group II were NSBB (Non-selective beta-blocker Group) subjects (n=40) who were given 10 mg propranolol daily for osteoporosis and the dose was subsequently increased based on the subject's response in a dose-dependent manner. The change in the condition of the subjects was assessed after 6 months as improved or deteriorated. Group III was CSBB (Cardio-selective β-blocker Group) subjects (n=40) who were given the same treatment as the control group along with 5mg bisoprolol daily based on the patient's response. Subjects were monitored for 6 months after therapy to assess any change in illness rate for regression or development.

For all the subjects, urine samples and venous blood samples were collected after an overnight fast for blood and the first void in the morning for urine with creatinine correction.

ISSN: 2515-8260 Volume 09, Issue 06, 2022

The laboratory tests performed were thyroid function tests, 25-hydroxyvitamin D level, liver function test, and blood chemistry panel. At baseline, laboratory tests done were testosterone, Luteinizing hormone (LH)/follicle-stimulating hormone (FSH), and serum protein electrophoresis calcium/creatinine ratio. Duration of bisphosphonates was assessed and intake of beta blockers before inclusion in the study. Bone mineral density was assessed with DXA (gold-standard) at spine L1-L4, at forearm radius, and left femur (total and neck) to assess bone density in three regions.

Follow-up biochemical analysis was done on urine DPD (human deoxypyridinoline), urine cross-linked N-terminal telopeptides of type 1 collagen (NTX), and serum C-telopeptide

Fragment of type 1 collagen (CTX) was done at 6 months recall time using the ELISA. ELISA was also used for detecting bone turnover markers. For CTX-1 concentration in human serum samples, analytical ELISA was used following the Chubb SS[6] in 2012. Urine NTX ELISA to assess NTX amount in human urine samples was based on Kanakis I[7] in 2004 and ELISA test or urine DPS following Hamwi A[8] in 2001.

The data collected were assessed statistically using logistic regression and multivariate statistical techniques. The data were presented in tabulated and descriptive formats. SPSS version 22.0, 2013, Armonk, NY: IBM Corp and post-hoc test, Turkey analysis, chi-square test, and Pearson correlation were utilized. The data were expressed as mean and standard deviations and as percentages and numbers with a 0.05% significance level.

RESULTS

120 subjects were randomly divided into 3 groups. Group I had control subjects (n=40) who were given conventional osteoporosis treatment and were released after 6 months of completing treatment. Group II were NSBB (Non-selective beta-blocker Group) subjects (n=40) who were given 10 mg propranolol daily for osteoporosis and the dose was subsequently increased based on the subject's response in a dose-dependent manner. The change in the condition of the subjects was assessed after 6 months as improved or deteriorated. Group III was CSBB (Cardio-selective β-blocker Group) subjects (n=40) who were given the same treatment as the control group along with 5mg bisoprolol daily based on the patient's response. There were 30% (n=12) males and 70% (n=28) females in Group I, 5% (n=2) males and 95% (n=38) females in Group II, and 100% (n=20) females in Group III. The females were significantly higher compared to males with p=0.01. In group I, there was more than 60% (n=24) normotensive and 40% (n=40) hypertensive subjects, in Group II, there was an increase of 65% (n=26) hypertensives, and in Group III, the number of hypertensives further increased to 75% (n=30) subjects. However, it was statistically non-significant with p=0.14. There were 20% (n=8) smokers in Group I, 95% (n=38) in group II, and 100% (n=40) non-smokers in Group III with p=0.09. No fractures were seen in 10% (n=4) subjects of Group I, in 20% (n=8) subjects of Group II, and 30% (n=12) subjects of group III. One previous fracture in 40% (n=16), 55% (n=22), and 35% (n=14) subjects of Group I, II, and III respectively. Two fractures in 50% (n=20), 20% (n=8), and 35% (n=14) subjects respectively from Group I, II, and III respectively. Three previous fractures were reported in only 5% (n=2) of subjects of Group II (Table 1).

ISSN: 2515-8260 Volume 09, Issue 06, 2022

The mean BMI of the study subjects for Groups I, II, and II was 31.7±4.3, 32.6±6.4, and 33.3±6.3 kg/m2 for groups I, II, and III at baseline which was statistically non-significant with p=0.75. The height was highest for Group I followed by group II and least for Group III with respective mean values of 161.2±6.5, 159.7±6.6, and 155.6±6.4 cm and p=0.05. The mean weight was also comparable between the three study groups at baseline with p=0.84. The mean age for Groups I, II, and III were 60.3±6.2, 61.7±4.5, and 59.5±4.4 years respectively for Groups I, II, and III with p=0.35 (Table 2).

The study results showed that the mean 5-year vertebral fracture risk was comparable in group I at baseline and y6 months with p=0.16. For Group II and III, the risk was significantly higher before therapy compared to 6 months after therapy with p=0.004 and 0.01 respectively. For 5-year hip fracture risk, it was comparable for Group I at baseline and 6 months with p=0.14. For groups II and III, hip fracture risk was significantly higher at baseline compared to 6 months after therapy with p=0.005 and 0.01. Also, 6 months difference between groups was significant with p=0.006. Similar results were seen for non-vertebral fracture risk with significant reduction after 6 months of therapy in groups II and II with p=0.004 and 0.01 respectively. For group I, BMD was comparable at baseline and 6 months with p=0.94. For group II, BMP increased significantly from 0.8±0.3 to 0.9±-0.3 from baseline to 6 months with p<0.001 and for Group II with p<0.001. The non-significant difference was seen between groups at baseline and 6 months with p=0.66 and 0.07 respectively. The T scores were comparable between three groups at baseline with p=0.55 and at 6 months, it was significantly different with p=0.001. For group, I, mean T scores were comparable with p=0.14. For Group II and III scores were significantly better at 6 months after therapy compared to baseline with p<0.001 for both (Table 3).

On assessing the bone turnover markers, urine DPD was comparable between 3 groups at baseline (p=0.23) and was higher for Group I at 6 months followed by groups III and II (p<0.001). Urine DPD decreased significantly in all three groups at 6 months with p<0.0001 for all three groups. Urine NTX was comparable at baseline in three groups with p=0.96 and was significantly higher for group I compared to groups II and III (p<0.001). NTX decreased significantly in all three groups at 6 months compared to baseline with p<0.0001 for all three groups. Serum CTX was significantly higher for group I at baseline with p=0.03 and was comparable between 3 groups at 6 months with p=0.06. The reduction was statistically significant for all the 3 groups at 6 months from baseline with p<0.001 for all three groups (Table 4).

DISCUSSION

The present study included 120 subjects that were randomly divided into 3 groups. Group I had control subjects (n=40) who were given conventional osteoporosis treatment and were released after 6 months of completing treatment. Group II were NSBB (Non-selective beta-blocker Group) subjects (n=40) that were assessed after 6 months as improved or deteriorated. Group III was CSBB (Cardio-selective β-blocker Group) subjects (n=40) who were given the same treatment as the control group along with 5mg bisoprolol daily based on the patient's response.

ISSN: 2515-8260 Volume 09, Issue 06, 2022

The study results showed that the mean 5-year vertebral fracture risk was comparable in group I at baseline and 6 months with p=0.16. For Group II and III, the risk was significantly higher before therapy compared to 6 months after therapy with p=0.004 and 0.01 respectively. For 5-year hip fracture risk, it was comparable for Group I at baseline and 6 months with p=0.14. For groups II and III, hip fracture risk was significantly higher at baseline compared to 6 months after therapy with p=0.005 and 0.01. Also, 6 months difference between groups was significant with p=0.006. Similar results were seen for non-vertebral fracture risk with significant reduction after 6 months of therapy in groups II and II with p=0.004 and 0.01 respectively. These findings were consistent with the previous studies of Salari Sharif P et al[9] in 2011 and Yang S et al[10] in 2011 where authors reported decreased fracture risk for all vertebral, non-vertebral, and hip fractures in osteoporosis subjects after 6 months of treatment.

It was seen that BMD was comparable at baseline and 6 months with p=0.94. For group II, BMD increased significantly from 0.8±0.3 to 0.9±-0.3 from baseline to 6 months with p<0.001 and for Group II with p<0.001. The non-significant difference was seen between groups at baseline and 6 months with p=0.66 and 0.07 respectively. The T scores were comparable between three groups at baseline with p=0.55 and at 6 months, it was significantly different with p=0.001. For group, I, mean T scores were comparable with p=0.14. For Group II and III scores were significantly better at 6 months after therapy compared to baseline with p<0.001 for both. These results were in agreement with the studies of Park SG et al[11] in 2018 and Cosman F et al[12] in 2014 where authors, in their studies reported significantly better BMD and T scores in their subjects after osteoporosis treatment compared to those without treatment.

Concerning the bone turnover markers, urine DPD was comparable between the 3 groups at baseline (p=0.23) and was higher for Group I at 6 months followed by groups III and II (p<0.001). Urine DPD decreased significantly in all three groups at 6 months with p<0.0001 for all three groups. Urine NTX was comparable at baseline in three groups with p=0.96 and was significantly higher for group I compared to groups II and III (p<0.001). NTX decreased significantly in all three groups at 6 months compared to baseline with p<0.0001 for all three groups. These results for bone turnover markers were comparable to the studies of Rossini M et al[13] in 2016 and Javed F et al[14] in 2012 where similar results for bone turnover markers were reported for urine analysis as in the present study.

The study results showed that Serum CTX which was significantly higher for group I at baseline with p=0.03 and was comparable between 3 groups at 6 months with p=0.06. The reduction was statistically significant for all the 3 groups at 6 months from baseline with p<0.001 for all three groups. These findings were comparable to the results of Akkawi I[15] in 2018 and Zhnag M et al[16] in 2010 where authors reported a significant reduction of serum CTX after treatment for osteoporosis as also seen in the results of the present study.

CONCLUSION

Considering its limitations, the present study concludes that CSBB and NSBB can help in improving bone mineral density with decrease bone turnover markers and fracture risk in subjects with osteoporosis. NSBB has a more pronounced effect on reducing fracture risk at

ISSN: 2515-8260 Volume 09, Issue 06, 2022

all three studied locations. Also, a significant reduction in bone turnover markers was seen particularly in s-CTX compared to the CSBB group. The limitations of this study were smaller considered population, shirt monitoring, and biased related to the geographic location warranting further long-term studies planned longitudinally.

REFERENCES

1. Sennerby U, Farahmand B, Ahlbom A, Ljunghall S, and Michaëlsson K. Cardiovascular diseases and future risk of hip fracture in women. Osteoporosis International. 2007;18:1355-62.
2. Wilper AP, Woolhandler S, Lasser KE, McCormick D, Bor DH and Himmelstein DU. A national study of chronic disease prevalence and access to care in uninsured US adults. Annals of internal medicine. 2008;149:170-6.
3. Singh AP, Jain M. Singh S, Rangari P. Management of proximal humerus fracture - a case-control prospective study. IJMSDR. 2018;2:4:172-94.
4. Murarka k, Agrawal R, Rangari P, Murarka A. Hemiarthroplasty of intracapsular femoral neck fracture with Austin Moore prosthesis. IJMSDR. 2019;3:263-70.
5. Rajshekhar S, Rajasekhar M, Baghel VS, Rangari P. Long pfn nailing in comminuted high subtrochanteric fractures of the femur in elderly patients- a hospital-based clinical trial. IJMSDR. 2019;3:33-9.
6. Chubb SP. Measurement of C-terminal telopeptide of type I collagen (CTX) in serum. Clinical biochemistry. 2012;45:928-35.
7. Kanakis I, Nikolaou M, Pectasides D, Kiamouris C, and Karamanos N. Determination and biological relevance of serum cross-linked type I collagen N-telopeptide and bone-specific alkaline phosphatase in breast metastatic cancer. Journal of pharmaceutical and biomedical analysis. 2004;34:827-32.
8. Hamwi A, Ganem A-H, Grebe C, et al. Markers of bone turnover in postmenopausal women receiving hormone replacement therapy. Clinical Chemistry and Laboratory Medicine (CCLM). 2001;39:414-7.
9. Salari Sharif P, Abdollahi M and Larijani B. Current, new and future treatments of osteoporosis. Rheumatology international. 2011;31:289-300.
10. Yang S, Nguyen ND, Center JR, Eisman JA, and Nguyen TV. Association between beta-blocker use and fracture risk: the Dubbo Osteoporosis Epidemiology Study. Bone. 2011;48:451-5.
11. Park SG, Jeong SU, Lee JH, et al. The changes in CTX, DPD, osteocalcin, and bone mineral density during the postmenopausal period. Annals of rehabilitation medicine. 2018;42:441.
12. Cosman F, de Beur SJ, LeBoff M, et al. Clinician's guide to prevention and treatment of osteoporosis. Osteoporosis international. 2014;25:2359-81.
13. Rossini M, Adami S, Bertoldo F, et al. Guidelines for the diagnosis, prevention, and management of osteoporosis. Reumatismo. 2016;68:1-39.
14. Javed F, Khan SA, Ayers EW, et al. Association of hypertension and bone mineral density in an elderly African American female population. Journal of the National Medical Association. 2012;104:172-8.

ISSN: 2515-8260 Volume 09, Issue 06, 2022

15. Akkawi I and Zmerly H. Osteoporosis: current concepts. Joints. 2018;6:122-7.
16. Zhang M, Li Y and Liu Y. Study on the influencing factors for bone mineral density among 24831 people in Changchun. Chin J Osteoporos. 2010;16:125-7.

TABLES

S. No	Characteristics	Group I		Group II		Group III		p-value
		%	n=40	%	n=40	%	n=40	
1.	**Gender**							
a)	Males	30	12	5	2	0	0	**0.01**
b)	Females	70	28	95	38	100	20	
2.	**Blood pressure**							
a)	Normotensive	60	24	35	14	25	10	0.14
b)	Hypertensive	40	16	65	26	75	30	
3.	**Smoking status**							
4.	Non-Smokers	80	32	95	38	100	40	0.09
5.	Smokers	20	8	5	2	0	0	
6.	**Previous fracture**							
a)	None	10	4	20	8	30	12	5.67
b)	One	40	16	55	22	35	14	
c)	Two	50	20	20	8	35	14	
d)	Three	0	0	5	2	0	0	

Table 1: Demographics and clinical data in 3 groups of study subjects

S. No	Parameters	Group I	Group II	Group III	p-value
1.	**BMI (kg/m2)**	31.7±4.3	32.6±6.4	33.3±6.3	0.75
2.	**Height (cm)**	161.2±6.5	159.7±6.6	155.6±6.4	**0.05**
3.	**Weight (kg)**	82.6±9.5	84.2±17.7	81.4±17.6	0.84
4.	**Age (years)**	60.3±6.2	61.7±4.5	59.5±4.4	0.35

Table 2: Demographics data at baseline in 3 groups of study subjects

S. No	Parameters	Group I	Group II	Group III	p-value
1.	**5-year vertebral fracture risk**				
a)	Before	8.5±2.3	8.3±2.2	7.7±2.2	0.53
b)	After	9.3±2.3	7.0±2.2	7.2±2.3	**0.008**
c)	p-value	0.16	**0.004**	**0.01**	
2.	**5-year hip fracture risk**				
a)	Before	5.6±2.6	5.3±2.5	4.7±2.5	0.54
b)	After	6.5±2.6	4.3±2.3	3.7±2.4	**0.006**
c)	p-value	0.14	**0.005**	**0.01**	

ISSN: 2515-8260 Volume 09, Issue 06, 2022

3.	**5-year non-vertebral fracture risk**				
a)	Before	22.6±3.7	22.6±3.5	21.1±3.5	0.54
b)	After	24.2±3.7	20.3±3.4	19.9±3.6	**0.007**
c)	p-value	0.18	**0.004**	**0.01**	
4.	**BMD (g/cm2)**				
a)	Before	0.8±0.3	0.8±0.3	0.8±0.3	0.66
b)	After	0.8±0.3	0.9±-0.3	0.9±-0.3	0.07
c)	p-value	0.94	**<0.001**	**<0.001**	
5.	**T-score**				
a)	Before	-3.5±0.3	-3.3±0.7	-3.6±1.2	0.55
b)	After	-3.7±0.4	-2.5±0.6	-2.7±0.9	**0.001**
c)	p-value	0.14	**<0.001**	**<0.001**	

Table 3: 5-year fracture risk, BMD, and T-scores in 3 study groups at baseline and 6 months

S. No	Parameters	Group I	Group II	Group III	p-value
1.	**Urine DPD (nmol/L)**				
a)	Before	27.6±6.5	23.3±6.2	26.3±7.2	0.23
b)	After	20.2±6.6	13.3±2.7	14.7±3.9	**<0.001**
c)	p-value	**<0.001**	**<0.001**	**<0.001**	
2.	**Urine NTX (nmol/L)**				
a)	Before	64.7±3.7	64.8±6.7	64.7±7.6	0.96
b)	After	57.4±3.3	34.7±5.7	33.4±3.5	**<0.001**
c)	p-value	**<0.001**	**<0.001**	**<0.001**	
3.	**Serum CTX (ng/ml)**				
a)	Before	86.2±25.7	44.7±42.8	63.5±43.3	**0.03**
b)	After	71.4±24.7	38.3±36.8	52.5±37.7	0.06
c)	p-value	**<0.001**	**<0.001**	**<0.001**	

Table 4: Intergroup comparison of bone turnover markers at baseline and 6 months following therapy