

Effect of the Antihypertensive Treatment on the Bone Mineral Density and Osteoporotic Fracture

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Abstract: The financial and social cost of hypertension and osteoporosis, clinically silent diseases, are determined by the consequences, such as a vascular disease and fractures. The relationship between these illnesses has not been clearly established, although many alterations in extracellular metabolism of calcium, which could determine the level of bone mineral density (BMD) in these patients, have been associated to hypertension. Despite these alterations, the lack of studies relating these two important diseases is surprising, and hypertension is not identified as a risk factor for osteoporosis.

Interestingly, there is a lack of information of the long-term effects of antihypertensive treatment on bone mineral density, although 50 % of the hypertensive population is made up of postmenopausal women. Most studies analyzed the effects of thiazides and, to a lesser degree, the effects of calcium antagonist.

The purpose of this review is evaluate the effect of the antihypertensive therapeutic group (diuretics, β -blockers, calcium antagonists, angiotensin converting enzyme) on the bone mineral density (BMD) and osteoporotic fracture.

Keywords: Hypertension, osteoporosis, thiazides, β -bloqueantes, antagonistas del calcio, ACEIs.

INTRODUCTION

Osteoporosis and hypertension are two diseases with a similar course. They show a high incidence and prevalence, and represent a problem that increases with age and the population aging occurring in the Western world. Osteoporosis and hypertension are clinically silent conditions that become evident by their complications (fractures and cardiovascular disease), causing high morbidity and mortality and a significant financial cost. Etiopathogenetically, they show a similar behavior, as both diseases have a genetic base and a polygenic heredity pattern influenced by various non-genetic factors. On the other hand, 50% of the hypertensive female population are postmenopausal women, and both diseases therefore coexist. Although, the increases in blood pressure (BP), occur with age in both men and women. The Framingham Study assessed the effect of change in menopausal status on BP levels in 1686 women who were premenopausal at the initial examination [1]. No significant differences were found in BP compared with age-matched premenopausal controls. Moreover, in humans, although oral contraceptives are frequently associated with increases in blood pressure, BP was not increased or was minimally in prospective clinical trials of hormone therapy in postmenopausal women [2]. These data warrant the interest in studying the relationship between osteoporosis and hypertension.

INCIDENCE OF OSTEOPOROSIS IN HYPERTENSION

Surprisingly, there are only a few reports published relating these two significant diseases, despite the facts

discussed above. Capuccio *et al.* [3] studied 8116 Caucasian women for 3.5 years and found a relationship between systolic blood pressure and femoral bone mineral density (BMD), but only in the group with higher values of systolic blood pressure. Tsuda *et al.* [4] noted an inverse relationship between systolic blood pressure and bone mass, as measured by lateral densitometry, but a small population was studied. In our hospital, the percentage of osteoporosis in postmenopausal hypertensive women was 22%, similar to the rate found in the Spanish general population of the same age [5]. In another of our series, males did not show either a higher incidence of osteoporosis as compared to the general population, and no relationship was found in them between bone mass and blood pressure [6].

The Canadian Multicentric Osteoporosis Study [7] analyzed the relationship between several chronic diseases, including hypertension, and bone mineral density in a wide group of men and women. Hypertension was associated to an increased bone mass in various sites and to a decrease in the number of vertebral deformities. The effect persisted after adjusting bone mineral density for several factors (age, weight, estrogen and thiazide use). The relationship between blood pressure and cortical and trabecular bone mineral content was measured by pQTC (peripheral Quantitative Computed Tomography) in a group of Polish males. No differences were seen between normotensive subjects and patients with systolic arterial hypertension. However, there was an inverse relationship between diastolic arterial hypertension and bone mineral content (BMC) [8]. In males, Orwoll *et al.* [9] found an association between arterial hypertension and a decreased bone mass after adjusting for age and weight.

The above studies used bone mass to define osteoporosis and showed no consistent results, but it should be noted that

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the populations analyzed were different, and there were marked differences in sample size.

The presence of osteoporosis can also be assessed through fragility fractures. Hypertension has not been considered as a risk factor for fracture in large epidemiological studies of osteoporotic fractures [10]. However, in a retrospective study conducted in our population of 996 patients with hip fracture and using a population control group of 3004 individuals over 65 years of age, the presence of hypertension increased fracture risk in women (OR: 1.45, 95% CI 1.2-1.7) after adjusting for age and sex. In males, hypertension was not a risk factor (OR: 1.2, 95% CI 0.9-1.6) [11].

FRACTURE MECHANISMS IN HYPERTENSION

In 2001, osteoporosis was defined as a systemic disease characterized by a decreased bone strength that promotes the occurrence of fractures [12]. Strength depends on two factors, bone mass and bone quality. Bone mass may be measured by bone densitometry, while bone quality may be measured using an invasive method such as histomorphometry. However, changes in bone turnover markers may give an indication of bone quality [13].

In addition to the above discussed bone factors, osteoporotic fractures result from falls causing trauma of variable severity. Hypertension may act upon bone strength and increase the frequency of falls.

CHANGES IN CALCIUM METABOLISM IN HYPERTENSION

Various changes in calcium metabolism have been reported in hypertension. The final effect of such changes is a modification of bone mass and bone quality. An increased calcium excretion in urine, decreased ionic calcium levels, increased AMPc levels in urine, increased PTH serum levels, elevated 1.25 dihydroxicholecalciferol levels, and an increased intestinal calcium absorption have been reported [14-19].

Hypercalciuria is the change most commonly found in hypertensive women. It is inversely related to bone mass, and is more marked in osteoporotic hypertensive women [5]. The cause of hypercalciuria is unknown, and two hypotheses have been proposed, the central blood volume hypothesis and the renal calcium leak hypothesis [20]. According to the first hypothesis, hypercalciuria is caused by a central blood volume expansion promoting calcium loss in urine, while the second hypothesis states that a tubular disorder occurs leading to calcium loss. In order to maintain calcium serum levels within normal limits, PTH levels must be increased. This secondary hyperparathyroidism is responsible for an increased bone turnover that decreases bone mass and impairs bone quality, decreasing strength.

FALLS

Falls are an additional factor related to fractures. The fall rate in people over 60 years of age ranges from 23% to 35%, 8% of which result in fractures [21-23]. The number of falls in hypertensive subjects may be increasing due to the presence of syncope associated to a decreased baroreflex sensitivity or to orthostatic hypotension caused by

antihypertensive drugs [24,25]. Although diuretics and beta-blockers have been associated to an increased number of falls, a meta-analysis showed no relationship between falls and use of beta-blockers, ACE inhibitors, central antihypertensives, nitrates, or calcium channel blockers [26]. Diuretic use increases the risk of falls, particularly in patients with musculoskeletal disease, although not all studies are conclusive.

ANTIHYPERTENSIVE DRUGS, BONE MASS AND FRACTURES

The therapeutic classes most commonly used for the treatment of hypertension, such as thiazides, beta-blockers, calcium channel blockers, ACEIs, and angiotensin receptor antagonists.

THIAZIDES

Thiazides are drugs routinely used to treat hypertension that may modify calcium metabolism and bone mass. Thiazides are the antihypertensive drugs for which more evidence is available of their effect on bone mass and fracture reduction.

They act directly upon cells involved in bone metabolism (osteoblasts, osteoclasts) or indirectly by decreasing urinary calcium excretion. Hydrochlorothiazide dose-dependently inhibits bone resorption by rat osteoclasts through inhibition of carbonic anhydrase [27]. It also acts upon the Na/Cl co-transporter of UMR-106 cells, an osteoclastic cell line, altering its function [28] and inhibits osteocalcin production by MG-63 cells (an osteoblastic cell line) [29].

In the kidney, thiazides act at the distal convoluted tubule by blocking the coupled resorption of Na and Cl through the thiazide-sensitive Na/Cl co-transporter. This effect triggers a Na/Ca exchanger promoting calcium influx and sodium efflux [30]. The result is a decrease in calciuria, a mild increase in calcemia, a decrease in PTH, and a decreased bone turnover. Some authors suggest that mutations in this co-transporter could be the link between osteoporosis and hypertension [31]. Cruz *et al.* [32] have reported an association between NCCT (Na-Cl co-transporter of the distal convoluted tube) mutations and an increased bone mass in patients with Gitelman syndrome, characterized by hypokalemia, metabolic alkalosis, hypocalciuria, hypomagnesemia, and a decreased blood pressure. Patients homozygous for this mutation show a higher bone mineral density as compared to heterozygous patients.

In experimental animals, thiazide use in ovariectomized rats demonstrated a decrease in bone turnover and a reduction in trabecular bone loss [33]. A similar effect was seen with indapamine [34].

Cross-sectional epidemiological studies, case and control studies, and randomized, placebo-controlled clinical trials have been conducted to assess the effect of thiazides on bone mass.

Thiazides showed a positive effect on bone mass in cross-sectional epidemiological studies, including the Cauley *et al.* study [35] on 9075 women over 65 years of age, in which a positive effect on bone mass was seen in patients who had used thiazides for more than 10 years.

Various case-control studies showed a beneficial effect of thiazides on fracture reduction, particularly when they were used long-term as the only drug. A meta-analysis of 30,000 patients showed a beneficial effect of thiazides in hip fracture reduction (OR: 0.82, 95% CI 0.73-0.91) [36]. A single case-control study showed an increase in the risk of fractures with thiazides related to an increased incidence of falls [37].

In a retrospective case-control study conducted in our population, thiazides were the only antihypertensive drugs that showed a protective effect on hip fracture (OR: 0.7, 95% CI 0.5-0.9 in women, and OR: 0.4, 95% CI 0.2-1 in men) [11]. In a prospective cohort study performed in the Netherlands, use of thiazides for over 365 days was associated to a decreased risk of hip fracture (OR:0.46, 95% CI 0.21-0.96) [38]. Risk increased when the drug was discontinued.

Reid *et al.* [39] studied 185 postmenopausal women who were randomized to receive thiazides or placebo. The follow-up period was 2 years. In treated patients, decreases were seen in calciuria and bone turnover markers, and an increased cortical bone mass was noted, but with no effect on trabecular bone. Wasnich *et al.* [40] found a lower bone mass loss in the distal radius and calcaneus in patients using thiazides after five years of follow-up. La Croix *et al.* [41] conducted a prospective, randomized, placebo-controlled, three-year study with low hydrochlorothiazide doses in subjects over 60 years of age. Patients were not hypertensive, and changes in BMD were assessed. A 1% increase in bone mass was obtained in 36 months, and the effect was dose-dependent in women. In men, the effect was not dose-dependent, probably due to treatment non-compliance.

The available evidence shows that thiazides can discretely increase bone mineral density and reduce fracture risk (Table 1). These drugs should be part of the therapeutic regime of osteoporotic hypertensive women, and possibly of all postmenopausal hypertensive women.

-BLOCKERS

The relationship between the sympathetic nervous system and bone metabolism has been known for a long time, but has attracted an increased interest since the discovery of leptin. There have been reports of adrenergic receptors in osteoblasts and osteoclasts, and of the presence of sympathetic nerve fibers in bone and bone marrow [42]. This suggests the existence of an anatomic structure relating bone and the sympathetic nervous system. Takeda *et al.* [43] identified in rats a neuronal network started by leptin that inhibited osteoblast activity through hypothalamic sympathetic activation and increased osteoclast function through IL-6 [44]. The end result was a decreased bone mass. This led to consideration of the use of drugs blocking the sympathetic nervous system to increase bone mass.

Pasco *et al.* [45] conducted a case-control study using data from women over 50 years of age included in the Geelong Osteoporosis Study. The odds ratio for fractures associated to the use of β -blockers was 0.68 (95% CI 0.49-0.96). This value applied to any fracture, and was maintained after adjusting for age, weight, medications, and lifestyle. A 2.5% increase in BMD was shown in patients on β -blockers (p: 0.03). A retrospective case-control study on a very large population (30,601 fractures and 120,819 controls), men and women with ages ranging from 30 to 79 years, has recently been reported. In this study, β -blockers decreased fracture risk (OR: 0.77, CI 95% 0.72-0.83), and the effect was sustained when they were associated to thiazides (OR: 0.71, CI 95% 0.64-0.79). Thiazides alone also showed a beneficial effect (OR: 0.80, CI 95% 0.74-0.86) [46]. The data were adjusted for BMI, smoking, and drugs (Table 2) shown this results. Despite such encouraging data, further controlled studies are required to confirm them.

CALCIUM CHANNEL BLOCKERS

Calcium channel blockers are drugs that block T calcium channels at vascular level and are widely used to treat hypertension. Few studies have assessed their impact upon

Table 1. Effects of Thiazides on Bone Mineral Density (BMD) and Fractures

Reference	Design	Population	Findings
Cauley <i>et al</i> ^a	Cross-sectional cohort	Women over 65 years	Increase of BMD
Wasnich <i>et al</i> ^b	Longitudinal cohort	Hypertensive and not hypertensive men	Decrease of loss of BMD
Reid <i>et al</i> ^c	RCT	Postmenopausal women	Decrease of bone markers and increase of cortical bone
La Croix <i>et al</i> ^d	RCT	Not hypertensive men and women	Increase of BMD
Jones <i>et al</i> ^e	Metaanalysis	13 studies (29800 patients)	Decrease hip fracture risk (OR: 0.82)
Schoofs <i>et al</i> ^f	Prospective cohort	General population	Decrease hip fracture risk (OR: 0.46)
Perez-Castrillón <i>et al</i> ^g	Case-control study	General population	Decrease hip fracture risk (OR: 0.70)

Table 2. Effects of β -Blockers and ACEIs on Bone Mineral Density (BMD) and Fractures

Reference	Design	Population	Drug	Findings
Pasco <i>et al</i> ^a	Case-control study	Women over 50 years	β -blockers	Decrease fracture risk (OR: 0.68) and increase BMD
Schlienger <i>et al</i> ^b	Case-control study	General population	β -blockers	Decrease fracture risk (OR : 0.77)
Perez-Castrillón <i>et al</i> ^c	Longitudinal cohort	Hypertensive women	ACEIs	Increase BMD in women with DD genotype
Schlienger <i>et al</i> ^d	Case-control study	General population	ACEIs	Decrease fracture risk (OR : 0.81)

a: 45, b: 46, c: 62, d: 46

bone mass or remodeling markers. Fagher *et al.* [47], in a study conducted on hypertensive patients treated with verapamil 480 mg/day, found a statistically significant increase in calcium levels. Albers *et al.* [48], in a study on 11 males given nifedipine (40 mg/day) for three years, found no differences in bone mass and turnover markers as compared to the control group. No differences were seen with nitrendipine in a study on 30 patients with a 52-week follow-up [49]. A decrease was seen in plasma calcitonin levels in patients treated with nifedipine and nisoldipine [50]. Amlodipine was assessed in an 8-week study that showed no changes in bone remodeling markers [51].

There is no evidence available on the value of calcium channel blockers for the treatment of osteoporosis associated to hypertension, but poor quality studies with small numbers of patients, short follow-up periods, and no fracture assessment have been conducted.

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS (ACEIs)

Angiotensin II has been postulated to be able to act upon the cells involved in bone metabolism either indirectly, by regulating flow in bone marrow capillaries [52], or directly through receptors located in osteoblasts that would promote the release of mediators that would in turn activate the osteoclasts responsible for bone resorption [53]. At osteoblast level, angiotensin II stimulates DNA synthesis, cell numbers, and collagen synthesis by osteoblast precursors, and decreases the mineralization promoted by mature osteoblasts [54,55]. The end result would be a decreased bone mass. Thus, the use of drugs that decrease angiotensin II levels could be useful for treatment of osteoporosis. On the other hand, angiotensin II may act upon calcium metabolism by an endocrine mechanism. Healthy volunteers receiving this peptide showed a decrease in ionic calcium and a PTH increase that could activate bone turnover, decreasing bone quantity and quality [56]. In women with the DD genotype of the angiotensin-converting enzyme, who have high angiotensin II levels, elevated PTH levels, increased calciuria, and a trend to a lower bone mass have been noted [57].

Despite these data, there are few studies assessing the impact of ACEIs on phosphorus and calcium metabolism and bone mass. In a 12-week study, quinapril, an angiotensin-converting enzyme inhibitor, reduced calciuria

by 15% [58]. This study did not assess bone mass or other parameters of phosphorus and calcium metabolism. Townsend *et al.* [59] found no impact of captopril on parameters of calcium metabolism. No effects were seen either in ovariectomized rats using moexipril as ACEI [60,61]. Bone mass had not been measured in any of the studies conducted in humans. Perez-Castrillón *et al.* [62] conducted a trial assessing the impact of 2 angiotensin-converting enzyme inhibitors, quinapril and enalapril, in hypertensive men and women who were followed up for 52 weeks. The study objective was to assess the changes seen in calcium metabolic parameters, bone turnover markers, and bone mineral density. No changes were seen in bone mass when the overall population was considered, but a beneficial metabolic effect was noted. After one year of treatment, calcium blood levels were higher, and calciuria decreased. Association of thiazides enhanced the effect. On subgroup analyses, women with the DD genotype treated with ACEIs showed a statistically significant increase in BMD. As previously discussed, this subgroup shows the highest angiotensin II levels.

The potential impact of these drugs on fracture reduction was evaluated in a retrospective case-control study, and no benefits were seen [11]. It should be noted that the DD genotype occurs in 30% of the population, and the study evaluated the overall population, regardless of the ACE genotype. A case-control study including a very large population showed a beneficial effect of ACEIs on fracture reduction when used over a long time period (OR: 0.81, 95% CI 0.73-0.89) [46]. Table 2 shown this results.

Based on the available data, ACEIs may be considered to be of value in subgroups of hypertensive patients with osteoporosis, but studies with greater numbers of patients and longer follow-up periods are required.

ANGIOTENSIN RECEPTOR ANTAGONISTS

These drugs may have a beneficial impact upon bone mass through a similar mechanism to ACEIs, preventing the harmful effect of angiotensin II on bone. A single study conducted in rats with losartan has been reported. This study found no significant changes in bone mineral density, bone mineral content, or morphometric parameters in treated rats as compared to the control group [63]. No studies in humans have been reported.

CONCLUSIONS

Based on published data available to date, evidence (level B) has been found of bone mass increase and fracture reduction in hypertensive patients for three therapeutic classes, namely, thiazides, β -blockers, and ACEIs. There was an evidence level A for thiazides when bone mass was considered. This implies the use of these drugs, either alone or combined, for treatment of hypertensive patients with osteoporosis.

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