Clinic Rev Bone Miner Metab (2015) 13:185–193
DOI 10.1007/s12018-015-9186-9

HYPERTENSION AND BONE

Effect of Beta-Blockers on Bone Mineral Density, Bone Turnover Markers and Fractures: A Clinical Review

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Published online: 1 July 2015

Abstract The increased sympathetic nervous activity causes bone loss, via an increase in osteoclastic bone resorption and a decrease in osteoblastic bone formation, suggesting an important regulating role for the SNS in bone metabolism. Such findings may indicate that pharmacological beta-blockade could be a target to increase bone mass and reduce the risk of fractures. This review summarized the impact of beta-blockers on bone mineral density, bone turnover markers and fracture risk.

Keywords Beta-blockers · Propranolol · Bone mineral density · Bone turnover markers · Procollagen type I N-terminal peptide · C-terminal type I collagen telopeptide · Vertebral fractures · Non-vertebral fractures · Falls

Introduction

The interplay between bone metabolism and atherosclerosis is still an interesting area of clinical and basic research [1]. In fact, some medications used to treat osteoporosis and cardiovascular diseases have been suggested to be useful for both processes [2, 3].

Since bones are widely innervated, in the last decade, a new window has been opened with the discovery of a role for the sympathetic nervous system (SNS) in the regulation of bone metabolism [4]. Takeda et al. [5] confirmed that osteoblasts express beta-adrenergic receptors, and SNS has been shown to regulate osteoblast function. Thus, SNS activation reduces osteoblast proliferation and stimulates bone resorption by increasing RANKL expression. Recently, a more complex pathway implicating leptin as a link between SNS and bone metabolism has been suggested [6]. Overall, the long-term net effect can be a loss of cancellous bone mass.

In this sense, pharmacological beta-blockade has been suggested as a target to increase bone mass and reduce the risk of fractures [7–9].

However, in a real-world scenario, patients with cardiovascular diseases usually are taking many medications, such as thiazides, calcium channel blockers, angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers, being difficult to ascertain which one or even what combination of drugs may be responsible for the effect on bone metabolism. Another interesting issue is to know whether differences in this effect were related or not to the class of beta-blocker medications (BB), that is, a selective or a non-selective agent. A third leading point when analyzing the relationship between BB and bone mineral density (BMD) or fragility fractures is whether a dose-dependent or cumulative time-dependent dose response is present.

The effects of BB on bone metabolism have been reported in the last decade, although results are not yet conclusive. To improve knowledge of this relationship, the purpose of this paper is to review the impact of BB on BMD, bone turnover markers (BTM), falls and fracture risk. To do this, we searched in PubMed for papers containing the following terms: “bone”; “bone mineral density”; “bone mass”; “beta-blockers”; “propranolol”; “bone markers”; “osteocalcin”; “procollagen type 1

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n-terminal propeptide"; "C-terminal telopeptide of type 1 collagen"; "fracture"; "vertebral fracture"; "non-vertebral fracture"; "hip fracture"; "falls"; "forearm fracture." Secondary references were also reviewed.

Beta-Blockers and Bone Mineral Density

Clinical studies on the effect of BB on bone parameters are usually of cross-sectional nature and complicated by the heterogeneous baseline characteristics of the populations analyzed, the type of BB and the time of use, being therefore difficult to draw solid conclusions. The duration of BB use may also be a key point, since the mechanism by which BB could influence BMD is expected to be prolonged, at least to exert a clinically relevant effect. Besides, large placebo-controlled trials with long-term follow-up are lacking in this field. Thus, the role of BB on BMD has been addressed in several observational studies [10–20]. Furthermore, most of patients on BB receive these agents due to cardiovascular diseases. The impact of hypertension or cardiovascular diseases themselves on BMD or fractures has to be considered when interpreting the results of the studies.

Table 1 summarizes the main results of studies analyzing the impact of BB treatment on BMD.

Pasco et al. [10] evaluated the association between BB use, documented by questionnaire and BMD or fractures, in a population-based study of women aged 50 years or older, from Geelong, Australia. They analyzed 569 women with radiological incident fractures sustained during a 2-year period (1994–1996) and 775 control without fractures. BB were associated with higher BMD at the total hip (2.5 %) and ultradistal forearm (3.6 %), after adjusting for age, weight, height and thiazide use. Longer exposure to BB was related to higher BMD, but the association did not reach statistical significance at any skeletal site. This was the first report in humans showing a positive association between BB use and BMD (and also fractures, reviewed later on). However, the small sample size may have limited the power to detect significant differences at other sites, such as lumbar spine. Besides, BMD was measured 2 months after the fracture occurred, and bone mass could be affected by the fracture itself. In fact, no differences regarding the effect of BB on BMD were detected in the group of women without fractures.

Renjmark et al. [11] did not confirm the results of the Australian study. Thus, they found no association between BB use and lumbar spine or femoral neck BMD, in the Danish Osteoporosis Prevention Study (DOPS), a population-based study of 2016 perimenopausal women. Nevertheless, the small size of the BB group was a clear limitation of this study.

Reid et al. [12] analyzed cross-sectionally and longitudinally 8412 women ≥65 years old who participated in the fourth visit of the Study of Osteoporotic Fractures (SOF). Of them, 1099 were receiving BB. The follow-up period was 7 years. Current use of any medication was defined as use during the previous 2 weeks. BB were classified as being β_1-selective or non-selective and as being taken in high or low doses according to the midpoint of the recommended dose range. As expected, baseline characteristics of both groups (BB users vs. non-users) were quite different, specifically in anthropometric, use of medications or cardiovascular history. Although crude values for hip BMD (measured by dual X-ray absorptiometry—DXA) were slightly higher in BB users, adjustment for weight alone canceled out this finding. No differences were detected regarding selective or non-selective BB in terms of BMD. In women with a new DXA performed at visit 6 (after a follow-up of 4 years), bone loss at the hip was similar between groups, with unchanged data when selectivity of BB was analyzed. Therefore, BB use and hip BMD or the rate of bone loss over time were unrelated in the SOF cohort.

Levasseur et al. [13] found similar results using data from another prospective population-based study (EPIDOS) in 7598 French women aged 75 years or older. They observed a 2 % increase in femoral neck BMD in women on non-cardioselective BB compared with those without, but this difference was no longer present when adjusted for confounders. Duration of BB use was unrelated to BMD at any site.

Turker et al. [14] conducted a prospective case–control study in 50 patients with cardiovascular diseases receiving BB and 150 patients admitted to an Orthopedic Department from Turkey who served as controls. Lumbar spine and total hip BMD were significantly higher in cases than in controls. They concluded that BB use was associated with an increase in BMD. This study should be interpreted with caution due to its design and the lack of adjustment for confounding variables.

Bonnet et al. [15] in a case–control study evaluated the association of BB with BMD and bone geometry (assessed by DXA at femoral neck), and microarchitecture (analyzed by the H mean fractal parameter at the calcaneus), in 158 postmenopausal women referred for bone density testing and 341 age-matched controls. They found a 3 % significant increase in BMD at the lumbar spine and a 4 % increase at the femoral neck, in BB users compared to controls. This increase was followed by significantly higher cortical width at the femoral neck of women on BB. Femoral shaft measurement did not differ between cases and controls, but the H mean parameter was significantly higher in the BB group and persisted after adjustment for BMD, regardless of the site of measurement, suggesting a

Table 1 Summary of studies analyzing the effect of BB on BMD

Author [references]	Sex/age	*n*	Type of study	Result
Pasco et al. [10]	W/≥50 years	569 cases 775 controls	Case–control	Higher total hip and ultradistal forearm BMD in BB users
Rejnmark et al. [11]	W/45–58 years	2016 (38 on BB)	Cross-sectional	No association between BB and lumbar spine or femoral neck BMD
Reid et al. [12]	W/≥65 years	8412 (1099 on BB)	Cross-sectional	No association between BB and hip BMD.
			Longitudinal (7-year follow-up)	No association between class of BB and hip BMD
				No changes in bone loss at the hip over time
Levasseur et al. [13]	W/≥75 years	7598 (283 on BB)	Cross-sectional	No association between BB and femoral neck or total body BMD
				No association between duration of BB use and BMD at the hip or total body
Turker et al. [14]	W and M/60–80 years	50 cases 150 controls	Case–control	Higher lumbar spine and total hip BMD in BB users
Bonnet et al. [15]	W/41–96 years	158 cases	Case–control	Higher BMD at lumbar spine and femoral neck in BB users
		351 controls		Higher cortical width in BB users
				Better trabecular microarchitecture in BB users
Pérez-Castrillón et al. [16]	M/59 ± 11 years	40 (30 on BB)	Longitudinal (1-year follow-up)	No association between cardioselective BB and femoral neck BMD in men with history of myocardial infarction
Yang et al. [17]	W and M/≥50 years	3488 (673 on BB)	Cross-sectional	Higher lumbar spine and femoral neck BMD in women and men on BB
Sosa et al. [18]	W/65 ± 10 years	74 cases 111 controls	Case–control	No association between BB and lumbar spine or femoral neck BMD or QUS parameters in postmenopausal women with coronary heart disease
Bleicher et al. [19]	M/70–97 years	1122	Longitudinal (2-year follow-up)	Less bone loss at the hip in BB users
Agaçayat et al. [20]	M/≥55 years	67 on BB	Retrospective case–control	Higher BMD (measured by CT) at maxilla in BB users versus CCB users
		79 on CCB 148 controls		No differences between men on BB and controls
Reid et al. [21]	W/66 ± 8 years	41 (20 on BB)	Randomized placebo-controlled trial (3-month follow-up)	No association between the use of propranolol (160 mg/day) and lumbar spine or total proximal femur BMD

W women, *M* men, *BB* beta-blockers, *BMD* bone mineral density, *CCB* calcium channel blockers, *QUS* quantitative ultrasound, *CT* computed tomography

better trabecular structure. In this study, about 40 % of subjects were hormone therapy replacement users and, approximately 16 %, were taking an anti-osteoporotic agent, although the authors seem to adjust for these variables, and differences remain statistically significant.

Pérez-Castrillón et al. [16] analyzed the effect of cardioselective BB on bone mass and biomechanical properties of the femoral neck in 40 men with acute myocardial infarction followed up during 1-year. They found that these BB did not modify BMD or biomechanical elements, assessed by DXA.

A recent epidemiological study has shed new light in the association between BB and BMD [17]. The Dubbo Osteoporosis Epidemiology Study, although it was designed to evaluate the risk of fractures with BB use, also evaluated BMD (at lumbar spine and femoral neck, by DXA) in 3488 participants of either sexes aged 50 years or more. The proportion of men on selective, non-selective and other BB combinations was 77, 18 and 5 % respectively, and these figures were similar to women (71, 21 and 8 %). Men and women on BB had significantly higher BMD at both sites than non-users, and these differences

persisted after adjusting for the main confounders. BB use accounted for <1 % of BMD variance once adjusted for age, weight and lifestyle factors. Moreover, the association between BB and BMD was mainly found in participants on non-selective agents. However, the effect of dose duration, cumulative dose and time-effect were not analyzed.

Sosa et al. [18] conducted a case–control study on 74 postmenopausal women with a history of coronary heart disease (acute myocardial infarction or angina pectoris) in the previous 6 months and 111 age-matched controls. Lumbar spine and proximal femur BMD were determined by DXA. Heel quantitative ultrasound (QUS) was also performed. Cases showed higher BMD than controls at femoral neck, trochanter and total hip. However, these differences were canceled out when adjusting for potential confounding factors, including age, body mass index and BB use. No differences were found between cases and controls regarding QUS parameters. Therefore, in these women with coronary heart disease, the use of BB was unrelated to BMD, measured by DXA, or to QUS parameters.

The first longitudinal study analyzing the association between BB and hip BMD loss in older men was published by Bleicher et al. [19]. They analyzed the predictive factors of the rate of BMD loss in 1122 Australian men, aged 70–97 years, from the CHAMP study. BMD was measured at the hip (DXA) over 2 years. Men on BB had significantly less bone loss, and this association was maintained after adjusted for confounding variables, including the use of nitrates, statins and thiazides. In multivariate analysis, the use of BB and walking more than a kilometer per day were the two factors related to a lesser bone loss in the participants included in this population-based study. Nevertheless, the exact number of men receiving BB was not specified, and medication was self-reported, and therefore, results must be taken with caution.

Long-term effects of some antihypertensive drugs on BMD in men were analyzed in a recent paper [20]. This was a retrospective study conducted in Turkish men older than 55 years, and BMD was assessed by cone-beam computed tomography of the jaw area. They studied 3 groups of patients: men taking BB ($n = 67$), those receiving calcium channel blockers ($n = 79$) (both for more than 5 years) and a control group without antihypertensive medications ($n = 148$). They found significantly better BMD values at the maxilla, among the patients on BB compared with the patients who had been receiving calcium channel blockers. However, no differences between any group on medication and controls were detected. The study has several limitations, such as the self-report of medications, the small number of patients included and the lack of adjustment for confounding variables, such as hypertension itself. Besides, since standardized values for the evaluation of BMD with cone-beam computed tomography are still lacking, the results of this study are of limited clinical value.

The only randomized placebo-controlled trial assessing the effect of BB on bone metabolism was conducted by Reid et al. [21] in 41 healthy postmenopausal women. They compared the effect of propranolol (160 mg/day) on BTM, over a 3-month period. Besides, they analyzed BMD in both groups and observed that no significant difference was found at lumbar or total proximal femur measurements between women on BB and those allocated to placebo.

Beta-Blockers and Fractures

Different case–control studies and meta-analysis have investigated the association between BB use and risk of fracture. The studies include populations using a range of BB agents varying in dose and duration.

Beta-Blockers Reduce the Risk of Fractures

In several case–control studies, the current use of BB has been demonstrated to be associated with a reduced risk of fractures [10, 15, 22–28, 34, 36]. These clinical studies suggest that pharmacological blockade of the beta-adrenergic system is beneficial to the human skeleton. A study [22] included 124,655 cases that sustained a fracture and 373,962 age- and gender-matched controls showed, after adjustment for potential confounders, that the risk of any fracture was reduced by 9 % [odds ratio (OR) 0.91; 95 % confidence interval (CI) 0.88–0.93] in BB users. A similar result was reported by Pasco et al. [10] in women from a population-based cohort in Australia. As we have previously mentioned, BB use was documented for 569 women with confirmed incident fractures and 775 controls without incident fracture. OR for any fracture associated with BB use was 0.68 (95 % CI 0.49–0.96), that is, a 32 % decrease in the risk of any fracture.

Another case–control study [23] using the UK General Practice Research Database (GPRD), included 30,601 patients (aged 30–79 years) with an incident fracture diagnosed between 1993 and 1999 and 120,819 age- and sex-matched controls. The authors found that current use of BB was associated with a reduced risk of fractures, when taken alone or in combination with thiazide diuretics. Wiens et al. [24] in a meta-analysis including case–control and cohort studies reported a lower risk of fractures in elderly people using BB compared with non-users (pooled risk ratio RR 0.86; 95 % CI 0.70 and 0.98). Nevertheless, no significant associations were found between fractures and exposure to alpha-blockers.

Bonnet et al. [15] studied the association between BB use and fracture rates in postmenopausal women (944 women, 158 women on BB and 341 age-matched controls) and concluded that the OR for fracture (at all sites) in the BB users was 0.56 (95 % CI 0.30–0.99). De Vries et al. [25] in two case–control studies using data from the UK GPRD and the Dutch PHARMO Record Linkage System (RLS) showed that the use of BB was associated with a reduced risk of hip/femur fracture in both study populations. However, the protective effect of BB was only present among patients with a history of use of other antihypertensive agents (GPRD adjusted OR 0.72, 95 % CI 0.64–0.83; PHARMO RLS adjusted OR 0.76, 95 % CI 0.67–0.86), but not in patients using only BB (GPRD adjusted OR 0.97, 95 % CI 0.82–1.14; PHARMO RLS adjusted OR 1.01, 95 % CI 0.90–1.14). The same author found increases in the risk of hip/femur fracture in patients on higher doses of β_2-agonists, in a population-based case–control study (6763 cases) using the Dutch PHARMO database [26].

Yang et al. [17] reported that in men aged 50 years or older from the Dubbo Osteoporosis Epidemiology Study, BB use was associated with lower fracture risk [adjusted OR 0.49; 95 % CI 0.32–0.75] compared with non-users. They found virtually the same results when older women were analyzed. These authors in a meta-analysis [27] of 13 observational studies (907,000 men and women aged 40–80 years) showed that BB use was associated with an average 17 % reduction in the risk of any fracture (RR 0.83), hip fracture (RR 0.83) and vertebral fracture (RR 0.81).

A more recent meta-analysis [28] of 16 studies (seven cohort and nine case–control studies) including 1,644,570 subjects confirmed the previous findings and suggested that the risk of any fracture is significantly reduced in subjects receiving BB as compared to non-users (16 studies, pooled ES = 0.86, 95 % CI 0.78–0.93). Besides, the risk of hip fracture was lower in both women and men receiving BB (women: pooled ES = 0.86, 95 % CI 0.80–0.91, $I^2 = 1$ %; and men: pooled ES = 0.80, 95 % CI 0.71–0.90, $I^2 = 0$ %). RR of any fracture was approximately 15 % lower in patients treated with BB compared to controls. This risk reduction is observed in men and women and for all major fracture sites (hip, vertebral and forearm) and remained robust in sensitivity analyses. However, dose dependency was not established. Finally, using adjusted indirect comparisons, they found that β_1-selective agents were significantly more effective than non-selective BB in reducing the risk of any fracture (six studies, β_1-selective blockers vs. non-selective BB: pooled ES = 0.82, 95 % CI 0.69–0.97). Assuming the overall lifetime risk of any osteoporotic fracture at the age of 50 to be 30 % [29], one osteoporotic fracture is prevented over the life course of every 30 treated patients.

Beta-Blockers Increased or Not Changed the Risk of Fracture

However, some studies have found an increase in the risk of fracture in BB users [11, 18]. Thus, Rejnmark et al. [11] reported a statistically significant increase in clinical and vertebral fractures associated with BB use. This study was carried out in a cohort of 2016 older women (the Danish Osteoporosis Prevention Study). BB use was associated with a threefold increase in fracture risk (adjusted OR 3.3; 95 % CI 1.1–9.4). Analyses on duration of treatment showed that women who had been treated for more than 8 years had a higher fracture risk (OR 5.3; 95 % CI 1.1–26.3) than those treated for <8 years (OR 2.4; 95 % CI 0.6–9.5).

In other studies, the use of different antihypertensive drugs is associated with the risk of fracture. Butt et al. [30] assessed 301,591 newly treated hypertensive community-dwelling elderly patients during 2000 and 2009 (1463 hip fractures identified) who started an antihypertensive drug. They had a 43 % (IRR 1.43; 95 % CI 1.19–1.72) increased risk of hip fracture during the first 45 days of treatment, although only BB (RR 1.58; 95 % CI 1.01–2.48) and ACEI (RR 1.53; 95 % CI 1.12–2.10) demonstrated statistically significant association.

A case–control study [18] on 74 postmenopausal Spanish women who had recently suffered from coronary heart disease and 111 age-matched controls analyzed vertebral (diagnosed by lateral, thoracic and lumbar X-rays) and non-vertebral prevalent fractures (assessed by examination of medical records). The prevalence of all fragility factures was slightly higher in patients with coronary heart disease, but not to a significant extent. In a logistic analysis to identify factors associated with all fractures, BB were positively associated with fragility fractures.

In other studies, no association between BB and risk of fracture is found [12, 13, 21, 31–33, 35]. The small case–control study published by Jensen et al. [31] in the early 1990s showed no significant association between femoral neck fractures and BB use. Levasseur et al. [13] in 7600 older women (mean age 80 years) from the EPIDOS cohort did not find any association between BB use and fracture (HR 1.2; 95 % CI 0.9–1.5), after a mean follow-up of 3.6 years.

Reid et al. [12] analyzing the SOF database showed no significant effect between BB use and the unadjusted (HR 0.92; 95 % CI 0.81–1.05) or adjusted risk of any fracture (HR 0.87; 95 % CI 0.70–1.00). Thorell et al. [32] in 38,407 individuals aged 75 years and older (2 % had a hip fracture) reported that the use of BB agents was not associated with an increased risk for hip fracture after adjustment for

age, gender and multimorbidity level (OR 0.92; IC 95 %, 0.80–1.07).

Table 2 summarizes the studies analyzing the effect of BB on fractures.

Beta-Blockers and Risk of Falling

Antihypertensive medications have long been implicated as a potential cause of falling in older people [37]. Falling is the main etiologic factor in more than 90 % of hip fractures [38]. The reported anti-fracture potential of BB should be carefully weighed against the side effects associated with their use. BB have several adverse effects, such as bradycardia, hypotension, depression, confusion, blurred vision, and may result in fall injuries. Starting BB agents in the elderly has been associated with an immediate increased risk of falls. A study [39] including elderly patients aged ≥65 years (2407 participants) followed up during 2–3 years showed an increased fall risk in subjects on non-selective BB compared with non-users (HR 1.41; 95 % CI 1.12–1.78). However, a meta-analysis [40] of the impact of 9 classes of medications on falls, in patients over 60 years, did not find any relationship with the use of BB (OR 1.01; 95 % CI 0.86–1.17). A systematic review and meta-analysis [41] conducted to evaluate the effect of some drugs and falls in people aged 60 years and older concluded that BB use was not associated with falls (OR 0.93; CI 95 % 0.77–1.11). A more recent meta-analysis [42] analyzed the risk of fall injury in elderly people treated with the five main classes of antihypertensive drugs (thiazide diuretics, ACEI, angiotensin receptor blockers, calcium channel blockers and BB) and did not reveal a clear association between antihypertensive drugs and risk of fall injuries.

Gribbin et al. [43] in a case–control study showed a reduced risk of falls for BB currently prescribed in older people after adjustment for prior coronary heart disease, co-morbidities and other antihypertensive agents (OR 0.90; IC 95 %, 0.85–0.96).

Taken together, these studies do not clearly support that the use of BB increases the risk of fall injuries in the elderly.

Table 2 Summary of studies analyzing the effect of BB on the risk of fracture

References	Type of study	OR/RR (95 % CI) Any fracture	OR/RR (95 % CI) Hip fracture
Pasco et al. [10]	Case–control	0.68 (0.49–0.96)	W: 0.56 (0.24–1.33)
Rejnmark et al. [11]	Case–control	3.30 (1.10–9.40)	
Schlienger et al. [23]	Case–control	0.83 (0.76–0.91)	
Renjmark et al. [22]	Case–control	0.91 (0.88–0.93)	W: 0.86 (0.76–0.98)
			M : 0.89 (0.71–1.13)
Bonnet et al. [15]	Case–control	0.56 (0.30–0.99)	
De Vries et al. [25]	Case–control	0.82 (0.74–0.91)	W: 0.83 (0.74–0.93)
			M : 0.77 (0.60–0.98)
De Vries et al. [26]	Case–control	0.87 (0.80–0.95)	W: 0.90 (0.82–1.00)
			M: 0.77 (0.64–0.93)
Sosa et al. [18]	Case–control	3.27 (1.42–7.51)	
Levasseur et al. [13]	Cohort	1.20 (0.90–1.50)	
Reid [21]	Cohort	0.87 (0.75–1.00)	W: 0.66 (0.49–0.90)
Gage [33]	Cohort	0.84 (0.70–1.00)	
Meisinger [34]	Cohort	0.60 (0.37–0.96)	
Yang [17]	Cohort	0.71 (0.54–0.93)	W: 0.90 (0.51–1.56)
			M : 0.50 (0.17–0.90)
Solomon [35]	Cohort	0.95 (0.89–1.02)	
Song [36]	Cohort	0.70 (0.66–0.73)	
Yang et al. [27]	Meta-analysis (13 OS)	0.83 (0.71–0.93)	0.83 (0.70–0.92)
Toulis et al. [28]	Meta-analysis (7 cohort; 9 case–control studies)	0.86 (0.78–0.93)	W: 0.86 (0.80–0.91)
			M: 0.80 (0.70–0.90)

OR odds ratios, *RR* relative hazard, *W* women, *M* men, *OS* observational studies

Beta-Blockers and Bone Turnover

As we have commented on above, recent studies have generally shown that increased sympathetic nervous activity causes bone loss via an increase in bone resorption and a decrease in bone formation. These effects are associated with β_2-adrenergic activity present in both osteoblastic and osteoclastic cells [4]. Isoproterenol, a β-adrenergic agonist, leads to bone loss in mice [44]. Nevertheless, propranolol, a β-adrenergic antagonist, had the opposite effects, that is, it increases bone mass in mice [45] and suppress bone resorption by inhibiting RANKL-mediated osteoclastogenesis in a model of experimental periodontal disease [46].

On the other hand, leptin has been shown to regulate bone formation and bone resorption via the SNS. Thus, the effect of propranolol on ovariectomy-induced osteoporosis may be exerted, at least in part, through the regulation of leptin signaling, and there may be an interaction between the SNS and leptin on the regulation of bone metabolism [47]. However, the role of the adrenergic nervous system in bone metabolism is unclear, although some studies suggest that it has an anabolic effect on bone [48]. In experimental models, chemical sympathectomy impairs bone resorption by inhibiting preosteoclast differentiation, resulting in a decrease in the number of osteoclasts and thus a reduction in the resorption surface [48, 49].

Concerning the effect of BB on BTM, there are a few studies in humans with conflicting results. Thus, an observational study evaluated BB exposure in association with serum levels of C-telopeptide and bone-specific alkaline phosphatase in 197 women aged 50–59 years. Twenty-four BB users were identified at baseline. After controlling for concomitant use of hormone therapy, C-telopeptide levels were 6.7 % lower among BB users ($p = 0.02$). No association was detected between bone-specific alkaline phosphatase and BB use. These data suggest that BB might suppress bone resorption with relative preservation of bone formation [50]. Another epidemiological study in perimenopausal Danish women showed 20 % lower serum osteocalcin levels in women treated with BB compared to untreated women ($p < 0.001$) [11].

On the other hand, a negative calcium balance has previously been described in hypertensive patients with low levels of plasma ionized calcium (Ca^{2+}) and an increased urinary excretion of calcium. The cause of this effect is unclear. In this sense, Lind et al. [51] analyzed the effect of different antihypertensive agents on indices of systemic mineral metabolism in 319 subjects with essential hypertension. They found that treatment with different BB leads to a decrease in fasting urinary calcium excretion and an increase in the proportion of serum Ca^{2+}. These authors based on the behavior of BB in these patients suggest that the activity of the SNS is involved in the alterations of calcium metabolism in hypertension.

The main studies assessing the relationship between BB and BTM were prospective randomized placebo-controlled trials. The first one was a prospective pharmacological intervention trial comparing the effects of BTM on propranolol (160 mg/day) and placebo over 3 months, in 41 normal postmenopausal women. The authors found that procollagen type I N-terminal propeptide (P1NP) and total alkaline phosphatase activity were not significantly changed by this BB. Urine free deoxypyridinoline declined by approximately 10 % between 0 and 6 weeks in the BB group and was stable thereafter, but serum C-terminal telopeptide of type I collagen was not significantly different between groups. Only serum osteocalcin declined by almost 20 % in the first 2 weeks of propranolol treatment, and this effect increased over time ($p < 0.0001$). They concluded that propranolol did not affect bone metabolism, although serum osteocalcin concentration decreased significantly [21]. The second randomized controlled trial included 32 healthy postmenopausal women randomized to receive propranolol (80 mg/day) or no treatment during 12 weeks. The main outcome measure was the change in serum P1NP and C-terminal telopeptides of collagen type I (CTX), between both groups. Propranolol showed no effect on any of both BTM, and therefore, the authors concluded like the previous trial that the non-selective BB, propranolol, do not affect human bone turnover [52].

Conclusions

Since there is growing evidence that bone metabolism may be, at least in part, controlled by SNS, the effect of β-adrenergic pharmacological blockade on BMD, BTM and fractures has been analyzed in the last decade.

Concerning the effect of BB agents on BMD, the evidence mainly relies on observational studies with several methodological weaknesses. Besides, information about dose- or time-dependent response of these drugs on BMD is very limited. Therefore, we can conclude that, to date, there is no convincing evidence that BB have any beneficial or detrimental effect on BMD in men or women. Concerning fractures, BB use has been consistently associated with a reduced risk of fracture, although the effect size is likely to be modest. However, there is limited information on the association with cumulative dose and type of BB used. Whether the effect is mediated through decreased bone resorption and/or increased bone formation remains unclear. There is no clear conclusion that the use

of BB increases the risk of fall injuries in the elderly population.

Compliance with Ethical Standards

Conflict of interest José L. Hernández and Carmen Valero declare that they have no any conflict of interest regarding this paper.

Animal/Human studies The article does not contain any studies with human or animal subjects performed by the any of the authors.

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