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REVIEW

Antihypertensive medications, bone mineral density, and fractures: a review of old cardiac drugs that provides new insights into osteoporosis

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Abstract Osteoporosis is increasing in prevalence and importance as society's age, with the clinical consequence of fractures of the hip, spine, and upper extremity, leading to impaired quality of life, loss of function and independence, and increased morbidity and mortality. A major risk factor for osteoporosis is older age, and cardiovascular diseases also share this risk factor; therefore, osteoporosis and cardiovascular disease often coexist and share risk factors. Medications used for the treatment of cardiovascular diseases, in particular antihypertensive drugs, have been shown in a variety of studies of varying designs to modulate bone health in both a positive or negative manner. In this article, we reviewed the pharmacology, potential mechanisms, and possible effects on bone mineral density and fracture risk of commonly prescribed antihypertensive medications, including thiazide and non-thiazide diuretics, beta-blockers, calcium channel blockers, renin–angiotensin–aldosterone system agents, and nitrates.

Keywords Osteoporosis · Bone health · Fractures · Hypertension · Cardiovascular medications

Introduction

Osteoporosis is a common and chronic condition, and the major clinical consequences of this disease are osteoporotic fractures of the upper extremity, spine, and hip. Nearly 50 million Americans (26 % of women aged $\geq$ 65 years and over 50 % of women aged $\geq$ 85 years) are affected by osteoporosis, with total direct health care costs estimated to $US 12–18 billion [1]. Therefore, osteoporosis creates a major burden for the individual as well as huge cost to the health care system.

Recent studies have indicated the existence of a potential relationship between bone health and cardiovascular health [2, 3]. Both bone health and cardiovascular health share common etiological factors such as older age, postmenopausal status, diabetes, and lifestyle factors such as smoking, diet, and physical activity [4]. Several studies suggest that vascular calcification is an actively regulated process and shares many features with bone development and metabolism [5], and women with hypertension have significantly lower bone mineral density (BMD) at the femoral neck than those without [6]. Indeed, independent of BMD, hypertension is an independent risk factor for fragility fracture [adjusted hazard ratio (HR), 1.49; 95% CI, 1.13–1.96] [7], and it is associated with accelerated bone loss in elderly white women [8]. We recently showed that heart failure, independent of BMD and cardiovascular risk factors, is associated with 30 % increased risk of major osteoporotic fractures [9]. Although observational in nature, in aggregate, studies such as these suggest a potential link between cardiovascular disease (particularly hypertension) and bone health.

Cardiovascular medications used for hypertension, such as thiazide and non-thiazide diuretics, beta-blockers, and calcium channel blockers, are also the most commonly prescribed medications in the developed and developing world [10–12], and the question arises then whether or not therapy for one condition can modulate the other in either positive or negative manner. In this article, we review the

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currently available evidence on the pharmacology, potential mechanisms, and possible effects on bone mineral density and fracture risk of commonly prescribed antihypertensive medications, including thiazide and non-thiazide diuretics, beta-blockers, calcium channel blockers, renin–angiotensin–aldosterone system agents, and nitrates.

Literature review

Thiazide diuretics

Pharmacology

Thiazide diuretics can affect kidney, intestine, and bone and thereby modulate calcium homeostasis. In the kidney, thiazides inhibit the thiazide-sensitive sodium chloride co-transporter (NCC) in the distal tubule and exert natriuretic and calcium-sparing effects [13]. In the intestine, thiazides enhance calcium uptake and suppress parathyroid hormone secretion [14]. Overall, thiazides reduce urinary excretion of calcium by about 40 % [15, 16].

Potential mechanisms affecting bone health

Thiazides exert direct effects on bone by stimulating osteoblast differentiation and bone mineral formation through osteoblast differentiation markers runt-related transcription factor 2 and osteopontin [17]. The NCC is also expressed in human osteoblast and osteoblast-like cells, which, when blocked by a thiazides, enhances bone calcium uptake [18]. These mechanisms could explain why, independent of their renal and intestinal effects, thiazides are able to exert a direct positive homeostatic effect on bones [19]. In studies of bendroflumethiazide, there were dose-dependent decreases in urinary calcium excretion, no change in PTH levels, a dose-dependent increase in plasma 1,25(OH)2D levels and concomitant increases in osteocalcin (a marker of bone formation), and decreases in bone-specific alkaline phosphatase (a marker of bone resorption) [20, 21].

Clinical evidence

In a longitudinal, observational study in elderly men with mean follow-up for 5 years, thiazides reduced the rate of bone loss at the calcaneus and radius [22]. Similar result was seen in post-menopausal women [23]. In a population-based cohort of 248 older women, the mean BMD was 9.6 % greater in the lumbar spine ($P < 0.01$) and 5.4 % greater in the whole skeleton ($P < 0.01$) among thiazide users than in controls [24]. A Cochrane review, including twenty-one observational studies with nearly 400,000 participants, reported reduction in risk of hip fracture by 24 % among long-term thiazide users compared with nonusers; there were no trials [25].

In summary, thiazide diuretics increase (or prevent decreases) in BMD in both men and women and, in observational studies, are associated with a reduction in fracture risk.

Loop diuretics

Pharmacology

Loop diuretics increase the urinary excretion of sodium chloride by selective inhibition of the Na+, K+, 2Cl co-transporters in the loop of Henle and distal nephron [26]. Loop diuretics promote sodium and water excretion via the kidney and mitigate excessive sodium and water retention. Therefore, loop diuretics are used for heart failure as well as a part of combination therapy for difficult-to-treat hypertension [27].

Potential mechanisms affecting bone health

Treatment with loop diuretics is associated with significantly increased urinary calcium excretion, and increased levels of PTH and 1,25-dihydroxyvitamin D [28]. Long-term treatment with furosemide causes hypocalcaemia, resulting in elevation of PTH and increased levels of bone-specific alkaline phosphatase, an indication of accelerated bone remodeling [29].

Clinical evidence

A prospective study in older women indicated that loop diuretic users had greater loss of total hip BMD than non-users (mean annualized % BMD −0.87 vs −0.71, $P = 0.03$) after a mean of 4.4 ± 0.6 years [30]. The risks of neither falls nor fractures were greater in loop diuretic users than in nonusers [30], findings that were replicated in older men [31]. In a randomized-controlled trial, one-year treatment of bumetanide decreased BMD, and subjects treated with bumetanide had increased markers of bone turnover compared with placebo [32]. Given that the placebo group was treated with calcium and vitamin D supplements, in this trial bumetanide at the least antagonized the positive effects of calcium and vitamin D supplements. In another study, bumetanide dose-dependently increased renal calcium loss with a concomitant increase in plasma PTH and 1,25(OH)2D levels [20]. A recent study indicated the clinical association of hyponatremia during the use of loop diuretics with an increased risk of osteoporosis associated fractures, and the authors suggested that a moderate but persistent loss of both bone sodium and calcium could be exerted by loop diuretics [33]. Finally, in a large cohort

study with 376,061 subjects, falls were more common among loop diuretic users than with other antihypertensive agents although there was no difference in fracture risk [34].

In summary, via direct (loss of BMD) and indirect (increased falls) mechanisms, it seems loop diuretics have a negative effect on bone health and are associated with increased risk of fractures.

Spironolactone

Pharmacology

Spironolactone is a potassium-sparing diuretic that exerts effect by inhibition of mineralocorticoid receptor; mineralocorticoid excess causes hypertension as well as inducing adverse remodeling of vasculature [35].

Potential mechanisms affecting bone health

In rodent model, hyperaldosteronism induced hypercalciuria and hypermagnesuria and secondary hyperparathyroidism with increased bone resorption [36]. Spironolactone in combination with thiazides prevented bone resorption in a similar model [37]. In patients with primary hyperaldosteronism, there is significantly higher 24-h urinary calcium excretion that is associated with a decreased BMD and increased vertebral fracture risk [38].

Clinical evidence

In a study including 226 patients (46 with an aldosterone-producing adenoma, 70 with bilateral adrenal hyperplasia, and 110 with essential hypertension), Ceccoli and colleagues showed that the secondary hyperparathyroidism in primary hyperaldosteronism patients was reversible after treatment with spironolactone [39]. In addition, in 24-month follow-up, a significant improvement in BMD at all measured skeletal sites was observed [39]. As well, in a retrospective chart review of patients with heart failure, including 167 cases with a single-incident fracture age and race matched to 668 controls without fractures, spironolactone use was associated with a reduction in risk of major fractures [40].

In summary, spironolactone has the potential to preserve BMD in the setting of primary or secondary hyperaldosteronism and may be associated with a reduction in the risk of fracture.

Beta-blockers

Pharmacology

Beta receptors are the sympathetic component of the autonomic nervous system. Beta-adrenergic receptors have been subdivided into three types: beta-1 (heart and vessels), beta-2 (pulmonary tissues), and beta-3 (adipose tissue) [41–43]. Bone cells express beta-2 adrenoceptors, although low levels of beta-1 and beta-3 adrenoceptors are also present [44]. Beta-blockers (BB) exert their effect by inhibition of beta-adrenergic receptors and are widely used in the treatment of hypertension and heart failure. These agents are often described in terms of their "cardio-selectivity" depending on their selective action of beta-1 receptor-blocking properties [45]. Nonselective BB have action on beta-2 and beta-3 receptors and thus tend to exert their effects beyond heart. Like many other receptor blockers, in higher doses, cardio-selective BB lose their selectivity.

Potential mechanisms affecting bone health

An intact autonomic nervous system contributes to the maintenance of healthy bone tissue, and perturbations of the system could induce abnormal bone remodeling. Increased sympathetic nervous activity causes bone loss via an increase in bone resorption and a decrease in bone formation [46]. Increased bone resorption is based on the stimulation of both osteoclast formation and osteoclast activity. These effects are associated with beta-2 adrenergic activity present in both osteoblastic and osteoclastic cells [47]. Decreased bone formation is based on the inhibition of osteoblastic activity through beta-2 adrenergic receptors on osteoblasts. In animal models, there is substantial evidence of sympathetic nerve fibers in bone tissue and functional adrenergic receptors in osteoblasts and osteoclasts which has effect on osteoblast proliferation, osteoblast maturation, and osteoclast development [48, 49]. In contrast, sympathetic system inactivation in rats results in a significant decrease in osteoclast number and osteoclast activity [50–52]. In a recent study in human osteoblasts, fenoterol, a beta-2 agonist, nearly doubled RANKL mRNA and this increase was inhibited by propranolol indicating that in human bone cells, bone turnover might be modulated by the sympathetic nervous system [53, 54].

Clinical evidence

Data from the Dubbo Osteoporosis Epidemiology Study reported that in men 50 years or older, BB use was associated with higher BMD at the femoral neck (0.96 vs. 0.92 g/cm^2, $P < 0.01$) and lumbar spine (1.32 vs. 1.25 g/cm^2, $P < 0.01$), and a lower fracture risk [adjusted odds ratio (OR): 0.49; 95% CI, 0.32–0.75] than when BB were not used; findings were nearly identical in older women [55]. In a retrospective cohort of 501,924 Korean patients (age 65 and older), beta-1 selective BB reduced the risk of fractures compared to other classes of antihypertensive agents [56]. In a meta-analysis of

13 observational studies including 907,000 men and women with ages ranging from 40 to 80 years, BB use was associated with an average 17 % reduction in the risk of any fracture [risk ratio (RR) 0.83], hip fracture (RR 0.83), and vertebral fracture (RR 0.81) [57]. The associations between BB use and fracture risk were independent of age, BMD, and clinical risk factors. Subgroup analysis suggested that the association was mainly found in beta-1 selective BB, not in the nonselective agents. A more recent meta-analysis of 16 studies (7 cohort and 9 case–control studies), involving 1,644,570 subjects, confirmed these earlier findings and suggested that the relative risk of any fracture is approximately 15 % lower in patients treated with BB compared to controls [58]. Of note, there were no randomized-controlled trials involving BB.

In summary, the available data, from both animal experiments and observational studies, suggest that selective BB use is associated with higher BMD and may be independently associated with a reduced risk of fracture.

Renin–angiotensin–aldosterone active agents

Pharmacology

The renin–angiotensin–aldosterone system (RAAS) plays a central role in the control of blood pressure and has been an important target of antihypertensive medications. There are several groups of drugs in this category that affect different parts of the RAAS axis, including angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blocker (ARB), which are widely used for hypertension, heart failure, and cardiovascular and renal protection. RAAS agent operates not only systemically but also locally in several tissues including bone [59]. Recent studies indicate that RAAS, which plays a central role in modulating blood pressure and remodeling vasculature, might also contribute to bone health [60].

Potential mechanisms affecting bone health

Osteoblasts and osteoclasts express angiotensin-II type 1 receptor in cell cultures, suggesting the existence of local RAS in bone. In vitro, angiotensin I stimulates bone resorption in co-cultures of osteoclasts with osteoblastic cells, and this action inhibited ACE inhibitors [61]. Angiotensin-II induces the expression of receptor activator of NF-kappaB ligand (RANKL) in osteoblasts, leading to the activation of osteoclasts, whereas these effects are blocked by an angiotensin-II type 1 receptor blockade (e.g., olmesartan) [62]. Therefore, it is thought that angiotension II accelerates bone resorption by activating osteoclasts via RANKL induction [63]. In animal studies, both ACE inhibitors and ARBs have been shown to preserve bone density [61, 64].

Clinical evidence

In a prospective cohort study of 50 menopausal women with hypertension, the ACE inhibitor fosinopril prevented loss of BMD in lumbar spine and femoral neck compared with untreated controls [65]. A cross-sectional study of 3887 Chinese patients (1929 women and 1958 men) showed that ACE inhibitor use was independently associated with higher femoral neck BMD in women, and higher BMD at all skeletal sites in men, after adjusting for many potential confounders including other antihypertensive agents, osteoporosis and cardiovascular risk factors, and lifestyle measures [66] although a more recent prospective cohort study in 3,494 American men could not definitively replicate these findings [67]. On the other hand, a population-based pharmacoepidemiological case–control study, including 124,655 fracture cases and 373,962 age and sex-matched controls, demonstrated that the relative risk of any fracture was reduced by 7 % (OR, 0.93; 95% CI, 0.90–0.96) in users of ACE inhibitors compared with nonusers [68]. There were no differences between according to sex and age in these results. Finally, in a meta-analysis of 54 studies, there was only one study with ACE inhibitors (134 patients), and this showed a significant reduction in fractures among users compared with nonusers (RR 0.81, 95% CI, 0.73–0.89) [69].

In summary, in animal models, the RAAS seems to tie the cardiovascular system together with bone health, and in humans, ACE inhibitors (but not ARBs) seem to improve BMD and have a protective effect against fracture risk.

Calcium channel blockers

Pharmacology

The calcium channel blockers are group of medications that inhibit the voltage-activated inward influx of calcium from the extracellular medium. These agents have potent cardiovascular effects and are used for the treatment of hypertension because of their vasodilatation properties as well as negative inotropy and chronotropy [70]. In addition, these agent inhibit intracellular calcium release, block post-junctional alpha-adrenoceptors, interact with calmodulin, inhibit cyclic AMP phosphodiesterase, stimulate Na+-, K+-activated ATPase, and directly interact with the contractile proteins [71–73]. Commonly, they are classified according to chemical structure and site of action as dihyropyridine (selective to vascular tissues) and non-dihyropyridine (relatively selective for myocardium) calcium channel blockers [74, 75].

Potential mechanisms affecting bone health

During resorption, osteoclasts can sense changes in ambient Ca2+ concentration. This triggers a sharp cytosolic Ca2+ increase through both Ca2+ release and Ca2+ influx. The change in cytosolic Ca2+ is transduced into inhibition of bone resorption [76]. For example, benidipine hydrochloride can regulate growth and differentiation of osteoblasts and stimulates the function of these cells [77]. In animal models, amlodipine at doses of 1 and 3 mg/kg significantly increased calcium and phosphorous concentrations in the femurs of ovariectomized rats, compared to controls [78]. Amlodipine might exert its effect through a direct inhibition of osteoclast function and/or suppression of PTH secretion and subsequent inhibition of osteoclast activity [79, 80].

Clinical evidence

In one 12-week study, amlodipine increased vitamin D levels significantly in patients with a newly diagnosed hypertension compared to the ARB valsartan [81]. Conversely, in another trial, 8-week treatment of amlodipine (with or without estrogen) was not associated with a marked influence on bone metabolism [82]. In a study with 11 postmenopausal women with osteoporosis, nifedipine inhibited PTH secretion although it did not affect osteocalcin levels [83], and in another study, in 11 males, nifedipine was not associated with markers of bone health [84]. There are no randomized trials of the effect of calcium channel blockers on BMD or fracture.

In summary, the data on calcium channel blockers and bone health are limited and inconclusive, but it seems unlikely that these agents have any clinically important effects on bone.

Nitrates

Pharmacology

Nitric oxide (NO) is a potent vasodilator that acts via activation of cyclic GMP [85]. The nitrate group of medications acts as donor of NO thereby causing vasodilatation and decreases in preload and afterload, and is commonly used for angina, heart failure, and as a potential adjunct treatment for hypertension [86].

Potential mechanisms affecting bone health

Proinflammatory cytokines induce NO production in osteoblast-like cells which plays a role in regulating cell growth [87]. Inducible production of nitric oxide in osteoblast-like cells and in fetal mouse bone explants is associated with suppression of osteoclastic bone resorption [88]. In animal models, nitroglycerine (NTG) ointment, a NO donor, prevents bone loss in ovariectomized rats compared with vehicle controls, and when compared with baseline, treatment with NTG significantly increased BMD in ovariectomized rats by about 20 % [89, 90].

Clinical evidence

In a prospective study in 6,201 elderly women (317 took daily nitrates and 74 took them intermittently), those taking daily nitrates had slightly greater hip BMD compared to nonusers. By contrast, women using nitrates intermittently had substantially greater hip BMD than nonusers suggesting the possibility of tachyphylaxis to bone-sparing effects [91]. Finally, in the UK, a cohort study was conducted that included 124,655 subjects who had sustained a fracture during 2000 and 373,962 age- and sex-matched controls [92]. In adjusted analyses, use of nitrates was associated with a 11 % reduced risk of any fracture in women and men and a 15 % reduced risk of hip fracture in women but not men [92]. Of note, use of nitrates with a short duration of action was associated with greater reductions in fracture risk than use of slow-release preparations, again pointing to the potential for tachyphylaxis.

In a randomized-controlled trial in 144 healthy postmenopausal women with a hip BMD T score between 0 and −2.5, isosorbide mononitrate (ISMO) 5 or 20 mg/day was compared with placebo for 12 weeks [93]. Compared with placebo, women randomized to 20 mg of ISMO had a 45 % decrease in N-telopeptide and a 23 % increase in serum bone-specific alkaline phosphatase, while 5 mg of ISMO led to a 36 % decrease in N-telopeptide and a 16 % increase in serum bone-specific alkaline phosphatase. This pattern suggests that ISMO both decreases bone resorption and increases bone formation in a dose-dependent manner [94].

In summary, nitric oxide donors tend to preserve or increase BMD, and in observational studies, these agents appear to be associated with a reduction in fracture. Intermittent use of nitrates seems to have more of a bone-sparing effect than continuous use, raising concerns about tachyphylaxis.

Conclusions

Bone health and cardiovascular health seem to be linked, and almost all cardiovascular drugs used for hypertension that we examined were associated with beneficial effects on bone either in vitro and in vivo and, in human studies, were associated with increases (or preservation) of BMD and/or a reduction in osteoporotic fractures (see summary Table 1). The only exceptions appeared to be loop diuretics

Table 1 Summary of the potential mechanisms and effects of cardiovascular medications for hypertension on bone mineral density and fracture risk

Medications	Potential mechanism affecting bone health	Effect on bone mineral density	Effect on osteoporotic fracture risk
Thiazide diuretics	Direct stimulation of osteoblasts	↑	↓
	Bone formation		
Loop diuretics	Increased urinary calcium loss	↓	↑
	Falls risk		
Spironolactone	Inhibition of aldosterone receptors	↑	↓
Beta-blockers	Inhibition of beta-adrenergic receptor in bone	↑	↓
Angiotensin-converting enzyme inhibitors	Inhibition of angiotensin-converting enzyme in local RAAS in bone	↑	↓
Angiotensin-II receptor blocker	Direct blockade for Angiotensin-II receptor	↔	↔
Calcium channel blockers	Inhibition of voltage-gated calcium channel	↔	↔
Nitrates	Donates nitric oxide	↑	↓
	Suppression of osteoclast		

Upward arrow (↑) indicate positive, downward arrow (↓) negative, and horizontal arrow (↔) indicate neutral effect

(adverse effects) and calcium channel blockers (little or no effects). However, all of these conclusions are based almost entirely on observational studies or a handful of trials with surrogate measures of bone turnover.

One might ask whether it is even possible or feasible to undertake randomized trials of antihypertensive medications with fracture endpoints or at the least, BMD-related endpoints? While possible in theory (as evinced by trials, we have described with loop diuretics and nitrates), we believe in general such trials would be prohibitive because so many antihypertensive medications are available to physicians and because of the large numbers and long timelines required to accrue events. There is one approach we would suggest could work, and it is endocrine specialists who are best positioned to make this happen. In future trials of new antihypertensive agents, if self-reported and radiograph-confirmed fractures as well as injurious falls are prospectively collected as serious adverse events (SAE), then important high-quality data might be generated. Furthermore, if nested within such a large trial, even a small sample of patients with BMD and biomarkers at baseline and study end would be informative for mechanistic subgroup analyses.

Regardless, for so many different pathways and signaling systems to be affected by different medications used to treat hypertension and to generally have a positive effect on bone health suggests several potential common pathways that might lead to both adverse cardiovascular events and adverse skeletal events. Even though the available data are inadequate (and almost bereft of trials) to recommend the use of cardiovascular medications to improve bone health, we believe the totality of evidence still has two implications.

First, for scientists, much basic and translation work needs to be done to better understand the links between cardiovascular disease (in particular hypertension) and osteoporosis. Second, for clinicians, when their patients need hypertension treatment and their patient is also at high risk of fracture, there is some guidance about which agents to forgo if possible (loop diuretics) and which agents to choose (thiazides, cardioselective beta-blockers, ACE inhibitors)—all else equal.

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