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Review Article

Osteoporosis and Osteoporotic Fracture: Contribution of Hypertension and Anti-hypertension Medications

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Abstract

Hypertension and osteoporosis are two major public health burdens of the general population, which share many of the same risk factors such as advance age, early menopause, smoking and physical inactivity. Many experimental studies suggested that there is biological link between hypertension, anti-hypertension medications and bone. However, existing human evidence on the contribution of hypertension and anti-hypertension medications to osteoporosis and osteoporotic fracture is either scarce or conflicting. We reviewed existing publications on the topic. Multiple biological mechanisms are involved in the relationship between hypertension and bone, and most of them suggested that hypertension has a deteriorative effect on human skeleton. However, existing human studies on the association between hypertension and bone mineral density are still controversial. In contrast, we found consistent evidence suggesting that hypertension is a risk factor for osteoporotic fracture. There are fewer controversies that Beta-blockers and thiazide diuretics are protective against osteoporosis and osteoporotic fracture. In conclusion, hypertension is a risk factor for osteoporotic fracture and the relationship is likely independent on bone mineral density. The protective effect of beta-blockers and thiazide diuretics is needed to be taken account on the associations. Further studies are highly demanded.

Keywords: Hypertension; Bone mineral density; Osteoporosis; Osteoporotic fracture; Anti-hypertension medications.

Introduction

Osteoporosis and its consequent fracture represent a major public health problem worldwide, because **they are** highly prevalent among the elderly population, and lead to chronic pain, long-term disability, loss of independence and mortality. By using Dual-energy X-ray Absorptiometry (DXA), approximately one half of women and 40% of men aged 60 years or older are found to have osteoporosis [1]. Over 50% of postmenopausal women and 33% of elderly men over age of the 60 years will have an osteoporotic fracture [2]. For patients with hip fracture, 12-41% will die within the first six months from the consequence of the fracture or other associated complications [3-5].

Similarly, hypertension imposes a major burden to health care system all over the world. **A cross-sectional survey in U.S. concluded that approximately 24% of the U.S. adults have hypertension** [6]. The worse consequence of hypertension is not the disease itself, but its associated diseases including stroke, ischemic brain lesions, silent brain infarcts, atherosclerosis, myocardial infarction and other cardiovascular disease (CVDs)[7-10] which are the top killers worldwide.

Worldwide, anti-hypertension medications are the top prescribed medications due to the high prevalence of high blood pressure among the community. Regardless of the variation between countries, calcium channel blockers and angiotensin converting enzyme (ACE) inhibitors are generally the most widely used medications for the treatment of hypertension. If we consider thiazide and non-thiazide diuretics together, those diuretics are the most commonly prescribed anti-hypertensive drugs in the most countries as they are the first-line recommended agents for hypertension treatment [11]. The less expensive antihypertensive drugs are more commonly prescribed than more costly drugs. Between countries, the overall use of anti-hypertensive drugs is considerably higher in the U.S. than in Canada, France, Norway or the UK [12].

The contribution of hypertension and anti-hypertension medications to osteoporosis and osteoporotic fracture is poorly understood. Hypertension and osteoporosis are two major public health burdens of the general population, which share many of the same risk factors such as advance age, early menopause, smoking and physical inactivity. Many experimental studies suggested that there is a biological link between hypertension, anti-hypertension medications and bone[13-17].However, existing human evidence on the contribution of hypertension and anti-hypertension medications to osteoporosis and osteoporotic fracture is either scarce or conflicting [18-23].Given the high prevalence of hypertension and osteoporosis in the elderly population, understanding the contribution of hypertension and anti-hypertension medications to osteoporosis and osteoporotic fracturewill substantially improve general health of humans.This review will summarize the issue.

Hypertension, Osteoporosis and Osteoporotic Fracture

Mechanisms between hypertension and bone

Hypertension and bone mineral density (BMD) have a major pathophysiologic link between blood pressure regulation and calcium metabolism. High blood pressure is associated with abnormalities

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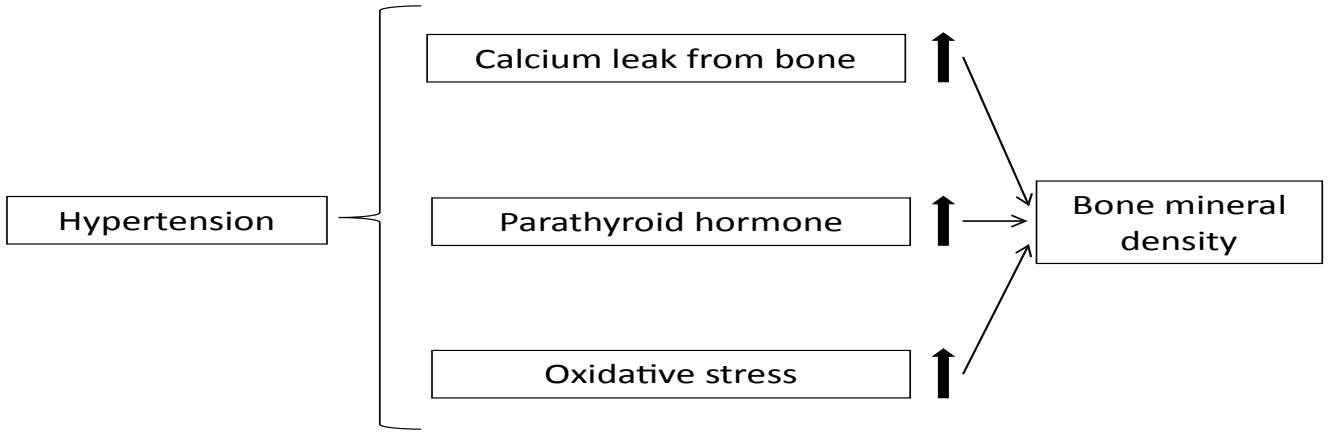

Figure 1: Mechanisms between hypertension and bone.

of calcium metabolism, which induces increased calcium leak from bone [13-15]. The calcium leak from bone will be eventually excreted by kidney in the form of urine [20]. In support, hypertension has been shown to be associated with hypercalciuria and hypercalciuria is related to decreased BMD[24-26].

Hypertension-bone relationship is related to **parathyroid hormone** (PTH) [27]. It has been shown that the circulating level of PTH is positively correlated with blood pressure [28,29]. The elevated PTH due to hypertension leads to an increased bone resorption, decreased bone mass and bone quality [27].

Finally, the oxidative stress pathway may be involved in the hypertension-bone relationship, because oxidative stress is well correlated with hypertension [30-32]. High level of oxidative stress due to excessive reactive oxygen species increases bone loss by inhibiting bone formation and promoting bone resorption [33,34]. Those abnormalities related to hypertension may eventually be responsible for increased bone loss and low BMD [19,35].

Hypertension and bone mineral density

Although hypertension has been shown to have a deteriorative effect on the human skeleton, the association between hypertension and BMD are still controversial due to conflicting findings from previous studies (Table 1). We did a systematic literature searchusing MeSH terms in the Pubmed (Key words: high blood pressure, hypertension, bone, BMD and osteoporosis). Then, the references of selected papers were also checked.Nine studies were identified after the search. Among those studies, five of them suggested that participants with hypertension had lower BMD than non-hypertensive controls [19,36-39]. However, the results were not consistent with four other studies [20,40-42], which suggested that hypertension and BMD were unrelated.

Hypertension and osteoporotic fracture

Although the association between hypertension and BMD is still unclear, hypertension is a risk factor for fractures (Table 2). A case-control study including 124,655 fracture cases and 373,962 age- and gender-matched controls suggested that hypertension was associated with a 1.2-fold increase in risk of fractures [43]. A similar result was observed in a Swedish population-based study, in which diagnosis of hypertension increased the multi-variable-adjusted hip fracture risk by 1.6-fold [44]. A recent data derived from the Dubbo Osteoporosis Epidemiology Study indicated that the positive relationship between hypertension and fracture risk is likely independent of BMD [39]. It has also been suggested that the effect of hypertension on fracture affects women more strongly than men [21], but the explanation for this is still unclear.

In the current fracture risk assessment models (FRAX® or Garvan Bone Fracture Risk Calculator), hypertension is still not a recognized risk factor for osteoporotic fracture largely because of a lack of prospective studies. Therefore, future prospective studies with large sample size are warranted to validate whether treatment of hypertension will reduce the risk of CVDs and osteoporotic fracture simultaneously.

Anti-Hypertension Medications, Osteoporosis and Osteoporotic Fracture

Table 1: Existing studies on the association between hypertension and bone mineral density.

Studies	Design	Participants	Results
Tsuda et al. [19]	Cross-sectional	31 hypertensive women and 14 normotensive controls	Lumbar spine BMD in hypertension vs. in non-hypertension group: 0.58 vs.0.67 g/cm^2; *P*< 0.05
Lidfeldt et al. [40]	Cohort	6886 women	Wrist BMD was positively associated with systolic and diastolic blood pressure: *P*< 0.001
Perez-Castrilon et al. [20]	Cross-sectional	82 women aged 36-76 years with hypertension and 40 normotensive postmenopausal women	Lumbar spine BMDin hypertension vs. in non-hypertension group: 1.06 vs. 1.05 g/cm^2; *P*> 0.05
Afghani and Johnson, [37]	Cross-sectional	33 obese Hispanic women	Systolic blood pressure against bone mineral content: r = -0.31; *P* = 0.001
Mussolino and Gillum [41]	Cross-sectional	3306 premenopausal and postmenopausal women	Hypertension was not associated with total proximal femoral neck BMD (Quartile 1 vs. 4): OR = 0.92 (0.65-1.30)
Marina and Ivan [38]	Cross-sectional	300 postmenopausal women	Systolic blood pressure in osteoporosis vs. in normal BMD group: 151 vs. 121 mm Hg; *P*< 0.001
Olmos et al. [42]	Community-based cross-sectional	636 postmenopausal women	Lumbar spine BMD in hypertension vs. in non-hypertension group: 0.93 vs. 0.90 g/cm^2; *P*< 0.05
Yazici et al. [36]	Retrospective analysis	586 postmenopausal women	Systolic blood pressure against femoral neck BMD: r = -0.143, *P* = 0.01
Yang et al. [39]	Prospective	1032 men and 1701 women	Women femoral neck BMD in hypertension vs. in non-hypertension group: 0.79 vs. 0.82 g/cm^2; *P* = 0.02

Table 2: Existing studies on the association between hypertension and fracture risk.

Study	Design	Subjects	Fracture type	Relative risk (95% confidence interval)
Perez-Castrillon et al. [21]	Case-control	Women: 365 hip fractures, 586 controls; Men: 79 hip fractures, 446 controls	Hip fracture	Women: 1.49 (1.3-1.8); Men: 1.2 (0.9-1.6)
Sennerby et al. [97]	Case-control	Women only: 1,327 hip fractures; 3170 controls	Hip fracture	2.76 (1.98-3.84)
Sennerby et al. [44]	Cohort study	31,936 Swedish twins from age of 50 years	Hip fracture	1.59 (1.36-1.85)
Vestergaard et al. [43]	Case-control	124,655 fracture cases; 373,962 controls	Any fracture	Short-term hypertension: 1.27 (1.20-1.34); Long-term hypertension: 1.11 (1.00-1.23)
Yang et al. [39]	Prospective	1032men and 1701 women	Any, hip and vertebral fracture	Any fracture: 1.53 (0.94-2.48) for men and 1.49 (1.13-1.96) for women; Hip fracture: 1.16 (0.44-3.08) for men and 1.48 (0.84-2.60) for women; and Vertebral fracture: 1.67 (0.76-3.66) for men and 1.12 (0.74-1.70) for women

Beta-blockers

Mechanisms between beta-blockers and bone: Since beta-adrenergic receptors have been identified on osteoblast-like cells in culture, beta-adrenergic agonists are able to efficiently activate beta-receptors on osteoblast cells and stimulate bone resorption in intact mouse calvariae in vitro[45-47]. The effect of BBs on bone formation was also found to be centralised while leptin was identified as a potent inhibitor of bone formation acting through the central nervous system [48,49]. Furthermore, evidence of a sympathetic regulation of bone metabolism in animal models suggested that leptin deficiency results in a low sympathetic tone, and genetic or pharmacological ablation of adrenergic signalling leads toleptin-resistance and high bone mass [16]. Similarly, BBs as anti-sympathetic agents, have been postulated to increase bone mass via the same pathway, andeventually act locally through beta-2 adrenergic receptors on bone osteoblasts [16]. In addition, the production of other bone-active cytokines (e.g. PTH, RANKL and interleukin-11 etc.)can be stimulated by beta-agonists, and bone resorption can be inversely decreased by beta-antagonists [50-52]. There is also evidence suggesting that propranolol increases cross-linking of type 1 collagen in other tissues [53],which may enhance tensile strength of bone.

Beta-blockers and bone mineral density: The association between beta-blocker (BB) use and BMD was initially raised by Pasco et al.[54], who concluded that BB use was associated with a 2.5% higher BMD at the hip after adjusting for age, anthropometry and use of thiazide diuretics. Further observational studies also supported the findings that BB users had higher hip BMD and lumbar spine BMD [55,56]. However, the findings are not consistent with other studies, which include a randomised control trial [57-59]. Although the majority of them suggested that BBs had a beneficial effect on BMD, conflicting findings were still observed. This discrepancy is likely attributable to the variations in study design and study subjects.

Beta-blockers and fracture risk: Although there are some controversies, majority of existing studies suggested that BBs are associated with reduced fracture risk. A recent meta-analysis of 13 observational studies suggested that BB use was associated with an average of 17% reduction in the risk of any fracture [39]. However, there is a possibility of false positive as existing publications are observational and are easily subject to certain bias. Therefore, future randomised control trails are required to rule out this possibility.

Thiazides

Mechanisms between thiazide diuretics and bone

The relationship between thiazide diuretics and bone has been discussed over the past few decades, and involves several possible mechanisms. First, thiazide could exert their beneficial effect on bone by decreasing urinary calcium excretion by 25-40% [17,60]. Second, thiazides are associated with increased level of metabolic alkalosis, which is an inhibitor of bone resorption [61,62]. Third, *vitro* evidence suggests that thiazides directly inhibited osteocalcin secretion of osteoblast-like cells [63,64].

Thiazide diuretics and bone mineral density

The association between thiazide diuretic use and BMD is well-established with the majority of the studies suggesting that thiazides are associated with increased BMD. Initially, Transbol et al.[65] found that the beneficial effect of thiazides on BMD is only present in the first six months of use, after which the BMD difference between thiazide users and placebo users is no longer significant. After this study, a number of studies [42,66-70], including two RCTs [22,71], consistently suggested that thiazide users have significantly higher BMD than non-users, but the magnitude of the association is relatively small. However, the results were not consistent with one study conducted in children with idiopathic hypercalciuria [72]. This is probably because the urine in those patients contains excess calcium, mainly from bone, which may down-regulate the positive effect of thiazides on BMD.

Thiazide diuretics and fracture risk

Although the majority of current studies have shown that thiazides are protective against bone fragility, the association between thiazide diuretics and fracture risk is still controversial due to conflicting findings from previous published studies. In a meta-analysis of five cohort studies, use of thiazide diuretics was associated with an approximately 25% reduction in the risk of hip fracture [23]. The relationship between thiazides and hip fracture presents a significant heterogeneity if the studies are limited to case-control studies [23]. Other evidence suggested that thiazide use has a similar or stronger effect on reducing the risk of other type of fractures [73,74]. At present, the evidence for physicians to recommend the use of thiazide diuretics for osteoporotic fracture prevention is still insufficient, but physicians should be aware that use of thiazides may receive an additional benefit in reducing fracture risk during the hypertension treatment.

Other Anti-Hypertension Medications

Other anti-hypertensive medications and bone mineral density

In contrast to thiazide diuretics, non-thiazide diuretics exert an opposite effect on calcium homeostasis and bone metabolism by increasing renal calcium excretion [75,76]. A cross-sectional study of 348 white women over the age of 70 years found that use of loop diuretics was associated with lower BMD at the femoral neck and trochanter [77]. A prospective cohort study of 8,127 postmenopausal women extended the finding that loop diuretics use was associated with greater bone loss [78]. However, other studies suggest that loop diuretics were not necessarily related to low BMD [76,79,80]. A few studies have assessed the influence of potassium-sparing diuretics on BMD, but the available evidence indicated that they were unrelated in a cohort of 5,995 men [80].

ACE inhibitors have been shown to have a beneficial effect on bone fragility. In addition, it has been demonstrated that ACE inhibitors were associated with improved periosteal callus formation and fracture healing [81]. In Hong Kong, a cross-sectional study of 3887 Chinese men and women suggested that ACE inhibitor use was associated with higher femoral neck BMD in men and women [82]. However, the findings were unable to be replicated in an U.S. study, in which the use of ACE inhibitors marginally increased bone loss in older men [83].

Few studies have assessed the effect of calcium channel blockers and alpha blockers on BMD. It has been found that calcium channel blocker use increases serum calcium and inorganic phosphate concentrations, but had no effect on bone turnover markers or BMD [84]. The use of alpha blockers has been shown to be associated with higher BMD after adjusting for age and body weight in a cohort of Chinese men [85]. However, it is still unclear as to why the use of alpha blockers causes high bone mass.

Other anti-hypertensive medications and fracture risk

The association between non-thiazide diuretics and fracture risk remains inconsistent. A meta-analysis of 11 observational studies suggested that non-thiazide diuretics, including loop diuretics, were not associated with increased fracture risk [86]. A recent large cohort of Medicare beneficiaries concluded that loop diuretics were associated with the highest rate of fracture risk compared with other anti-hypertension medications [87]. The association between loop diuretics and fracture is more likely to be observed in prolonged use of the diuretics than short-term use of the medications [79]. There is limited evidence for potassium sparing diuretics and fracture risk, but the available evidence showed the relationship between such diuretics and osteoporotic fractures is still controversial [88,89].

The effect of ACE inhibitors on fracture reduction is still inconclusive due to conflicting results from previous studies. A large scale case-control study showed that long term used of ACE inhibitors was associated with reduced fracture risk [88]. Similarly, in a Danish case-control study, use of ACE inhibitors was associated with a 7% and 14% decreased risk of any fracture and hip fracture, respectively [90]. However, the beneficial effect of ACE inhibitors on fractures was not seen in another retrospective case-control study [21].

Although calcium channel blockers have been shown to have a positive effect on bone remodelling [91], few studies have evaluated the effects of the medications on fracture risk. A case-control study of 124,655 fracture cases and 373,962 controls found that treatment with calcium channel blockers was modestly associated with an reduced risk of fracture [90]. Subgroup analysis by type of calcium channel blockers indicated the reduced risk of fracture was more pronounced in the users of non-dihydropyridine than in the users of dihydropyridine [90]. However, the above results were not consistent with a Danish study, in which a two-fold higher risk of fracture was observed in calcium channel blocker users than in non-users [92].

The relationship between alpha blockers and fracture risk is still unclear due in large to the limited available evidence. In a population based case-control study, current users on alpha blockers had an approximately two-fold higher risk of hip fracture than non-users [93]. Similar results were also found in a Korean study, in which

alpha blockers use was also associated with greater fracture risk [94]. Apart from the above two studies, no further studies have evaluated the contribution of alpha blockers to fracture risk [86].

Conclusions

Hypertension is a risk factor for osteoporotic fracture and the relationship is likely independent of BMD. Although hypertension itself has been demonstrated to increase fracture risk, hypertension is not a well-established risk factor for fracture based on current fracture risk assessment guidelines [95,96]. The reason for this is likely due to the use of beta-blockers, thiazide diuretics or other anti-hypertension medications. Therefore, it is clinically important to further assess the contribution of hypertension to osteoporosis and fracture after taking account of the protective effect of anti-hypertension medications.

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