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

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ABSTRACT

Background: As bone mass decreases due to osteoporosis, bone fragility increases. Research in the literature indicates that beta blocker users had a higher bone mineral density and a lower risk of fracture. Few research, meanwhile, have shown that either selective or non-selective beta blockers had no influence on the risk of fracture in individuals with osteoporosis. **Aim**: The purpose of this study was to evaluate the impact of selective and non-selective beta-blockers on the risk of fracture in individuals with osteoporosis who were Indian.

Methods: Using cardio-selective beta-blockers (CSBB), non-selective beta-blockers (NSBB), and a control group, 120 osteoporosis patients of both genders were split into 3 groups. Bone turnover markers, BMD (bone mineral density), FR (fracture risk), and T-scores were evaluated in each individual, and conclusions were drawn.

Results: It was observed that there was a significant difference in mean T-scores between the three groups after six months of testing. When comparing the receiving group with non-selective beta-blockers (NSBBs) to the control group, there was a substantial increase in bone mineral density. The CSBB and NSBB groups had a statistically lower fracture risk. Additionally, both the NSBB and CSBB groups showed lower levels of bone turnover indicators as compared to the control group.

C**onclusion**, CSBB and NSBB can assist in lowering bone turnover markers and fracture risk in individuals with osteoporosis while also increasing bone mineral density. At all three of the locations under study, the impact of NSBB on lowering fracture risk is more noticeable. Additionally, s-CTX showed a significantly lower level of bone turnover indicators than the CSBB group did.

Keywords: bone turnover indicators, bone mineral density, beta-blockers, and fracture Risk of fracture

INTRODUCTION

Reduced bone mineral density and accelerated bone tissue degradation characterize osteoporosis, a bone condition that affects a vast population worldwide. A BMD (bone mineral density) T-score 2.5 standard deviations or more below peak bone mass is considered osteoporosis based on WHO guidelines. Osteoporosis in the elderly occurs in two forms: type I (postmenopausal) and type II (aging-related senility). One of the most harmful consequences of osteoporosis is fractures, which raise death rates and cause significant damage. Osteoporosis and related fractures can provide a significant cost burden requiring skilled workers and sufficient supplies, adding to an already intolerable load. Therefore, it is imperative to ascertain the diverse risk factors linked to osteoporosis, thereby elevating the issue to the forefront of study.1

Numerous common and significant risk factors for osteoporosis include a history of smoking, use of high-caffeine beverages, gender, age, low estrogen levels, diabetes, and hypertension.

Age-related conditions such as hypertension and osteoporosis are brought on by interactions between hereditary and environmental factors, with hypertension serving as a significant risk factor for osteoporosis. On the relationship between hypertension and osteoporosis, however, the literature presents contradicting findings. BMD (bone mineral density) has been shown to be harmed by hypertension.[2]

Raised blood pressure and femoral neck bone loss have been linked, according to a study conducted on a predominantly female population. Hip fractures have also been linked to hypertension-related calcium loss. There was no correlation seen in other literature data between high blood pressure and poor bone mass. It has been discovered that subjects with osteopenia and osteoporosis, with or without hypertension, have equivalent bone mineral density.[3] In order to lower blood pressure and treat hypertension, beta-blockers, which are adrenergic receptor antagonists, release renin from the kidney and block the heart's adrenergic receptor channels. Recently, it has also been observed that beta-blockers impact bone metabolism and fracture repair. It is uncommon to find that osteoblast-like cells have been shown to exist with adrenalergic receptors. The development of osteoclasts requires M-CSF (colony-stimulating factors) and RANKL (receptor activator of nuclear factor kappa-B ligand), while the osteoclastogenesis is triggered by adrenoreceptor activation.[4]

Beta blocker users have lower fracture risk and 30% more bone mineral density throughout the torso, hips, and spine. According to a different study, beta blockers can target leptin and its signaling pathways in the hypothalamus to treat osteoporosis by stimulating a sympathetic positive tone. According to this theory, beta blockers that target leptin and its hypothalamic signaling pathway can be used to exacerbate osteoporosis.[5] The available literature on the relationship between beta blockers and osteoporosis is lacking.

Therefore, the purpose of the current study was to evaluate the impact of selective and non-selective beta-blockers on the risk of fracture in Indian participants who had primary osteoporosis.

MATERIALS AND PROCEDURES

After receiving approval from the relevant ethical committee, the current investigation was conducted at... from. to. One hundred and twenty male and female participants with a verified diagnosis of primary osteoporosis were included in the study.

Subjects with BMD T-scores of 2.5 or higher and standard deviation below peak bone mass, as well as male and female participants, subjects aged 50 years or above, female osteoporotic participants, both normotensive and hypertensive participants, and subjects willing to participate in the study were the inclusion criteria for the research.

Subjects who were unwilling to participate or give consent, subjects taking medications that increase osteoporosis, such as corticosteroids, antidepressants, and anxiety medications, and subjects taking medications that improve osteoporosis, such as statins, nitrates, ACE inhibitors, and angiotensin receptor blockers, were all excluded from the study. All study participants gave their informed consent in both written and verbal forms after being fully told about the study's thorough design.

Following final inclusion, each topic had a thorough history taken, which was followed by an exam. Along with medical history, the demographics also included BMI, height, weight, gender, and age. Associated risk variables including alcohol consumption and smoking were also evaluated.

A known BMD calculator was evaluated together with a rise in T-scores and BMD using dual-energy x-ray absorptiometry, and fracture risk for the following five years was measured for each subject by evaluating change (enhancement) in fracture risk with Fracture Index. Three categories were used to classify previous fragility fractures: hip, non-vertebral, and clinical vertebral. The study evaluated the effects of reduction changes in urine DPD (urine-free deoxypyridinoline), urine NTX (urine cross-linked N-terminal telopeptides of type 1 collagen), and blood CTX (blood level of the C-telopeptide fragment of type 1 collagen) using enzyme-linked immunoassay (ELISA).

All the study subjects were advised 70 mg once weekly of Alendronate, 1mcg vitamin D3 daily, as well as 500 mg of calcium supplements taken once a day to maintain bone density. Three groups were randomly selected from among the participating subjects. Group I consisted of 40 control participants who received standard osteoporosis medication and were discharged from the study after six months. Group II consisted of 40 NSBB (Non-selective beta-blocker Group) participants who received 10 mg propranolol daily for osteoporosis. The dose was then increased in a dose-dependent way based on the subjects' response. After six months, the participants' condition was evaluated to determine if it had improved or deteriorated. Depending on the patient's reaction, Group III consisted of 40 CSBB (Cardio-selective β-blocker Group) patients who received the same medication as the control group in addition to 5 mg of bisoprolol daily. Following therapy, the subjects were observed for six months to evaluate any alterations in the rate of illness progression or regression.

Neural and venous blood samples were obtained from each patient following an overnight fast for blood and the first void in the morning for urine, both with and without creatinine adjustment. Thyroid function tests, blood chemistry panel, liver function test, and 25-hydroxyvitamin D level were the laboratory tests conducted. Baseline laboratory tests included calcium/creatinine ratio, serum protein electrophoresis, luteinizing hormone (LH)/follicle-stimulating hormone (FSH), and testosterone. Prior to research inclusion, the duration of bisphosphonates and beta blocker intake were evaluated. Three different parts of the body were evaluated for bone mineral density using DXA (gold-standard): the left femur (total and neck), the forearm radius, and the spine L1–L4.

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) were subjected to follow-up biochemical examination using the ELISA at a recall interval of six months. Additionally, ELISA was employed to find indicators of bone turnover. After the Chubb SS[6] in 2012, analytical ELISA was utilized to determine the levels of CTX-1 in human serum samples. Based on Kanakis I7 in 2004 and the ELISA test or urine DPS after Hamwi A[8] in 2001, urine NTX ELISA was used to determine the level of NTX in human urine samples.

Multivariate statistical methods and logistic regression were used to statistically evaluate the gathered data. Both tabular and descriptive formats were used to show the data. Turkey analysis, chi-square test, Pearson correlation, post-hoc test, and SPSS version 22.0, 2013, Armonk, NY: IBM Corp. was used. The results were presented as percentages, figures, and mean and standard deviations with a significance level of 0.05%.

RESULTS

Three groups of 120 participants were randomly selected. Group I consisted of 40 control participants who received standard osteoporosis medication and were discharged from the study after six months. Group II consisted of 40 NSBB (Non-selective beta-blocker Group) participants who received 10 mg propranolol daily for osteoporosis. The dose was then increased in a dose-dependent way based on the subjects' response. After six months, the participants' condition was evaluated to determine if it had improved or deteriorated.

Depending on the patient's reaction, Group III consisted of 40 CSBB (Cardio-selective β-blocker Group) patients who received the same medication as the control group in addition to 5 mg of bisoprolol daily. In Group I, there were 30% (n=12) men and 70% (n=28) women; in Group II, there were 5% (n=2) men and 95% (n=38) women; and in Group III, there were 100% (n=20) women. With p=0.01, the number of females was substantially higher than that of males. More than 60% (n=24) of the participants in Group I were normotensive, and 40% (n=40) were hypertensive. In Group II, the proportion of hypertensives grew to 65% (n=26), and in Group III, the proportion of hypertensives went even more to 75% (n=30).

With p=0.14, it was, nevertheless, statistically non-significant. Group I had 20% (n=8) smokers, Group II had 95% (n=38), and Group III had 100% (n=40) non-smokers (p=0.09). 10% (n = 4) of Group I participants, 20% (n = 8) of Group II subjects, and 30% (n = 12) of Group III subjects did not have any fractures. 40% (n = 16), 55% (n = 22), and 35% (n = 14) of Group I, II, and III participants, respectively, had experienced one prior fracture. Two fractures occurred in 50% (n = 20), 20% (n = 8), and 35% (n = 14) of participants from Groups I, II, and III, in that order. Just 5% (n=2) of Group II participants had a history of three fractures (Table 1).

At baseline, the study subjects' mean BMI for Groups I, II, and III was 31.7±4.3, 32.6±6.4, and 33.3±6.3 kg/m2, respectively. This was statistically non-significant with a p-value of 0.75. Group I had the highest height, followed by Group II and Group III had the lowest, with mean values of 161.2±6.5, 159.7±6.6, and 155.6±6.4 cm, respectively, and p=0.05. At baseline, the three study groups' mean weights were likewise identical (p=0.84). With p=0.35, the mean age of Groups I, II, and III was 60.3±6.2, 61.7±4.5, and 59.5±4.4 years, respectively (Table 2).

According to the study's findings, group I's mean 5-year risk of spinal fracture was similar at baseline and at six months (p=0.16). With p=0.004 and 0.01 for Group II and III, respectively,

the risk was considerably higher prior to therapy than six months following therapy. Group I's 5-year hip fracture risk was similar at baseline and at six months (p=0.14).

Hip fracture risk was considerably higher for groups II and III at baseline compared to six months post-therapy (p=0.005 and 0.01 respectively). Additionally, p=0.006 indicated a significant difference between groups after 6 months. Similar outcomes were observed for the non-vertebral fracture risk in groups II and II, with a substantial reduction observed at 6 months of therapy (p=0.004 and 0.01 respectively).

BMD for group I was similar at baseline and at six months (p=0.94). Between the baseline and six months, group II's BMP increased significantly (p<0.001), from 0.8±0.3 to 0.9±-0.3. At baseline and six months, there was a non-significant difference between the groups (p=0.66 and 0.07, respectively). At baseline, the T scores for the three groups were similar (p=0.55), but at six months, there was a significant difference (p=0.001). The mean T scores for group I were similar, with p=0.14. At six months following therapy, Group II and III ratings considerably improved from baseline, with p<0.001 for both (Table 3).

Urine DPD was similar for all three groups at baseline (p=0.23) when measuring the bone turnover markers, and it was greater for Group I at 6 months, followed by Groups III and II (p<0.001). After six months, urine DPD considerably decreased in all three groups, with p<0.0001. At baseline, urine NTX was similar for all three groups (p=0.96), with group I having considerably higher urine NTX than groups II and III (p<0.001). At six months, NTX was significantly lower in all three groups than at baseline (p<0.0001) for each group. Serum CTX was similar across the three groups at six months (p=0.06), but considerably higher for group I at baseline (p=0.03). At six months from baseline, the reduction was statistically significant for all three groups, with p<0.001 in each case (Table 4).

DISCUSSION

Three groups of 120 participants were randomly assigned to the current investigation. Group I consisted of 40 control participants who received standard osteoporosis medication and were discharged from the study after six months. Subjects in Group II (Non-selective beta-blocker Group; n = 40) were evaluated at the 6-month mark to determine whether their condition had improved or worsened. Depending on the patient's reaction, Group III consisted of 40 CSBB (Cardio-selective β-blocker Group) patients who received the same medication as the control group in addition to 5 mg of bisoprolol daily.

According to the study's findings, group I's mean 5-year risk of spinal fracture was similar at baseline and six months later (p=0.16). With p=0.004 and 0.01 for Group II and III, respectively, the risk was considerably higher prior to therapy than six months following therapy. Group I's 5-year hip fracture risk was similar at baseline and at six months (p=0.14). Hip fracture risk was considerably higher for groups II and III at baseline compared to six months post-therapy (p=0.005 and 0.01 respectively). Additionally, p=0.006 indicated a significant difference between groups after 6 months. Similar outcomes were observed for the non-vertebral fracture risk in groups II and II, with a substantial reduction observed at 6 months of therapy (p=0.004 and 0.01 respectively).

These results were in line with earlier research by Yang S. et al. (2011) and Salari Sharif P. et al. (2011), who found that after six months of therapy, osteoporosis patients had a lower fracture risk for all hip, non-vertebral, and vertebral fractures. BMD was found to be comparable at

baseline and after six months (p=0.94). Between the baseline and six months, group II's BMD rose significantly (p<0.001), from 0.8±0.3 to 0.9±-0.3. At baseline and six months, there was a non-significant difference between the groups (p=0.66 and 0.07, respectively). At baseline, the T scores for the three groups were similar (p=0.55), but at six months, there was a significant difference (p=0.001).

The mean T scores for group I were similar, with p=0.14. At six months following therapy, Group II and III ratings considerably improved from baseline, with p<0.001 for both. These findings corroborated those of research by Park SG et al.(2018) and Cosman F et al.(2014), the authors of which found that participants receiving osteoporosis treatment had noticeably higher BMD and T scores than those who did not.

Regarding the bone turnover markers, at baseline, the three groups' urine DPD was similar (p=0.23), but at six months, Group I had the highest DPD, followed by Groups III and II (p<0.001). After six months, urine DPD considerably decreased in all three groups, with p<0.0001.

At baseline, urine NTX was similar for all three groups (p=0.96), with group I having considerably higher urine NTX than groups II and III (p<0.001). At six months, NTX was significantly lower in all three groups than at baseline (p<0.0001) for each group. The present study's results regarding bone turnover indicators were in line with those reported in studies conducted in 2016 by Rossini M et al. and in 2012 by Javed F et al. These investigations also included urine analysis. According to the study's findings, serum CTX was considerably higher in group I at baseline (p=0.03) and was similar in the three groups after six months (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 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.

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TABLES

Characteristics	**Group I**		**Group II**		**Group III**		**p-value**
	%	**n=40**	**%**	**n=40**	**%**	**n=40**	
Gender							
Males	30	12	5	2	0	0	**0.01**
Females	70	28	95	38	100	20	
Blood pressure							
Normotensive	60	24	35	14	25	10	0.14
Hypertensive	40	16	65	26	75	30	
Smoking status							
Non-Smokers	80	32	95	38	100	40	0.09
Smokers	20	8	5	2	0	0	
Previous fracture							
None	10	4	20	8	30	12	5.67

One	40	16	55	22	35	14	
Two	50	20	20	8	35	14	
Three	0	0	5	2	0	0	

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

Parameters	**Group I**	**Group II**	**Group III**	**p-value**
BMI (kg/m2)	31.7±4.3	32.6±6.4	33.3±6.3	0.75
Height (cm)	161.2±6.5	159.7±6.6	155.6±6.4	**0.05**
Weight (kg)	82.6±9.5	84.2±17.7	81.4±17.6	0.84
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

Parameters	**Group I**	**Group II**	**Group III**	**p-value**
5-year vertebral fracture risk				
Before	8.5±2.3	8.3±2.2	7.7±2.2	0.53
After	9.3±2.3	7.0±2.2	7.2±2.3	**0.008**
p-value	0.16	**0.004**	**0.01**	
5-year hip fracture risk				
Before	5.6±2.6	5.3±2.5	4.7±2.5	0.54
After	6.5±2.6	4.3±2.3	3.7±2.4	**0.006**
p-value	0.14	**0.005**	**0.01**	
5-year non-vertebral fracture risk				
Before	22.6±3.7	22.6±3.5	21.1±3.5	0.54
After	24.2±3.7	20.3±3.4	19.9±3.6	**0.007**
p-value	0.18	**0.004**	**0.01**	
BMD (g/cm2)				
Before	0.8±0.3	0.8±0.3	0.8±0.3	0.66
After	0.8±0.3	0.9±-0.3	0.9±-0.3	0.07
p-value	0.94	**<0.001**	**<0.001**	
T-score				
Before	-3.5±0.3	-3.3±0.7	-3.6±1.2	0.55
After	-3.7±0.4	-2.5±0.6	-2.7±0.9	**0.001**
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

Parameters	**Group I**	**Group II**	**Group III**	**p-value**
Urine DPD (nmol/L)				
Before	27.6±6.5	23.3±6.2	26.3±7.2	0.23
After	20.2±6.6	13.3±2.7	14.7±3.9	**<0.001**
p-value	**<0.001**	**<0.001**	**<0.001**	
Urine NTX (nmol/L)				
Before	64.7±3.7	64.8±6.7	64.7±7.6	0.96
After	57.4±3.3	34.7±5.7	33.4±3.5	**<0.001**
p-value	**<0.001**	**<0.001**	**<0.001**	
Serum CTX (ng/ml)				
Before	86.2±25.7	44.7±42.8	63.5±43.3	**0.03**

After	71.4±24.7	38.3±36.8	52.5±37.7	0.06
p-value	**<0.001**	**<0.001**	**<0.001**	

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