Are beta-blockers useful in the prevention of osteoporotic fractures?

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Abstract. – **Atherosclerosis and osteoporosis are highly prevalent chronic diseases that affect populations of similar ages who are clinically asymptomatic until complications appear. Therefore, research into new drugs that are useful for both processes and may improve therapeutic compliance appears to be reasonable. β-blockers are widely used in the treatment of hypertension and its complications, ischemic heart disease and heart failure. Their use has been associated with a decrease in cardiovascular mortality. Experimental data have demonstrated that the sympathetic nervous system inhibits bone formation and increases resorption due to the binding of catecholamines to receptors located in osteoblasts. This produces a decrease in bone mineral density and a higher risk of fractures. The effect is eliminated by the administration of β-blockers.**

Retrospective case-control and cohort studies have shown a beneficial effect of β-blockers on fractures reduction, with a protective effect being observed in eight studies and no effect being found in two studies. The aim of this paper is review these data and the possible role of betablockers in the prevention of osteoporotic fractures in patients with cardiovascular disease.

Key Words:

Osteoporosis, Atherosclerosis, Beta blockers, Fractures.

Introduction

Atherosclerosis and osteoporosis are degenerative chronic diseases with a high incidence in developed countries, whose prevalence will increase as the population ages. They are silent processes with a great economic cost that becomes evident when the acute complications, including vascular accidents and osteoporotic fractures, become overt. Various epidemiological studies have shown an age-independent association between the two diseases[1,2].

Atherosclerosis, which plays a role in heart diseases, cerebrovascular accidents and peripheral arterial diseases, is responsible for most cardiovascular diseases. It is characterized by chronic arterial inflammation caused and exacerbated by disorders of the lipid metabolism and other clearly identified risk factors[3]. Numerous cross-sectional and, more interestingly, longitudinal studies have evaluated the relationship between cardiovascular disease and osteoporosis. Normally, subrogate markers (vascular calcification in atherosclerosis and bone mineral density [BMD] in osteoporosis) are used to evaluate the association between the two processes. Studies that use cardiovascular disease and fractures as disease markers tend to be more valuable. Magnus et al[4], using the NAHMES III data base, found an independent, statistically significant association between previous myocardial infarction and low bone mass. The effect was observed solely in men and was independent of age, race, alcohol consumption, physical activity and body mass index (BMI). Our group found a prevalence of osteoporosis of 39% in women and 26% in men in a small population with acute coronary syndrome, a higher prevalence than that of the general Spanish population of the same age and sex[5]. Another study found that bone mass was lower in patients with functional class II/III heart failure, adjusted by age and sex, compared with controls[6]. Sennerby et al[7] in a case-control study of 1327 fractures and 3170 controls, found that 25% of patients with fractures had cardiovascular

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disease compared with 12% of controls. After adjustment for various variables, hip fracture (the osteoporotic fracture producing the greatest morbidity and mortality) was associated with peripheral arterial disease and ischemic heart disease. A *post hoc* analysis of 2526 women from the Multiple Outcomes of Raloxifene Evaluation (MORE) with low bone mass or osteoporosis never treated for osteoporosis, analyzed the increase in vascular risk after a follow-up of 4 years[8]. Osteoporotic patients had a greater risk of cardiovascular morbidity and mortality which increased proportionally to disease severity. Women with more fractures at study entry or more severe fractures had a fivefold increased risk.

Both diseases require the use of drugs that can make therapeutic compliance, the main reason for treatment failure in both processes, difficult. Drugs that can act in both two diseases could improve compliance. The aim of this article is review these data and the possible role of β-blockers in the prevention of osteoporotic fractures in patients with cardiovascular disease.

Bone Remodeling and the Sympathetic Nervous System

Osteoporosis results from alterations in bone remodelling that cause an imbalance between formation and resorption, with increased resorption leading to reduced bone resistance and fractures[9]. Bone remodelling is a physiological process whose function is the permanent renovation of the skeleton to achieve biomechanically correct bone function. It consists of an initial phase of bone resorption followed by another of formation. Both phases are regulated by general, endocrine, local and paracrine factors.

Of the endocrine factors, the calciotropic hormones (PTH and vitamin D) and sexual hormones (mainly estrogens and, to a lesser extent, androgens) play a determining role. Other hormones, such as the thyroid hormones, growth hormone and leptin play a smaller role. Local factors include various cytokines and growth factors that regulate the process, with the inflammatory cytokines (IL-1, IL-6, TNF-α) playing a key role[10]. These also intervene in the development and rupture of atheroma plaque[5]. In all these processes there is a common final route, the RANK/RANKL/OPG system, which intervenes in the regulation of remodelling[11].

In addition to humoral, endocrine and paracrine control of bone remodelling, there is also a central control of bone formation. This central regulation involves leptin. Human leptin is a protein of 167 amino acids manufactured in fat cells (adipose tissue) that is involved in the regulation of the ingestion and consumption of energy. It acts by bonding with receptors located in many tissues, including bone and vessels. It intervenes in the regulation of bone mass by means of a central hypothalamic mechanism, exerting a double antagonistic effect on bone formation and resorption through the activation of the sympathetic nervous system and the Cocaine Amphetamine Regulated Transcript (CART)[12]. The discovery of the role of leptin in the regulation of bone metabolism led to interest in the role of the sympathetic nervous system in bone physiology. On the other hand, studies have shown that hyperleptinemia can exert a series of atherogenic effects, including the induction of endothelial dysfunction, increased inflammatory response and increased oxidative stress, and facilitates platelet aggregation and the vascular proliferation of smooth muscle cells[13].

Genetic studies by Ducy et al[14] showed that leptin and leptin receptor knockout mice had high levels of bone mass and hypothesized that leptin exerts an inhibiting effect on bone formation. They showed that the effect was not exerted directly on the osteoblasts but was mediated by the central nervous system. Intraventricular infusion of leptin in leptin-deficient mice normalized bone mass. Subsequently, the site of action of leptin was identified. The lesion of neurons in the ventromedial hypothalamic nucleus caused an increase in bone mass at the expense of increased formation, with the mice presenting a phenotype similar to the mice lacking leptin[15]. Intraventricular infusion of leptin was not able to correct this phenotype. This experiment showed that this group of hypothalamic neurons regulates bone formation from leptin.

Previously, the presence of adrenergic receptors in osteoblasts had been shown, with the β2-receptor connected to the adenylcyclase system being cloned in 1988[16]. Studies in periosteum-derived osteoblasts (SaM1) and lines derived from human osteosarcoma (SaOs-2, HOS, MG-63) detected mRNA of the adrenergic receptors β1, β2 and β3, with β2 having the greatest expression[17]. These results, together with the presence of adrenergic receptors in osteoblasts and the hypothalamic effect of leptin, suggested that the sympathetic nervous system could be the intermediary mechanism of leptin in the regulation of bone

Table I. Cross-sectional studies and risk of fracture.

Reference	Population	Number	Effect
Pasco JA et al[23]	Postmenopausal women	1344	Decreased fracture risk
Schlienger RG et al[24]	General population	150420	Decreased fracture risk
De Vries F et al[25]	General population	77598	Decreased hip fracture risk
Rejnmark L et al[26]	General population	498617	Decreased fracture risk
Schoo M et al[27]	General population	7892	Decreased fracture risk
Bonnet N et al[28]	Postmenopausal women	499	Decreased fracture risk

mass. Mice defective in the enzyme, dopamine β- hydroxylase, which is essential for the synthesis of epinephrine and norepinephrine, showed increased bone mass and reduced bone formation, measured histomorphometrically. Treatment with sympathicomimetic agents reduced the number of osteoblasts and the formation surface, which resulted in reduced bone mass[15]. This experiment showed that the sympathetic nervous system was able to reduce bone mass and was confirmed by other studies in which non ovariectomized rats treated with the β-agonist, clembuterol, showed reduced bone quantity, measured by densitometry, and quality, with alterations in bone microarchitecture and biomechanical properties[18].

The sympathetic nervous system has a detrimental effect on both elements of bone remodelling, reducing formation and increasing resorption, with a deleterious effect on skeletal resistance. Osteoblasts present β-adrenergic receptors whose activation inhibits osteoblastic proliferation through molecular clock regulation of c-myc and cyclin-D expression and activation of transcription factor ATF-4, a specific member of the CREB family[12,19], which allows activation of the osteoclasts, cells which initiate bone resorption and lack adrenergic receptors. The phosphorylation of ATF-4 in osteoblasts produced by the transcription of protein kinase A increases RAN-KL expression. This molecule is united to RANK located in the surface of the osteoclasts, facilitating its proliferation and activation and increasing bone resorption[20,21]. Moreover, RAN-KL has also been implicated in the destabilization of the atheroma plaque responsible for acute coronary syndrome, by modulating the liberation of enzymes that degrade the extracellular matrix[22]. For these reasons, the use of β-blockers may have a beneficial effect on the osteoporosis resulting from alterations in bone remodelling that cause an imbalance between formation and resorption, with increased resorption leading to reduced bone resistance and fractures.

β-*Blockers and Fracture Risk*

These discoveries led various research groups to study the effect of sympathetic nervous system blockade on fracture reduction, the main complication of osteoporosis and responsible for its morbidity and mortality. Ten studies have primarily evaluated the effect of β-blockers on reducing fractures. Six were cross-sectional studies of case-controls (Table I) and four were longitudinal studies with greater epidemiological interest (Table II).

In the Geelong Study, the use of β-blockers decreased the risk of fracture in a group of 1344 post-menopausal women by 32% (OR 0.68, 95%CI 0.49-0.96). However, when the main types of osteoporotic fractures (wrist, vertebra and hip) were analyzed separately, the statistical significance disappeared since the confidence interval included the unit. This may be due to the

Table II. Longitudinal studies and risk of fracture.

Reference	Population	Number	Effect
Rejnmark L et al[29]	Perimenopausal women	2016	Increased fracture risk
Lavasseur R et al[30]	Postmenopausal women	7598	No effect
Reid IR et al[31]	Postmenopausal women	8142	Decreased hip fracture risk
Meisinger C et al[32]	General population	1793	Decreased fracture risk

small number of fractures analyzed, which reduced the statistical power of the study substantially[23]. A large study (30,601 fractures and 120,819 controls) using data from the UK General Practice Database (GPRD) reported, in 2004, that the use of beta-blockers either alone (OR 0.77, 95%CI 0.72-0.83) or in association with thiazides (OR 0.71, 95%CI 0.64-0.79) reduced the risk of fractures. The data were adjusted by age, sex, BMI, smoking and other medications[24]. The effect appeared solely in patients currently taking beta-blockers and not in those who had previously used them. Although the study was retrospective, raising the possibility of bias, its validity is demonstrated by the large number of patients included and the fact that the beneficial effects were only observed in patients actively taking β-blockers, which demonstrates a causal relationship.

Recently, De Vries et al[25] analyzed the effect of β-blockers on hip fractures, the osteoporotic fracture with the greatest morbidity and mortality, in a case-control study using the GPRD (UK General Practice Database) and Dutch Pharmo Record Linkage System (RSL) databases. There were 22,247 hip fractures and 22,247 controls in the GPRD and 6763 fractures and 26,431 controls in the Pharmo RSL, with similar characteristics in both groups. The use of β-blockers reduced the risk of hip fracture in the GPRD (OR 0.83 95%CI 0.75-0.92) and the Pharmo RSL (OR 0.87 95%CI 0.80-0.95). The effect was not dose-dependent, and appeared in both sexes, all age groups and especially with highly selective beta-blockers. Interestingly, the benefits of β-blockers was only observed in patients who had received or were receiving hypertensive treatment with another drug. They concluded that the results did not support a causal relationship between β-blockers and reductions in hip fractures.

A similar Danish study[26] included 124,655 fractures and 373,962 controls, adjusted by age and sex. A total of 35835 patients (9117 fractures and 26,727 controls) were taking β-blockers. There was a statistically significant reduction in the number of total fractures (OR 0.91, 95%CI 0.88-0.93) hip fractures (OR 0.91, 95%CI 0.85-0.98). Unlike the study by De Vries et al[24], the effect was dose-dependent. The Rotterdam study[27] included 7892 people and found that the use of β-blockers reduced the risk of non-vertebral fractures (OR 0.67, 95%CI 0.46-0.97) but not vertebral fractures. Bonnet et al[28] in a case-control study of post-menopausal women which

included 158 patients receiving treatment with β-blockers and 341 controls found a risk reduction of 0.51 (95%CI 0.41-0.64), which appeared in all age groups and especially in people older of 70 years of age. The effect was maintained after excluding patients taking statins, thiazides, substitute hormonal therapy and drugs with effects on bone.

The four longitudinal studies on this subject have a greater epidemiological value than the aforementioned cross-sectional studies. The Danish Osteoporosis Study (DOPS)[29] a case-control study with a follow-up of 5 years, analysed 2016 perimenopausal women of whom only 38 were receiving β-blockers. There were 163 fractures during the follow-up and β-blockers were associated with a greater risk of fracture (OR 3.3.95% CI 1.1-9.4). The prospective EPIDOS study[30] carried out in France analysed the risk factors for osteoporotic fractures in the elderly and evaluated the effect of cardioselective β-blockers. The sample size was large (7598 women) but only 283 (3.4%) were receiving β-blockers. The mean age was 81 ± 4 years and the mean follow up 14±10 years. A total of 1211 non-vertebral fractures occurred and no association between β-blockers and the risk of fracture was found (OR 1.2, 95%CI 0.9-1.5). The lack of favourable results in these two studies may be due to the small number of patients taking β-blockers.

The Study of Osteoporotic Fractures (SOF)[31] included 8412 post-menopausal women followed for 7 years and found 431 wrist fractures and 585 hip fractures. β-blockers did not reduce the risk of hip fracture in either adjusted or unadjusted analyses. However, when β-blockers were divided into cardioselective and non-cardioselective groups, cardioselective β-blockers reduced the risk of hip fracture in adjusted (OR 0.66, 95%CI 0.49-0.90) and unadjusted models (OR 0.76, 95%CI 0.58-0.99). The Authors concluded that the effect of β-blockers on fracture reduction was not consistent.

The recent results of the MONICA study[32], which included 1793 people, older of 55 years, of whom 219 were taking β-blockers, found 263 fractures in the 10.7 year follow-up. In the different models analyzed, adjusted for various risk factors, an OR of 0.60 was obtained (0.37-0.96). The effect appeared solely with selective β-blockers.

The results of these studies are not in agreement. Most of the cross-sectional studies found that β-blockers had a beneficial effect, whereas

the longitudinal studies found that cardioselective β-blockers were the most efficacious.

β-*Blockers and Bone Resistance*

Osteoporosis is defined by a reduction in bone resistance that facilitates the appearance of fractures. The resistance is determined by bone mass, measured by BMD, and by bone quality, which has no single specific measurement parameter.

Several retrospective studies have analyzed the effect of on BMD (Geelong Osteoporosis Study, Study of Osteoporosis Fractures, Danish Osteoporosis Prevention Study, EPIDOS, Study of Bonnet et al, Rotterdam Study and the Lynn Study)[23,27-31,33]. The results are not uniform, showing positive or no effects. Pasco et al[23] found increased bone mass in the forearm and hip whereas the Rotterdam study[27] and another by Bonnet et al[28] found a benefit in the lumbar spine. The remaining studies found no beneficial effect of β-blockers on bone mass. Two small prospective studies have evaluated BMD response after a follow-up of one year. Turker et al[34] studied 50 cases and 100 controls and found a statistically significant increase in bone mass in the hip and spine in patients taking β-blockers. Perez-Castrillón et al[35] analyzed 40 patients with acute myocardial infarction, of which 30 were treated with β-blockers and 10 were untreated, and found no difference between the groups in hip bone mass.The densitometric response was evaluated with regard to the presence or absence of osteoporosis and no differences were found. However, all patients were treated with statins, which can act on bone metabolism, and may have biased the study. Atorvastatin diminishes the serum levels of RANKL in patients with acute myocardial infarction[36] and RANKL is a mediator in the increase in bone resorption induced by the sympathetic system[19].

There are few studies on the effect of β-blockers on bone quality. Perez-Castrillón et al[35] analyzed the effect of selective β-blockers on the biomechanical properties of the hip, measured by densitometry, in a group of patients with acute myocardial infarction, and found no differences between the treated group and controls. Bonnet et al[28] studied the biomechanical properties hip, also measured by densitometry, and found an increase in cortical thickness in patients receiving β-blockers. They also performed a fractal analysis of the texture of the calcaneus, a marker of bone microarchitecture, and found that treatment with β-blockers had a favourable effect.

Conclusions

Studies in experimental animals have established the theoretical basis for the role of the sympathetic nervous system in the regulation of bone mass, inhibiting bone formation and increasing bone resorption. This reduces the amount and quality of bone which results in reduced resistance and a greater number of fractures. β-blockers inhibit sympathetic nervous system activity and can correct its detrimental effects. Epidemiological studies show a favourable trend to fracture reduction, although the results are not conclusive, probably due to the different methodologies used. The current evidence suggests that the use of β–blockers in the treatment of the osteoporosis cannot be recommended but their probable beneficial effects on bone may add value to the treatment of cardiovascular diseases with a high prevalence of osteoporosis.

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