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## A Systematic Review on the Relationship between $\beta$ -blockers and Bone Health

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**Abstract:** Nowadays  $\beta$ -blockers are commonly used for a broad spectrum of diseases including cardiovascular diseases but their effects on the bone are an issue of concern. Animal studies support their protective effects on bone however, human studies are controversial. We followed this issue by conducting a systematic review of all existing materials through all available search engines. Results indicate a major controversy existing among studies. Most of studies are limited to lack of considering pharmacokinetic/pharmacodynamic properties of this class of drugs, Body Mass Index (BMI) as well as physical activity of patients, adequacy of sample size or ability to sub-analyze data, smoking behavior and patients' lifestyle that all can be a source of bias and cause controversy. Further studies by paying attention to above-mentioned bias sources are highly recommended to help making sure about the safety of this class of medications on bone.

**Key words:**  $\beta$ -blocker, osteoporosis, bone metabolism, fracture risk, review

### INTRODUCTION

Beta-blockers are a class of medications with extensive usage. These drugs are administered in several cardiovascular diseases including hypertension, ischemic heart disease, certain cardiac arrhythmias and some specific forms of neurologic disorders like migraine. There are two common types of beta-adrenergic receptors, type 1 and 2.  $\beta_2$ -receptors were recognized on human osteoblastic and osteoclastic cells (Moore *et al.*, 1993; Takeda *et al.*, 2002), making the sympathetic regulation of bone remodeling questionable. The effect of beta receptors on bone metabolism was shown in different *in vitro* and *in vivo* studies, however there is no conclusive data (Togari, 2002; Minkowitz *et al.*, 1991). In addition to several endocrine and paracrine/autocrine mechanisms affecting bone metabolism including Monocyte-macrophage Colony Stimulating Factor (M-CSF), osteoprotegerin-receptor activator of nuclear factor- $\kappa$ B ligand counteraction (OPG-RANKL), tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin-1 (IL-1), interleukin-6 (IL-6), interleukin-11 (IL-11), prostaglandins especially PGE2 (Abdollahi *et al.*, 2005; Salari *et al.*, 2008a, b, 2009; Salari-Sharif *et al.*, 2010; Yousefzadeh *et al.*, 2006; Salari Sharif and Abdollahi, 2010), sympathetic nervous system was identified to control this process. The role of

functional receptors for neuro-osteogenic factors on bone cells and probable existence of a neuro-osteogenic network have been recognized (Moore *et al.*, 1993; Togari, 2002; Lerner, 2002; Togari *et al.*, 1997). It has been demonstrated that beta receptor stimulation can induce osteoclastogenesis via induction of IL-6, IL-11 and PGE2 production and expression of osteoclast differentiation factor in osteoblasts (Takeuchi *et al.*, 2000). Also, expression of RANKL and OPG on osteoblasts is regulated by sympathetic nervous system which is mediated by  $\alpha$ - and  $\beta$ -adrenergic stimulation (Togari and Arai, 2008). The catabolic effect of sympathetic nervous system on bone was shown in several studies either (Togari and Arai, 2008). The finding of the role of leptin in modulating bone mass increased the level of evidence of the involvement of sympathetic nervous system in bone metabolism (Togari, 2002). The effect of  $\beta$ -receptors and their activation are briefly shown in Fig. 1. Leptin is secreted by adipocytes that regulate body weight. It was theorized that leptin may affect bone remodeling via direct effect on bone cells or central activation (Cornish *et al.*, 2002; Ducy *et al.*, 2000). Leptin inhibits bone formation by activating osteoblastic  $\beta$ -adrenergic receptors (Takeda *et al.*, 2002). Ducy *et al.* (2000) observed that leptin deficient mice have more osteoclasts and bone resorption parameters in association with higher bone

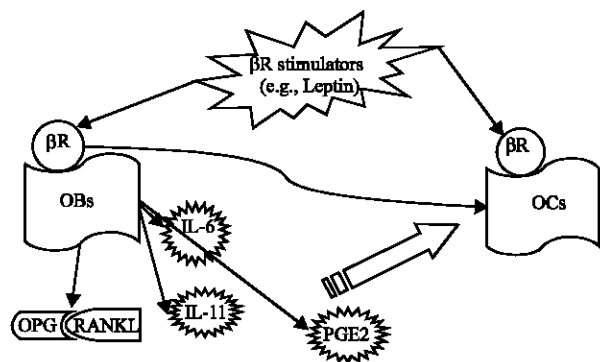


Fig. 1: The probable mechanism of action of  $\beta_2$ -receptor agonists on bone cells.  $\beta_2R$ :  $\beta_2$  receptors; OBs: Osteoblasts; OCs: Osteoclasts; OPG: Osteoprotegerin; RANKL: Receptor activator of nuclear factor  $\kappa B$  ligand; IL-6: Interleukin-6; IL-11: Interleukin-11; PGE2: Prostaglandin E2

mass which is quite unique. In addition Elefteriou *et al.* (2005) stated that carrying inactivate leptin gene is associated with high bone mass in human. Taken together and considering adipocytes in both mouse and human, it seems that leptin acts on bone in a regulatory pathway (Elefteriou *et al.*, 2004). The role of leptin on bone mass via central pathway was indicated by others (Ahima *et al.*, 2000; Ahima, 2004) and yet there is no promising evidence of direct effect of leptin on osteoblasts (Karsenty, 2006) mentioning that leptin influences bone resorption via sympathetic nervous system, in the way that sympathetic nervous system via  $\beta_2$  adrenergic receptors regulate bone mass (Elefteriou *et al.*, 2005).

Despite of the theoretic base of the impact of  $\beta$ -blockers on bone metabolism, to date there is no conclusive data available, while their increasing indication, prescription and usage make more patients vulnerable to their effects.

## MATERIALS AND METHODS

Various search engines and databases including Pubmed, Web of Science, Scopus and Google Scholar using the keywords of osteoporosis, sympathetic nervous system, leptin, adrenergic receptors,  $\beta$ -blockers, propranolol, bone markers and Bone Mineral Density (BMD) were searched. We limited our search to a special time period (2000-2010), however, there were no reliable investigation in this issue in human before this period of time. Only review articles including systematic review articles were excluded from study. Finally, 14 studies were reviewed systematically.

**Animal studies:** Several animal studies reported the involvement of sympathetic nervous system in controlling bone metabolism (Takeda *et al.*, 2002; Cherruau *et al.*, 1999). Studies in mice indicated that  $\beta$ -agonists stimulate bone resorption (Moore *et al.*, 1993), while  $\beta$ -blockers increase bone mass (Takeda *et al.*, 2002). Despite many animal studies on the association of  $\beta$ -blocker usage and bone mass, the subject still remains controversial.

**Human studies:** All of the relevant observational studies are shown in Table 1.

**$\beta$ -blockers and BMD:** In the study of osteoporotic fractures, 8412 postmenopausal women participated including 1099 women as  $\beta$ -blocker users and the rest as controls. Reid *et al.* (2005a) followed the subjects for 7 years. After 4 years significant differences in BMD was found in both groups, but after adjustment for weight, the differences were eliminated. They concluded that there is no relationship between  $\beta$ -blocker use and BMD and the relation of  $\beta$ -blocker with risk of fracture is conflicting.

A prospective case-control study evaluated the effect of  $\beta$ -blockers on BMD in 50 elderly  $\beta$ -blocker users, who were not taking anti-resorptive medications. In comparison with non-users, the investigators reported significantly higher BMD in all measured skeletal sites (Turker *et al.*, 2006).

**$\beta$ -blockers and fracture risk:** Schlienger *et al.* (2004) determined the association of  $\beta$ -blocker and thiazide usage with the risk of fracture in a case-control analysis. They enrolled 30601 case patients aged 30-79 years with an incident fracture diagnosis. They reported decreased risk of fracture with  $\beta$ -blocker usage alone or in combination with thiazide diuretics.

Rejnmark *et al.* (2006) investigated the relationship between fracture risk and  $\beta$ -blockers in a population-based pharmaco-epidemiological case-control study in 5 years. They conducted the study on 124655 patients with an incident fracture and 373062 controls. Significant decrease in fracture risk was observed in  $\beta$ -blocker users with no difference between men and women. Wiens *et al.* (2006) performed a meta-analysis on case-control and cohort studies for assessing the association between  $\beta$ -blockers and fracture risk. They found similar results which supports the preventive effects of  $\beta$ -blockers on fracture.

De Vries *et al.* (2007a, b) performed two case-control studies on data extracted from the UK General Practice Research Database (GPRD) and the Dutch PHARMO Record Linkage System (RLS). Only 29010 patients as

Table 1: Summary of the discussed studies

Reference	Study design	Sample size	Results	Conclusion
<b>Fracture risk</b>				
Schlienger <i>et al.</i> (2004)	Case-control analysis	151420 patients	↓FR	BBs reduces risk of fracture
Rejnmark <i>et al.</i> (2006)	Population-based pharmaco-epidemiological case-control study	124655 P	↓FR	BBs usage is associated with reduced FR
Weins <i>et al.</i> (2006)	Meta-analysis	-	↓FR	BBs lower FR
De Vries <i>et al.</i> (2007b)	Case-control	77598 P	↓FR	The association between Bbs and FR is not casual
Meisinger <i>et al.</i> (2007)	Observational for mean of 10.7 yrs	1793 P	↓FR	BBs use is associated with ↓FR
De Vries <i>et al.</i> (2007a)	Case-control study	6763 P	↓FR in higher doses of β2-agonists	FR in users of β2-agonists, corticosteroids and Ach are the same
<b>BMD</b>				
Reid <i>et al.</i> (2005a)	Observational study (7 yrs)	8412 PMW	No change in FR	The data are not consistent
Turker <i>et al.</i> (2006)	Prospective case-control study	50 elderly	Higher BMD	BBs increase BMD
<b>Bone markers</b>				
Reid <i>et al.</i> (2005b)	RCT	41 PMW (160 mg propranolol or placebo)	↓OC, ↓DPD	Propranolol reduces osteoblast activity
Pasco <i>et al.</i> (2005)	Observational study (≥2 yrs)	197 W	↓CTX	BBs might suppress bone loss with relative preservation of bone formation
<b>BMD and bone markers</b>				
Perez-Castrillon <i>et al.</i> (2007)	Observational	40 M (with cardioselective BBs)	-	BBs do not modify bone mass
<b>BMD, fracture risk and bone markers</b>				
Rejnmark <i>et al.</i> (2004)	Prospective, open-label, multi-center (20 yrs)	2016 PEMW	↓FR, ↓OC	The possibility of decreasing bone formation activity
Pasco <i>et al.</i> (2004)	Population based, case-control	1344 W	Higher BMD	BBs are associated with higher BMD and lower FR
Bonnet <i>et al.</i> (2007)	Observational	944 PMW	Higher BMD in BBs users	The association of BBs use with ↓FR is via BMD
Sosa <i>et al.</i> (2010)	Case-control study	74 PMW	higher BMD in CHD patients at femur	PMW with CHD have higher BMD, independent association of BBs and fractures

Yrs: Year; PEMW: Perimenopausal women; FR: Fracture risk; OC: Osteocalcin; BBs: β-blockers; W: Women; BMD: Bone mineral density; PMW: Postmenopausal women; DPD: Desoxypyridinoline; CTX: C-telopeptide; P: Patient; M: Men; CHD: Coronary heart disease and Ach: Anticholinergics

cases and 48588 patients as controls with a first hip/femur fracture were selected. The investigators defined β-blocker usage as taking those medications 90 days before the index date. Data were adjusted according to patients' age, gender, medical history and medications. By considering 95% Confidence Intervals (CIs) and logistic regression analysis, current β-blocker usage was associated with reduced risk of fracture, but no relationship between cumulative dose of β-blocker and risk of fracture was observed. They indicated the protective effects of β-blockers only in subjects who were taking other antihypertensive drugs. Finally, they concluded that the effect of β-blockers on hip/femur fracture is not by chance.

In another study the correlation between fracture incidence and β-blockers were evaluated on 1793 patients 55-74 years. During the mean follow up of 10.7 years, the risk of fracture was lower in β-blocker users (Meisinger *et al.*, 2007).

De Vries *et al.* (2007a) evaluated the association of β2 agonists with fracture risk in a population-based case-control study on 6763 patients. They modified data according to their underlying respiratory disease and drug history. The investigators observed increase in risk of fracture in higher doses of β2 agonists. Although, the risk

reduced after modifications, fracture risk in users of β2 agonists, inhaled corticosteroids and anticholinergics was the same.

**β-blockers and bone markers:** In a randomized controlled trial, Reid *et al.* (2005b) assessed the effects of a β-blockers on bone turnover. The study was conducted on 41 normal postmenopausal women who took propranolol 160 mg day<sup>-1</sup> or placebo for more than 3 months. They measured serum osteocalcin, total alkaline phosphatase activity, β-C-terminal telopeptide of type I collagen (βCTX, β-CrossLaps), procollagen type I N-terminal propeptide (PINP), urine free deoxypyridinoline (fDPD) at baseline, 2 weeks, 6 weeks and 3 months and BMD of the lumbar spine and proximal femur at baseline and 3 months later. The results of their study showed 20% decrease in serum osteocalcin in the first 2 weeks which decreased more along with the study. No significant effect of propranolol on BMD and serum PINP, CTX and total alkaline phosphatase was found. Bone resorption markers, urine fDPD decreased 10% in 6 weeks which remained steady until the end of the study. This study could not support the protective effect of propranolol on bone formation (Reid *et al.*, 2005b).

Pasco *et al.* (2005) assessed the impact of  $\beta$ -blockers on bone metabolism and bone loss in 197 early postmenopausal women in a 2 year observational study. Only 24 patients were  $\beta$ -blocker user, whose serum CTX levels were lower, however the serum BAP did not show significant differences. They reported serum CTX levels as a predictor of adjusted rates of bone loss. The authors concluded that  $\beta$ -blockers decrease bone resorption with a possible protective effect on bone formation (Pasco *et al.*, 2005).

**$\beta$ -blockers, BMD and bone markers:** Perez-Castrillon *et al.* (2007) evaluated the effect of cardioselective  $\beta$ -blockers on bone mass and biomechanical properties of the femoral neck in males with acute Myocardial Infarction (MI). They performed the study on 40 men with acute MI, of them 21 patients were treated with atenolol and 9 patients treated with bisoprolol. All patients were on atorvastatin therapy. The investigators measured hip and femoral BMD, serum osteocalcin and urine desoxypyridinoline (DPD) at baseline and after one year. At first the higher percentage of osteoporosis was found in the treatment group. Serum osteocalcin decreased significantly in both groups with no significant change in urine DPD. Concerning the study, no supportive data was obtained.

**$\beta$ -blockers, BMD, fracture risk and bone markers:** Rejnmark *et al.* (2004) studied the effects of  $\beta$ -blockers on bone from different aspects including bone turnover, BMD and fracture risk. They did a comprehensive cohort study on 2016 premenopausal women. They indicated threefold increase in fracture risk along with increasing the risk with longer duration of  $\beta$ -blocker treatment more than 8 years. These findings were associated with 20% lower serum osteocalcin level; however the BMD did not change overtime.

In Geelong Osteoporosis study, a population based study, the relationship between  $\beta$ -blocker usage, BMD and fracture risk was evaluated. Pasco *et al.* (2004) performed the study on 569 women with an incident fracture and 775 controls; all were older than 50 years. They confirmed the association of higher BMD and lower fracture risk with  $\beta$ -blocker usage.

The influence of  $\beta$ -blockers on bone fracture, density, micro and macroarchitecture was assessed by Bonnet *et al.* (2007). The subjects were 944 postmenopausal women, 158 women were taking  $\beta$ -blocker and the rest of them considered as control group. In this study  $\beta$ -blocker usage was associated with higher BMD and higher cortical width at femoral neck (Bonnet *et al.*, 2007).

The impact of  $\beta$ -blockers on BMD and bone fracture was investigated in a case-control study in 74 postmenopausal women with recently diagnosed Coronary Heart Disease (CHD). Higher BMD in CHD patients at proximal femur and a slightly positive association between  $\beta$ -blockers and fractures (non-significant) were reported (Sosa *et al.*, 2010).

## DISCUSSION

In spite of relevant evidences of the contribution of sympathetic nervous system in bone architecture via different pathways, lack of enough potent clinical trials, complicates this issue. Some of the available studies were presented in the paper but none is potent enough to provide a clear-cut conclusion. The existence of some limitations in the mentioned studies in this field makes the decision more difficult which must be taken into account. Bias and many contributing factors affect the results and raise controversies over study interpretation and reliability (De Vries *et al.*, 2007a, b).

These limitations help us assess each conclusion more accurately in order to design a multidimensional and comprehensive investigation.

Common therapeutic uses of  $\beta$ -blockers are cardiovascular diseases, which today suggested having a common pathological base with osteoporosis. In addition, the patients with cardiovascular diseases mostly take more than one type of medication a day; therefore we have to consider those effects on bone. Regarding this fact, statins are one class which their effect on bone is under debate (Toh *et al.*, 2007) as well as the other thiazides and furosemide (with proven effects), Angiotensin Converting Enzyme Inhibitors (ACEIs), calcium channel blockers, nonsteroidal anti-inflammatory drugs (NSAIDs), etc. Therefore it is substantially necessary to distinct the effect of  $\beta$ -blockers on bone. In addition the impact of hypertension on BMD cannot be disregarded (Hanley *et al.*, 2003).

The other questionable issue is studying risk of fracture which does not seem to be logical, because many drugs or psychological conditions may affect central nervous system and increase risk of imbalance, fall and fracture. Some drugs influence muscle strength and cause muscle weakness which account for increasing risk of fracture. More importantly, substantial proportions of vertebral fractures are asymptomatic and cannot be recognized. Limiting the evaluation to the risk of fracture in some bones such as femur or hip is not reliable and the other type of fractures should be taken into consideration. BMD measurement at just one site is the other conflicting factor. In some studies, there is no baseline measurement of BMD that is a major factor has to be considered at first and for patient selection.

There is no data about smoking and patients' lifestyle which further complicates the conclusion. BMI as well as physical activity are other patient's data which have been missed in most studies; therefore we cannot ignore the contribution of these two important factors.

The pharmacodynamic and pharmacokinetic characteristics of  $\beta$ -blockers should be considered seriously. Regarding the lipophilicity of bone tissue, the lipid solubility properties of  $\beta$ -blockers, their first pass effect, metabolism and bioavailability will affect their clinical influence and might be considered in the future studies (Lopez-Sendon *et al.*, 2004). The type of  $\beta$ -blocker (selective or non-selective) may affect the results, so the difference in the balance between  $\beta$  receptors may cause different clinical outcomes.

Regarding the racial differences between patients and the science of pharmacogenomics, it is highly important to examine the effect of a drug on a population of different races and then analyze data according to their characteristics.

The small sample size and lack of ability to sub-analyze data more complicates the conclusion, while the effect of dose and duration of  $\beta$ -blocker usage is another critical issue for further evaluation. Some studies utilized self-reported medication use which its validity is limited and under question.

## CONCLUSION

Regarding all together, data are disappointed and controversial. Concerning the increasing population of patients whom were prescribing  $\beta$ -blockers for a broad spectrum of diseases from anxiety to arrhythmia, makes the judgment more difficult and problematic. Therefore a thorough, comprehensive clinical trial in a large sample size by considering the contributory factors as much as possible (especially in the field of their pharmacodynamic and pharmacokinetic properties) is highly recommended.

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