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Clinical study evaluating β -blockers use and fracture risk in patients with primary osteoporosis

Running title: β -blockers and primary osteoporosis

Mona Abd Elrafea Abdo

Master student, Department of Clinical Pharmacy, Faculty of Pharmacy, Tanta University, Tanta, Egypt,
Email: drmonaabdo14@gmail.com

Ph.D., Osama Mohamed Hasan Ibrahim

Professor of Clinical Pharmacy, Department of Clinical Pharmacy, Faculty of Pharmacy, Tanta University, Tanta, Egypt,
Email: osama.mohamed.ibrahim@pharm.tanta.edu.eg

Ph.D., Sahar Mohamed El-Haggar

Professor of Clinical Pharmacy, Department of Clinical Pharmacy, Faculty of Pharmacy, Tanta University, Tanta, Egypt,
Email: sahr.elhaggar@pharm.tanta.edu.eg

Ph.D., Salwa Elmorsy El-Sayed

D Associate professor of Rheumatology and Rehabilitation, Department of Rheumatology Disease, Faculty of Medicine, Tanta University, Tanta, Egypt,
Email: salwaelmorsy73@yahoo.com

Abstract--Background and objectives: In osteoporosis, low bone mass and growing fragility are main symptoms. BB users had greater BMD and/or decreased fracture risk, according to observational studies. Other studies found no effect of BB on fracture risk and osteoporosis disease. In this study, the effect of selective and non-selective BB on fracture risk in osteoporotic individuals was studied. Methods: A total of fifty osteoporotic patients of both genders were included in this randomized controlled, parallel, and prospective trial. Osteoporotic subjects were divided into three groups: a control group (CG), a non-selective beta-blocker group (NSBB), and a cardio-selective beta-blocker group (CSBB). T-score, fracture risk (FR), bone mineral density (BMD), and bone turnover markers were studied

as a result of this investigation. Results: After six months of follow-up, it was discovered that the T-score mean values of the three groups varied significantly. BMD was significantly higher in the group receiving non-selective beta-blockers (NSBB) than in the control group (CG). In the three categories of fracture risk region, the fracture risk was statistically decreased in both the NSBB and CSBB groups. Additionally, both the NSBB and CSBB groups demonstrated a decrease in bone turnover markers (BTM), as contrasted to the control group. Conclusion: NSBB or CSBB may assist improve BMD, decrease FR, and decrease BTM in osteoporosis. NSBB had a greater effect on decreasing the FR in the three locations studied. Additionally, it demonstrated a considerable reduction in BTM, particularly s-CTX, as compared to the CSBB group.

Keywords---Bone mineral density (BMD), Non-selective beta-blockers (NSBB), Beta-blockers (BB), Cardio selective beta-blockers (CSBB), Bone turn over markers (BTM), Fracture risk (FR).

Introduction

Millions of individuals worldwide have osteoporosis, a bone disorder.¹ Osteoporosis is defined by decreased bone mineral density and bone tissue destruction.² According to WHO criteria, osteoporosis is generally diagnosed when the bone mineral density (BMD) T-score is 2.5 standard deviations or more SD below peak bone mass.³ Osteoporosis manifests itself in two forms in the elderly: postmenopausal (type I), and senile (type II). Osteoporosis type I occurs following menopause, whereas type II arises due to aging.⁴ Osteoporosis fractures are one of the most dangerous effects of the disease, increasing the likelihood of mortality and severe damage. Aside from that, the high expense of osteoporosis and osteoporosis fracture care, as well as the need for competent personnel and enough material resources, are created an unacceptable burden. As a result, identifying risk factors for osteoporosis to avoid it has been a major focus of many research topics.

Hypertension, age, gender, diabetes, low estrogen levels, and coronary heart diseases are all major risk factors for osteoporosis, as well as drinks high in caffeine, and smoking habits.¹ Osteoporosis and hypertension are both age-related disorders and outcomes of the interplay between environmental and genetic variables. Hypertension is a substantial risk factor for osteoporosis.⁵ However, the question of whether osteoporosis and hypertension are linked remains disputed. Hypertension has been demonstrated to have a deleterious impact on bone mineral density (BMD).^{5, 6}

Cappuccio et al. (1999) studied over 3000 women and discovered a connection between bone loss around the femoral neck and elevated blood pressure.⁶ Hip fractures may be caused by hypertension-related calcium loss, according to the researchers. Other studies found no link between high blood pressure and low bone mass. Patients with osteoporosis and osteopenia had equal BMD

percentages, whether they had or did not have high blood pressure.^{7, 8} Hypertensive patients may be treated with adrenergic receptor antagonists (β -blockers), which lower blood pressure by inhibiting heart adrenergic receptor channels and releasing renin from the kidney.⁹ Beta-blockers may affect bone metabolism and fracture healing, according to recent studies.⁹ The osteoblast-like cells have been revealed to exhibit adrenergic receptors, which is unusual.^{10, 11} A receptor activator of nuclear factor kappa-B ligand (RANKL) and M-CSF are required for osteoclast development.¹² When adrenoceptors are activated in mouse bone marrow cells, osteoclast-genesis is initiated. A 30% reduction in fracture risk and a boost in BMD was seen in the spine, hips, and the whole body when beta-blockers were given to study participants.¹³ Another theory suggested that leptin signaling in the hypothalamus stimulated a positive, sympathetic tone, targeting either leptin or its signaling pathway by β -blocker, might be effective for osteoporosis.¹⁴ As per this theory, osteoporosis can be enhanced by using a beta-blocker that focuses on leptin or its signaling route in the hypothalamus.¹⁵ There is a dearth of research on the interaction between beta-blockers and osteoporosis. Thus, this study was conducted to fulfill a knowledge gap about the link between the usage of osteoporosis and beta-blockers (non-selective or selective) in primary osteoporotic patients.

Subjects and methods

Following a thorough explanation, all participants have signed a written consent form. This experiment was conducted in conformity with standard clinical practices of the Institutional Research Ethics Committee (REC) of Tanta University's College of Pharmacy and Tanta University Hospital Institutional Review Board (IRB). The study's clinical trial unique identifier number is NCT04704947.

Study design and patients' population

At Tanta University Hospital, Egypt, 50 women, and men who had been diagnosed with osteoporosis were selected to participate in this study, which was performed at the Rheumatology and Rehabilitation Department, from the end of January 2021 to the end of May in the same year. Using the exclusion and inclusion criteria illustrated in Figure 1, the patients were examined for their appropriateness to participate in the research.

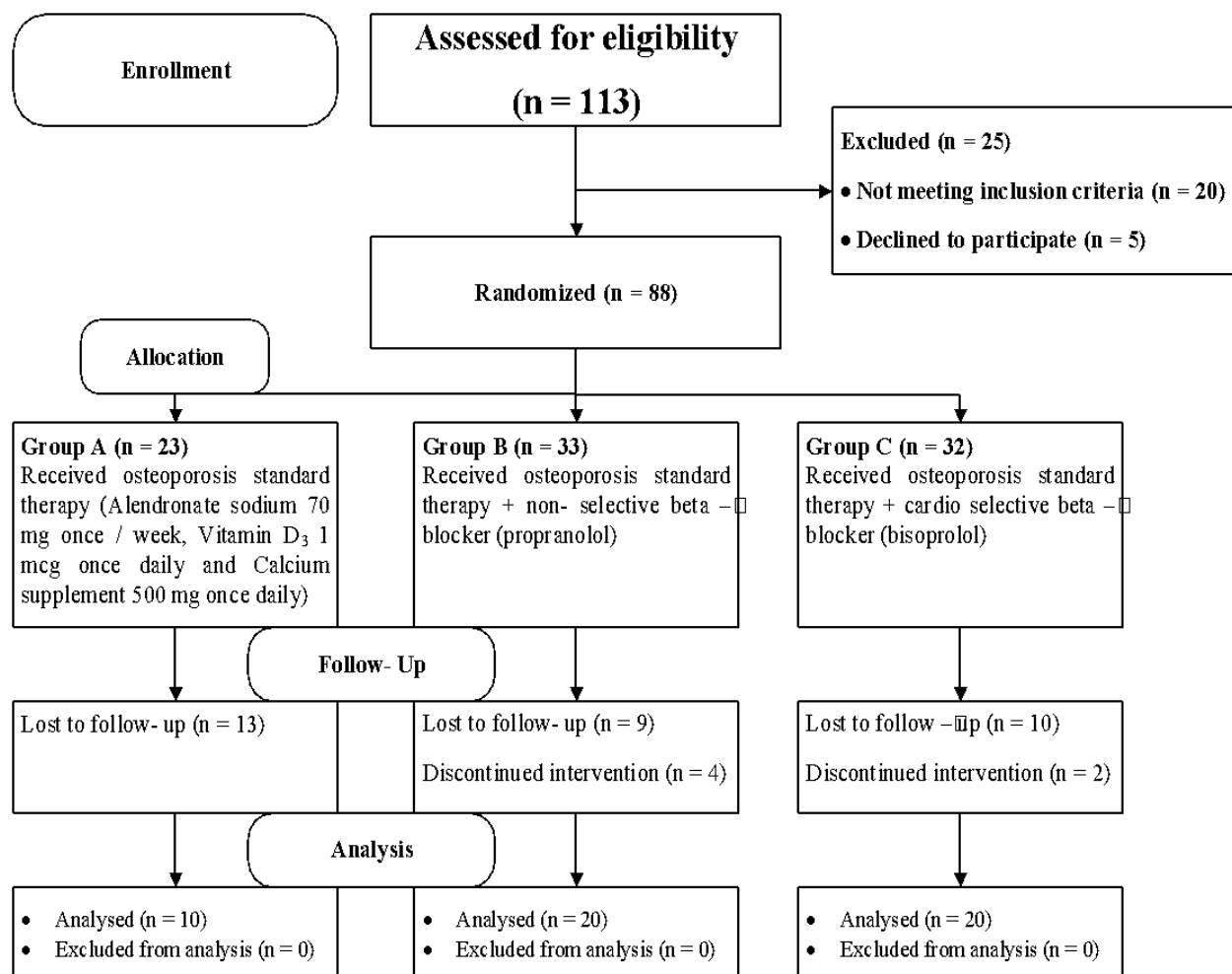


Fig 1. Consort flow diagram of the study design.

Inclusion criteria

A BMD T-score of 2.5 or more SD below peak bone mass is required for participants equal to or above 50 years old, male and female osteoporotic patients, and hypertensive and normotensive patients.

Exclusion criteria

Individuals on medications that may improve osteoporosis, including ARBs, ACEIs, Nitrates, and Statins. Patients who used medications that may exacerbate osteoporosis diseases, such as anti-anxiety medications, corticosteroid therapy, and antidepressants, are also on the list.

Patients refused to provide their consent and did not give it even after being told adequately about the risks involved.

Study endpoints

The primary endpoints

- 1) An increase in BMD and T-score was detected using dual-energy x-ray absorptiometry.
- 2) The change (enhancement) in fracture risk using fracture index with known BMD calculator, which calculated the fracture risk in the next five years (vertebral, non-vertebral, and hip fracture risk).¹⁶

The secondary endpoints

- 1) The change (reduction) in the blood level of the C-telopeptide fragment of type 1 collagen (CTX) was identified by ELISA.
- 2) The change (reduction) in urine cross-linked N-terminal telopeptides of type 1 collagen (NTX) in the urine of patient sample was measured by the ELISA method.
- 3) The change (decrease) in urine-free deoxypyridinoline (f DPD) was detected by the ELISA technique.

Study Protocol

Signing an informed consent form was a condition of participation in the trial for all patients who satisfied the eligibility requirements mentioned above. To preserve bone density, osteoporotic individuals are prescribed calcium supplement 500 mg once/day and Alendronate sodium 70 mg once weekly (Fosamax)[®], as well as Vitamin D3 1 mcg daily (osteoporosis standard treatment). Using a table of random numbers, the enrolled subjects were randomly allocated to one of the following groups:

Group A (control group) (CG): Ten patients with osteoporosis attended to the Rheumatology and Rehabilitation department. They were given the conventional treatment for osteoporosis. After six months of therapy, the patient was released.

Group B (Non-selective beta-blocker Group) (NSBB): Propranolol (Inderal)[®] 10 mg once a day was administered to 20 individuals with osteoporosis, which was subsequently raised in a dose-dependent manner according to a patient's response. After six months of medication and six months of follow-up, it was determined whether the condition had improved or deteriorated.

Group C (Cardio-selective β -blocker Group) (CSBB): As a result of this study, 20 osteoporotic patients were placed on the same medication as (CG) as well as a daily dose of bisoprolol (Concor)[®] 5 mg once a day titrated up according to patient response. Patients were monitored and evaluated for six months after therapy to see any change in the rate of illness development or regression, as demonstrated in Fig 1.

The following procedures were performed on all enrolled patients:

History taking with an emphasis on Demographic data were included the individuals' age, sex, weight, height, and BMI, as well as his or her complete medical and pharmaceutical history, and past medicinal history, emphasizing all sorts of prior fragility fractures which were categorized into three broad categories: clinical vertebral, non-vertebral, and hip prior fragility fractures.

Associated risk factors: Factors that affect a patient's health (e.g., alcohol usage, smoking, weight, and height) as well as the patient's medical history

Sample collection

Each patient's venous blood and urine samples were obtained twice.

Timing of sample collection

Serum: After an overnight fast, in the morning (before 9 a.m.).

Urine: The first morning void following an overnight fast with creatinine correction.

The following are the standard laboratory tests

Blood chemistry panel and liver function test, 25-hydroxyvitamin D level, and thyroid function were tested. The baseline laboratory tests include serum protein electrophoresis calcium/creatinine ratio, Luteinizing hormone (LH)/follicle-stimulating hormone (FSH), and testosterone. Studies looked at how long patients were on bisphosphonate medication and whether or not they were taken BB before being included in the study. DXA was used to measure BMD at the AP spine L1-L4, at the left femur (Neck and Total), and at the forearm radius to recognize the density of the bone at these three regions. Bone mineral density is also now determined by (DXA) technique, which is the gold standard for BMD evaluation.

Biochemical analysis

Follow-up tests on human deoxypyridinoline (urine DPD), serum C-telopeptide fragment of type 1 collagen (CTX), and urine cross-linked N-terminal telopeptides of type 1 collagen (NTX) were performed before and after six months of follow-up, and all these biomarkers were measured via ELISA.

Methods for analyzing biochemical markers

ELISA testing for the detection of BTM

Analytical ELISA test for CTX-I

According to Chubb S. (2012), this test was used to assess the concentration of CTX-I in a patient's serum sample.¹⁷

Urine NTX ELISA test

This test was utilized to determine the amount of NTX in a human urine sample, according to Kanakis I. (2004).¹⁸

Urine DPD ELISA test

This test was employed to examine the DPD level in the human urine specimen, according to Hamwi A. (2001).¹⁹

Statistical analysis

Tables were compiled using Microsoft® Office Excel 2016, a product of Microsoft Corporation. We utilized the SPSS statistical software tool to conduct statistical analyses (version 26.0, IBM corporation software group, USA). Statistical analysis was performed for each parameter according to the obtained data. The ANOVA test was used to get the mean values ($\pm$ SD) for the continuously variable to ascertain whether or not there was a statistically significant variation between the experimental and control groups. Researchers used TUKEY'S test of the Least Significant Difference (LCD) in the post-hoc analysis. In order to compare the mean values of each parameter before and after a six-month follow-up within each group, we used the paired samples t-test. Comparing two categorical variables was conducted by the chi-square test. T-scores were correlated with BTM levels using Pearson correlation. A significance level of $P < 0.05$ was deemed to be appropriate.

Results

An overview of the research population's demographics and medical history

Table 1 demonstrates how similar the characteristics of the three groups were at the beginning. There were only four men and 46 women in every 100 patients (8% and 92%, respectively). Ninety-four percent of patients who did not smoke made up 47 patients (94%). Whereas smokers accounted for three patients of the total (6%). Patients with one past fracture were the most common, accounting for 22 (44%) of the patients, followed by those with two prior fractures 16 (32%), three prior fractures were only one (2%), and those with no prior fractures was 11 (22%). The normotensive patients were 18 (36%), while the hypertensive patients included in the study were 32 (64%). In contrast, the mean ($\pm$ SD) of weight was 82.5 kg ($\pm$ 15.1), age was 60.3 years ($\pm$ 5.1), height was 158.3cm ($\pm$ 20.2), and the BMI was 32.7 ($\pm$ 5.4), as shown in Table 2. Chi-square was used to establish that gender distribution showed statistically significant difference.

Table 1
Demographic data and initial clinical features for each of the three evaluated groups

Parameters		Groups						Chi-Square	
		Group A (n=10)		Group B (n=20)		Group C (n=20)			
		N	%	N	%	N	%	X ²	<i>P-value</i>
Sex	Male	3	30.0	1	5.0	0	0.0	8.560	0.014 *
	Female	7	70.0	19	95.0	20	100.0		

Smoking	Non-Smoker	8	80.0	1	95.0	2	100.0	4.787	0.091
	Smoker	2	20.0	1	5.0	0	0.0		
	No	1	10.0	4	20.0	6	30.0		
Previous fracture	One	4	40.0	1	55.0	7	35.0	5.696	0.458
	Two	5	50.0	4	20.0	7	35.0		
	Three	0	0.0	1	5.0	0	0.0		
Blood pressure	Normotensive	6	60.00	7	35.00	5	25.00	3.559	0.169
	Hypertensive	4	40.00	1	65.00	1	75.00		
				3		5			

*Statistically significant difference among the three studied groups.

(Group A): Individuals with osteoporosis who received standard therapy for osteoporosis

(Group B): Osteoporotic patients receiving standard osteoporosis medication plus NSBB

(Group C): Osteoporotic individuals administered standard osteoporosis therapy plus CSBB

Table 2
Demographic statistics and clinical baseline features of the three analyzed groups

Parameters		Groups			ANOVA	
		Group A (n=10)	Group B (n=20)	Group C (n=20)	F	P-value
Age	Range	51 – 68	50 – 65	52 – 63	1.014	0.371
	Mean $\pm$ SD	60.1 $\pm$ 6.4	61.5 $\pm$ 4.7	59.3 $\pm$ 4.2		
Weight (kg)	Range	70 – 95	60 – 124	54 – 125	0.143	0.868
	Mean $\pm$ SD	82.4 $\pm$ 9.7	84.0 $\pm$ 17.9	81.2 $\pm$ 17.8		
Height (cm)	Range	150-170	147-174	145-170	3.197	0.050
	Mean $\pm$ SD	161.0 $\pm$ 6.7	159.9 $\pm$ 6.8	155.4 $\pm$ 6.6		
BMI	Range	27.2-39.5	25.8-48.1	24.2-47.1	0.258	0.774
	Mean $\pm$ SD	31.9 $\pm$ 4.1	32.8 $\pm$ 6.2	33.5 $\pm$ 6.1		

BMI = Body mass index

There is no statistically significant difference among the three studied groups.

Prior to therapy and six months after treatment in the three groups investigated for T-score, bone mineral density, and 5-year (non-vertebral, hip, and vertebral) fracture risk

The T-score is a critical diagnostic tool for osteoporosis, and it is one of the key outcomes in this study. The mean differences in T-score values after six months of treatment for groups B and C were -3.1 versus -2.3 and -3.4 versus -2.5, respectively. According to (table 3 and figure 2), there was a substantial (P-value less than 0.05) difference in the T-score mean values following six months of BB medication between (A and B groups), and the (A and C) groups.

After six months of CSBB and NSBB therapy, there was a significant variation in BMD mean values within the same group in B and C groups, with values of 0.6

versus 0.7, as seen in (Fig. 2 and Table 3). Concerning calculating the 5-year (hip, non-vertebral, and vertebral) fracture risk, after six months of medication with CSBB (group c) and NSBB (group B), non-vertebral fracture risk (FR) decreased from 21.3 and 22.4 to 19.7 and 20.1, respectively. After six months of therapy with the BB medication, there was a significant difference in non-vertebral FR between groups A, B, and C, as shown in (Table 3).

After six months, there was a substantial significant decrease in the 5-year hip fracture risk values in groups B and C ($P>0.05$): from 5.5 to 4.1 and from 4.9 to 3.9, respectively (See Table 3 for further information). Groups A and B and A and C had significantly different FR mean values after six months of BB ingestion ($P>0.05$) (Figure 3 and Table 3). The 5-year vertebral-FR was revealed a similar pattern. After six months of therapy with NSBB and CSBB, the FR mean values in the B and C groups reduced dramatically (Table 3 and Fig. 3). As per data, the mean values in B and C groups were reduced from 8.5 and 7.9 to 7.2 and 7 after therapy (Table 3 and Fig. 3). The FR values of the A & B and A & C groups differed significantly following six months of BB consumption.

Table 3
Bone mineral density, T-score, and 5-year fracture risk of (hip, non-vertebral, and vertebral) in the three examined groups prior and after six months of therapy

Parameters	Values (Mean $\pm$ SD)	Group A (n=10)	Group B (n=20)	Group C (n=20)	ANOVA <i>P-value</i>
T. Score	Before	-3.3 $\pm$ 0.5	-3.1 $\pm$ 0.9	-3.4 $\pm$ 1.0	0.575
	After	-3.5 $\pm$ 0.6	-2.3 $\pm$ 0.8 ^a	-2.5 $\pm$ 0.7 ^b	0.001
	P. value	0.162	<0.001*	<0.001*	
BMD (g/cm ²)	Before	0.6 $\pm$ 0.1	0.6 $\pm$ 0.1	0.6 $\pm$ 0.1	0.682
	After	0.6 $\pm$ 0.1	0.7 $\pm$ 0.1	0.7 $\pm$ 0.1	0.060
	P. value	0.962	<0.001*	<0.001*	
5-year non-vertebr al FR	Before	22.8 $\pm$ 3.9	22.4 $\pm$ 3.7	21.3 $\pm$ 3.7	0.521
	After	24.4 $\pm$ 3.9	20.1 $\pm$ 3.6 ^a	19.7 $\pm$ 3.8 ^b	0.007
	P. value	0.168	0.004*	0.011*	
5- year hip FR	Before	5.8 $\pm$ 2.4	5.5 $\pm$ 2.3	4.9 $\pm$ 2.3	0.525
	After	6.7 $\pm$ 2.4	4.1 $\pm$ 2.1 ^a	3.9 $\pm$ 2.2 ^b	0.006
	P. value	0.168	0.005*	0.015*	
5-year vertebral F.R	Before	8.7 $\pm$ 2.1	8.5 $\pm$ 2.0	7.9 $\pm$ 2.0	0.518
	After	9.5 $\pm$ 2.1	7.2 $\pm$ 2.0 ^a	7.0 $\pm$ 2.1 ^b	0.008
	P. value	0.168	0.004*	0.010*	

Group A (control group), group B (NSBB group), and group C (CSBB group),
BMD = Bone mineral density, FR = Fracture risk.

a. Statistically significant variation between A and B groups.

b. Statistically significant difference between A and C groups.

*Statistically significant variation within B and C groups.

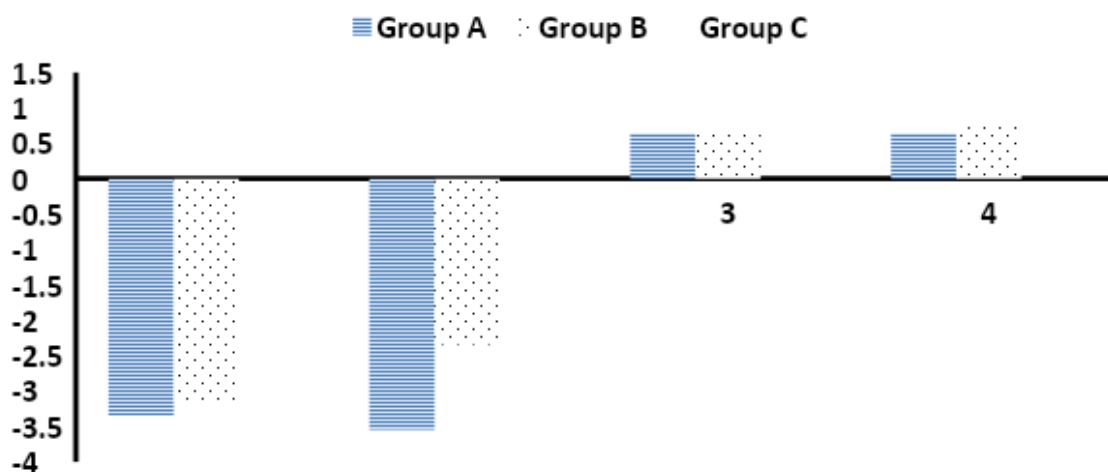


Fig 2. T-score and bone mineral density measurements were taken prior and after six months of medication in each of the three groups investigated.

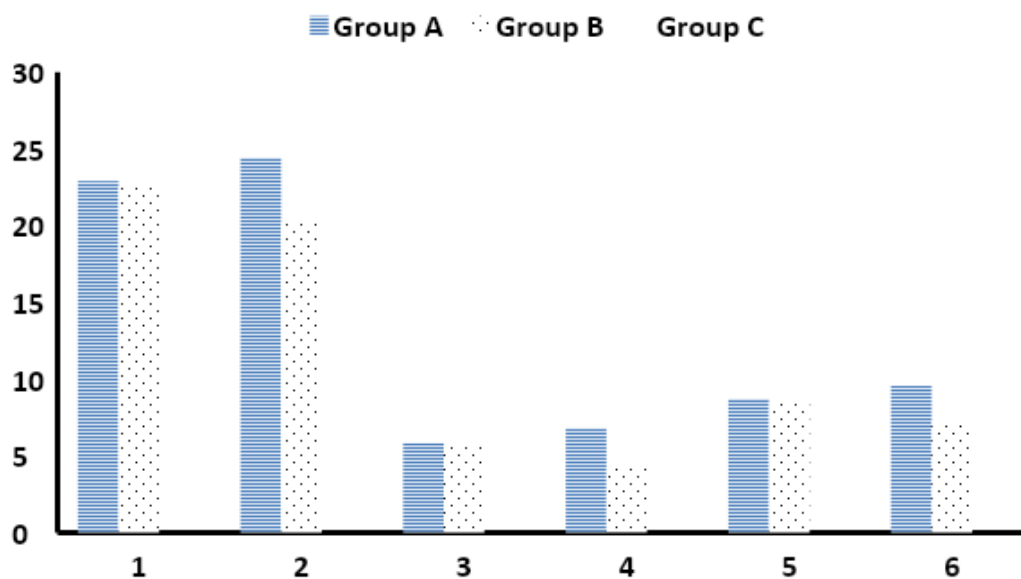


Fig 3. Five-year risk of fracture (hip, non-vertebral, and vertebral) prior to and after six months of therapy in the three studied groups.

Assessment of bone turnover markers (BTM) in the three examined groups prior and after six months of follow-up (secondary endpoints): NTX, CTX, and DPD

Interestingly, there was a substantial difference in mean CTX values prior to medication between the A and B groups, and between the A and C groups, at values of 86, 44.9, and 63.7, consecutively. However, following six months of NSBB and CSBB treatment, there was a substantial (P-value less than 0.001) reduction in the mean CTX values within the same B and C groups, respectively, from 44.9 and 63.7 to 38.5 and 52.7 (Table 4 and Fig 4). NTX levels in urine were significantly different across groups A, B, and C following six months of medication (Table 4). Mean values for each group ranged from 64.5, 64.6, and 64.9 before falling to 57.6, 34.9, and 33.2, respectively, due to treatment. Furthermore, the urine NTX mean values were substantially different between the A-B and A-C groups, with P-value less than 0.001 (Table 4 and Fig. 4). The mean values of urine NTX among A, B, and C groups also significantly varied with a P-value less than 0.001 using the ANOVA test (Table 4 and Fig. 4).

The levels of DPD in the urine of patients in groups A, B, and C varied considerably after six months of therapy with NSBB and CSBB (Table 4). There was a significant variation in urine DPD levels between the two A-B and A-C groups, and the three groups (Table 4 and Fig. 4).

Table 4
Between the three groups tested, the bone turnover markers before and after six months of therapy

Parameters	Mean ±SD	Group A (n=10)	Group B (n=20)	Group C (n=20)	ANOVA <i>P-value</i>
Serum CTX (ng / mL)	Before	86.0 ± 25.9	44.9 ± 42.6 ^a	63.7 ± 43.1	0.036
	After	71.2 ± 24.9	38.5 ± 36.6	52.7 ± 37.5	0.061
	P. value	0.020*	<0.001*	<0.001*	
Urine NTX (n. mol. /L)	Before	64.5 ± 3.9	64.6 ± 6.9	64.9 ± 7.4	0.984
	After	57.6 ± 3.1	34.9 ± 5.9 ^a	33.2 ± 3.7 ^b	<0.001
	P. value	0.001*	<0.001*	<0.001*	
Urine DPD (n. mol. /L)	Before	27.8 ± 6.3	23.5 ± 6.4	26.1 ± 7.0	0.217
	After	20.4 ± 6.4	13.1±2.9 ^a	14.9 ± 3.7 ^b	<0.001
	P. value	<0.001*	<0.001*	<0.001*	

urine NTX= urine cross-linked N-terminal telopeptide of type 1 collagen, **S-CTX** = Serum C-telopeptide fragment of type 1 collagen, and **urine DPD** = Human deoxy pyridinoline.

a. Statistically significant variation between A and B groups.

b. Statistically significant variation between A and C groups.

* Statistically significant variation within A, B, and C groups.

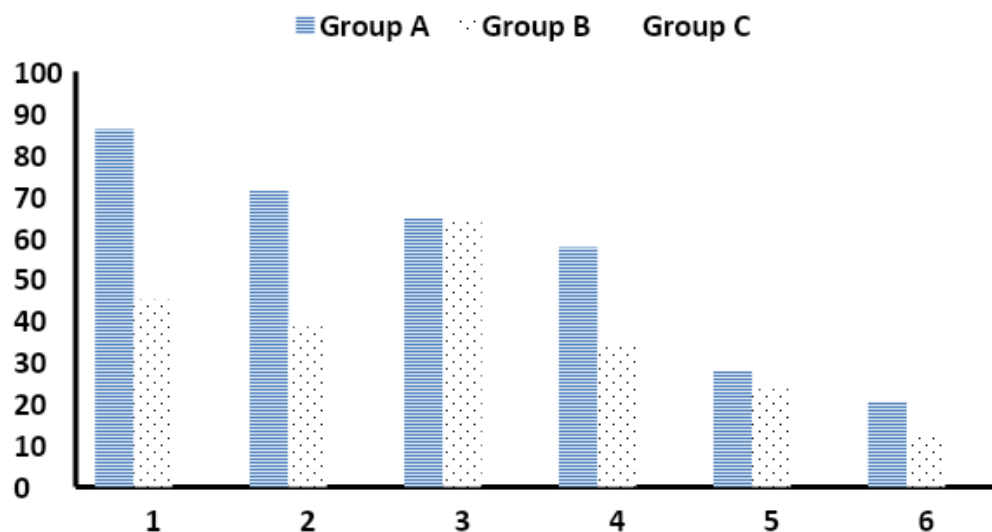


Fig 4. Prior to and after six months of therapy, bone turnover markers (BTM), serum (CTX), urine (NTX), and urine (f DPD) were measured in the three studied groups.

The correlation between BTM and T-score after six months of follow-up and BB-administration

Following BB-taking and six months of follow-up, Serum CTX, and urine DPD exhibited a significant negative correlation with T-Score with a P-value of 0.001*. A considerable negative association between urine NTX and T-score was found with a P-value of 0.032 (Table 5 and Figs 5-7).

Table 5

Pearson correlation coefficient between T-score and bone turnover markers (BTM) after six months of follow-up and BB use in the B and C groups

Correlations		
Pearson Correlation	T. Score After six months of follow-up	
	R	P-value
Serum CTX (ng/mL)	-0.650	<0.001*
Urine NTX (n. mol./L)	-0.339	0.032*
Urine DPD (n. mol./L)	-0.550	<0.001*

BTM= Bone turnover marker.

* Statistically significant variation among the studied groups.

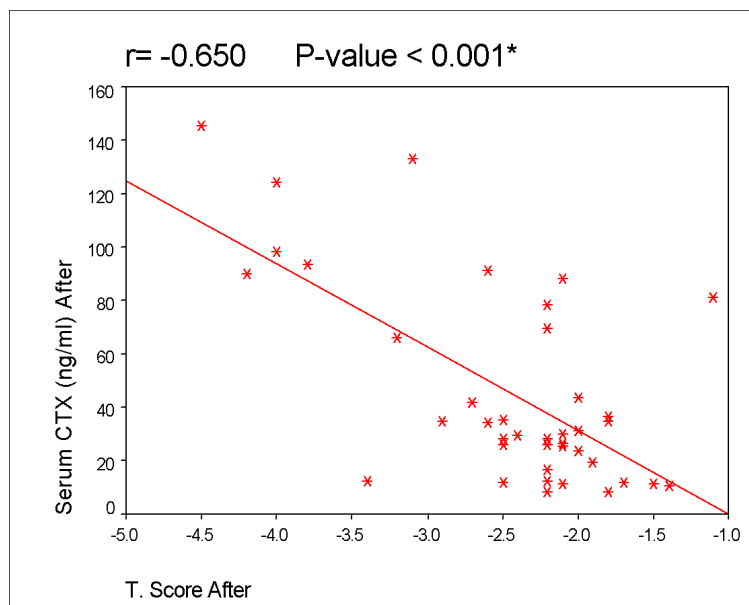


Fig 5. The correlation between T-score and serum CTX after six months of follow-up.

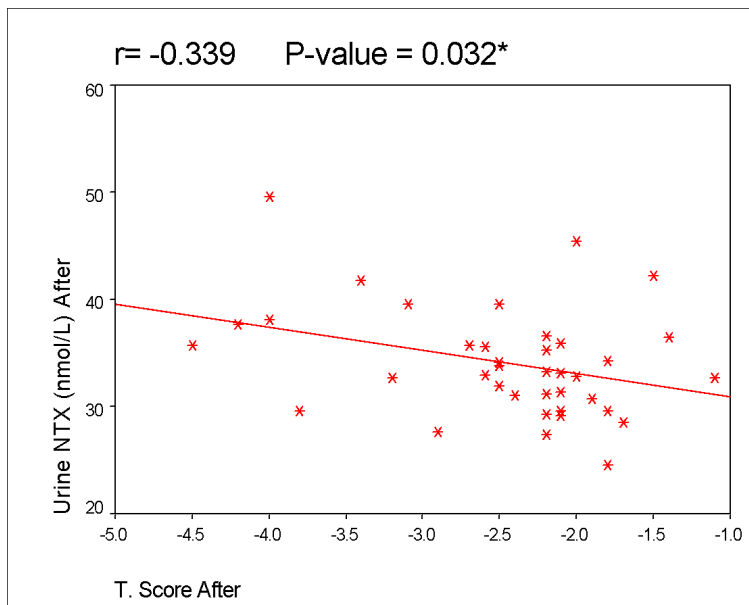


Fig 6. The correlation between T-score and urine NTX after six months of follow-up

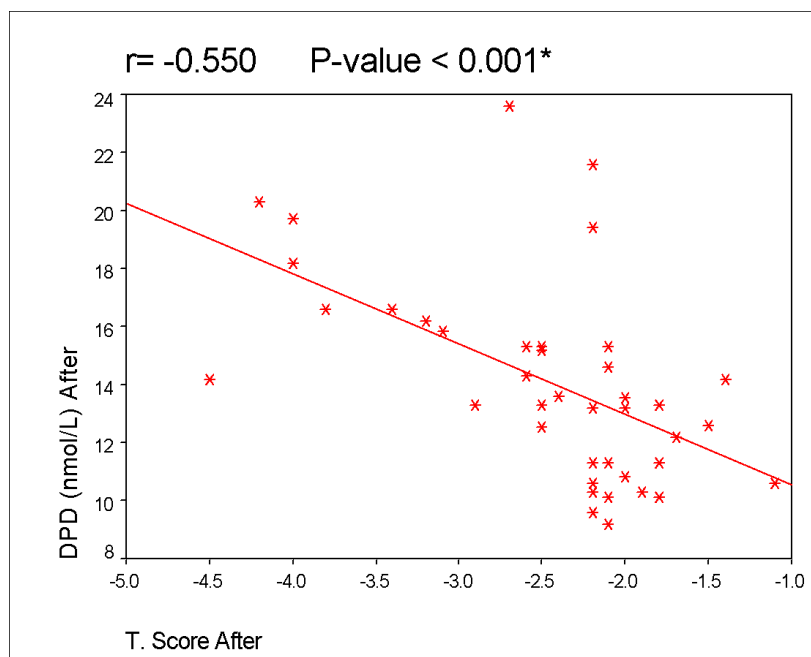


Fig 7. The correlation between T-score and urine DPD after six months of follow-up

Discussion

Health problems associated with aging, such as osteoporosis and hypertension, are caused by genetic and environmental causes.²⁰ Additionally, hypertension has been associated with an elevation in bone loss and fracture risk.²¹ Clinical data did not support this assumption despite several studies indicating the importance of the sympathetic nervous system to the growth and development of bones. There is some evidence that high blood pressure and osteoporosis are associated, although the precise connection is still debated. Osteoporosis has been connected to hypertension, one of the most common medical disorders for which beta-blockers are recommended.

Researchers conducted this research to see whether beta-blockers would affect osteoporosis, as there is a lack of human data on the illness. In this research, men's and women's bone health was investigated using non-selective and cardio-selective (BB) to demonstrate the drug's influence on bone health in men and women over the age of 50. Cardio selective beta-blockers (CSBB) and Non-selective beta-blockers (NSBB) are significantly reduced the T-score of patients in both groups (C and B). For the lower back and entire femur, patients in the BB group exhibited a better T-scores than those in the control group. The sympathetic nervous system seems to be in charge of bone mineral metabolism, as shown by a growing number of studies.^{11, 22} Many studies have shown an increase in BMD as a result of BB use.^{15, 23} Treatment with NSBB and CSBB resulted in an increase in BMD in the B and C groups. In postmenopausal women, Levasseur and his colleagues found that BB had no impact on bone

mass.²⁴ Following six months of non-selective or selective BB medication, the FR of non-vertebral fractures was significantly decreased in the B and C groups than in controls, which was contrasted to the control group findings. While recent research demonstrated that selective BB use was correlated with a lower fracture incidence, but non-selective BB use did not.²⁵ A comprehensive review and meta-analysis study revealed that BB significantly reduces fracture risk.²⁶ After six months of BB therapy, the 5-year hip, and vertebral FR was significantly reduced, regardless of whether the treatment was selective or not. FR values for hips and vertebrae were lower in the B and C treatment groups after six months than in the control group.

To better understand the bone turnover rate and the efficacy of osteoporosis therapy, researchers looked at bone turnover markers (BTMs). The effects of BB on BTM in humans have been studied sparingly, and the results have been conflicting. In a prior randomized controlled trial, Reid and his coworkers studied the impacts of BB on bone markers. After two weeks of propranolol treatment, serum osteocalcin levels were 20% lower. Serum C-terminal telopeptide of type I collagen (CTX) did not differ appreciably.²⁷ DPD levels in the urine (another BTM) decreased after six weeks of propranolol treatment, according to the same study. They addressed this discrepancy by positing that DPD is generated in the kidneys as a byproduct of the breakdown of cross-linking telopeptides, whereas propranolol acts directly on the kidney.²⁸ CTX, on the other hand, is immediately liberated from the bone due to the osteoclastic resorption process.²⁷ CTX levels were dramatically decreased in the present study after six months of propranolol and bisoprolol medication.

When BB was administered for six months, urine NTX and DPD levels decreased significantly within the B and C groups. A significant drop was also observed after six months between the A and B and A and C groups.

When assessing a person's fracture risk, both BMD and BTM should be considered. The osteoporosis group had higher BTM levels (s-CTX, u-DPD) than the control group.²⁹ After menopause, BMD begins to decline faster than it had previously.²⁹ Following six months of BB medication, a negative correlation between bone turnover markers (BTMs) and T-score was seen, with BTMs decreasing in conjunction with higher T-score and reduced osteoporosis. Despite some controversy concerning the anti-osteoporotic effect of BB. BMD, FR, and BTM were all enhanced in the current study with the administration of BB (selective or non-selective) and shown a beneficial impact on bone resorption by reducing BTMs.

Conclusion

Selective and non-selective BBs negatively impacted bone health biomarkers, especially the bone turnover markers (urine NTX, serum CTX, and urine DPD). The findings were statistically significant when contrasted to the control group. Moreover, we found that NSBB demonstrated a better effect in enhancing the FR in the three regions measured. In addition, it showed a significant decrease in BTM, especially s-CTX, compared to the CSBB group. This gives us the indication

that NSBB may be better than CSBB in enhancing osteoporosis, especially its beneficial effect in decreasing FR and decreasing s-CTX. After six months of investigation, we discovered a substantial negative correlation between BTM and T-score. Using BB to treat osteoporosis may result in decreased fracture risk (FR), increased bone mineral density (BMD), and decreased bone turnover markers (BTMs).

Limitations

The limitations of this study were the relatively small numbers of patients investigated. The obstacles that faced our teamwork were the period of follow-up (short period of treatment six months), and the lousy compliance of some patients that resulted in collecting others with more time-consuming.

Recommendation

We recommend repeating the study on many osteoporotic patients and with different dosage forms and doses of β -blockers to confirm its beneficial effects in enhancing osteoporosis disease and reducing fracture risk, especially in postmenopausal women.

Abbreviations

ALT: Alanine transaminase; **ANOVA:** Analysis of Variance; **AST:** Aspartate transaminase; **ELISA:** Enzyme-Linked Immunosorbent Assay; **UK:** United Kingdom.

Declarations

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Clinical trial registration number

Clinical Trials.gov Identifier: NCT04704947.

Ethical approval

Researchers who worked with human subjects followed the ethical guidelines set out by the Tanta University, Study Ethical Committee, the Helsinki Declaration, and any subsequent amendments or by other analogous codes of conduct. Revisions made to this document have been called the Helsinki Declaration.

Informed consent

All participants in the research were allowed to provide their informed permission.

Conflict of Interest

In order to avoid any appearance of a conflict of interest, the authors, Mona Abdo, Osama Ibrahim, Sahar El-Haggar, and Salwa El-Sayed, conducted this research independently and without any financial or commercial connections.

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Authors' contributions

The design, clinical and experimental trials, and data analysis were carried out by all writers. There was unanimous agreement on the final draught among the writers.

Release of information with the author's permission

Not applicable.

Availability of data and material

Please contact the corresponding author to get the data sets used and/or analyzed in this work.

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