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Association between beta-blocker use and fracture risk: The Dubbo Osteoporosis Epidemiology Study

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ABSTRACT

Introduction: In animal model, mice treated with beta-blockers (BB) had increased bone mass. In humans, high bone mass is associated with reduce fracture risk. The present study sought to test the hypothesis that BB use is associated with reduced fracture risk.

Materials and methods: Data from 3488 participants (1285 men) aged 50 years and above in the Dubbo Osteoporosis Epidemiology Study (DOES) were analyzed. Baseline characteristics of participants were obtained at the initial visit which had taken place between 1989 and 1993. Bone mineral density (BMD) at the lumbar spine and femoral neck was measured by dual energy X-ray absorptiometry (GE-LUNAR Corp, Madison, WI). Two hundred and sixty two (20%) men and 411 (19%) women had been on BB, as ascertained by direct interview and verification with medication history. The incidence of fragility fractures was ascertained during the follow-up period (1989–2008).

Results: In men, BB use was associated with higher BMD at the femoral neck (0.96 versus 0.92 g/cm^2, $P<0.01$), higher lumbar spine (1.32 versus 1.25 g/cm^2, $P<0.01$), and lower fracture risk than those not on BB (odds ratio [OR]: 0.49; 95% CI: 0.32–0.75). In women, BB users also had higher femoral neck BMD (0.83 versus 0.81 g/cm^2, $P<0.01$), higher lumbar spine BMD (1.11 versus 1.06 g/cm^2, $P<0.01$), and lower risk of fracture than non-users (OR 0.68, 95% CI: 0.53–0.87). 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 selective BB, not in non-selective BB.

Conclusion: Beta-blockers use, particularly selective BB, was associated with reduced fracture risk in both men and women, and the association was independent of BMD.

Introduction

Both osteoporosis and cardiovascular disease are major public health problems, because they are highly prevalent in the elderly population and are associated with reduced life expectancy. Approximately 25% of women and 10% of men aged 60 years or older are affected by osteoporosis [1–3]. In individuals aged 60 years and above, the residual lifetime risk of fracture is approximately 44% in women and 25% in men [1]. Several recent studies have suggested that men and women with fracture have higher risk of mortality compared with those without a fracture [4–6]. Cardiovascular diseases, including hypertension, are also commonly present in the elderly population. The National Health and Nutrition Examination Survey recently reported that the prevalence of hypertension and cardiovascular disease among U.S. insured working-age adults was 32% and 6% respectively [7].

Recent epidemiologic and basic research evidence suggests that osteoporosis and hypertension may be linked. Individuals with cardiovascular disease had lower bone mineral density (BMD) and increased risk of fracture [8,9]. Furthermore, hypertension itself has been associated with increased bone loss and increased risk of fracture [10]. However, the association between hypertension and bone density is complicated by the fact that hypertensive individuals are generally heavier than the normotensive population, and greater body weight is associated with greater BMD and lower fracture risk [11].

Animal studies suggested that osteoblasts have β2-adrenergic receptors, and mice treated with beta-blockers (BB, propranolol) had increased bone mass [12,13]. We therefore hypothesized that BB may increase BMD and reduce fracture risk in humans. The present study sought to test the hypothesis by examining the association between BB use and fracture risk in older individuals.

Abbreviation: BB, Beta-blockers.

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Study design and methods

Study participants

This study was part of the ongoing Dubbo Osteoporosis Epidemiology Study (DOES), which was initiated in mid-1989, with subsequent biennial visits. The participants were randomly drawn from the Dubbo city, which is located 400 km northwest of Sydney. The age and sex distribution of the Dubbo population closely resembled the Australian general population [14]. Participants with insufficient baseline data, or less than 50 years old were excluded from the present analysis. Overall, we included 3488 participants (1285 men) in the final analysis. The study was approved by the St Vincent's Campus Research Ethics Committee and written informed consent was obtained from all participants.

Measurement of risk factors

At baseline, participants were interviewed by a nurse coordinator who administered a structured questionnaire for anthropometric data (e.g. age, weight and height) and other lifestyle factors (e.g. smoking, alcohol use, physical activity and dietary calcium intake). Weight, without shoes, was measured (to the nearest 0.1 kg) on an electronic scale. Height, without shoes, was measured to the nearest 0.1 cm by a wall-mounted stadiometer. Smoking was defined as any past or present tobacco intake. Alcohol users were defined as past or present alcohol intake. Physical activity was estimated by the Framingham questionnaire, which includes five levels of physical activity: basal, sedentary, light, moderate, and heavy activity [15]. Dietary calcium intake was based on a food frequency questionnaire [16].

Bone mineral density (BMD, g/cm^2) at the femoral neck and lumbar spine was measured by dual energy X-ray absorptiometry (DXA) (GE-LUNAR Corp, Madison, WI). The coefficient of reliability of BMD measurement is 0.96 and 0.98 at the proximal femur and lumbar spine respectively [17].

Ascertainment of fracture

Low-trauma and non-pathological fractures were ascertained from X-ray reports which were taken at the two, or at times three, radiology services center from 1989 [18]. Fractures were included only if the report of fracture was definite and, on review, had occurred with low trauma (e.g. fall from standing height or less). Fractures clearly due to major trauma (such as motor vehicle accidents), those due to underlying diseases (such as cancer or bone-related disease), or those of digits, skull or cervical spine were excluded from the analysis. We did not assess morphometric vertebral fracture. All types of fragility fracture were classified into three main groups: any fracture (at all sites), hip fracture and clinical vertebral fracture.

Ascertainment of beta-blockers use

Current or past use of the medications was ascertained by direct interview and verification of the medication history. BB use was abstracted from the participants' medication records. All individuals with one or more prescriptions for BB treatment, which included selective and/or non-selective BB, were included in the analysis. Any participants who initially use BB after date of fracture were excluded from the analysis. In total, 262 (20%) and 411 (19%) BB users were identified in men and women respectively. Of BB users, the proportion of men on beta-1 selective, non-selective and other combined blockers was 77%, 18% and 5% respectively, and was similar to women (71%, 21% and 8% respectively). It was not possible to ascertain the duration and doses of BB use, so the cumulative dose effect and time effect were not addressed.

Data analysis

The primary aim of the study was to assess the association between BB use and fracture risk. The main statistical model was the logistic regression model, with fracture being the primary outcome, BB use the factor, and age, anthropometric factors, lifestyle factors and BMD the covariates. Because the distribution of covariates among BB users and non-users was unbalanced, we analyzed the data by the propensity score method [19–21]. Propensity score (PS) is a novel alternative to the traditional linear model for analyzing complex observational data. The method is designed to create groups of treated and control that have similar characteristics so that comparisons can be made within these matched groups. By making two groups comparable, the observational study emulates a randomized controlled trial, and thus allows a causal inference.

The PS is defined as the conditional probability of assigning to a group given a set of observed covariates. The analysis involved two steps. In the first step, we fitted a logistic regression with BB use (yes/no) being the outcome, and age, BMI, smoking, alcohol use, dietary calcium intake and physical activity being covariates. We then calculated the expected probability (or propensity score) of each individual being assigned to BB or not BB, accounting for that individual's baseline characteristics. In the second-step, we estimated the effect of BB assignment on fracture adjusted for the propensity score using a logistic regression model. All analyses were performed using the Statistical Analysis System (Version 9.1, SAS Institute Inc., Cary, NC).

Results

Baseline characteristics

At baseline, 20% ($n=262$) of men and 19% ($n=411$) of women were on BB (Table 1). In both sexes, BB users had significantly heavier weight, greater BMI, and higher BMD than non-users. There was no significant difference in terms of age, height, smoking and physical activity between BB and non-BB users. Although men and women on BB tended to have lower dietary calcium intakes and alcohol use than those not on BB, the difference was only statistically significant in women.

BB use and bone mineral density

The relationship between BB use and BMD was explored in both univariate and multivariate analyses for men and women separately. At baseline, men on BB had significantly higher femoral neck and lumbar spine BMD than those not on BB (Figs. 1 and 2). After adjusting for propensity score, the difference remained statistically significant (0.96 versus 0.92 g/cm^2, $P<0.01$ for femoral neck BMD, and 1.32 versus 1.25 g/cm^2, $P<0.01$ for lumbar spine BMD). Women on BB also had significantly higher femoral neck BMD (0.83 vs 0.81 g/cm^2; $P=0.009$) and (1.11 vs 1.05 g/cm^2; $P<0.0001$) than those not on BB. In the multiple linear regression model, BB use accounted for less than 1% of BMD variance, after adjusting for the effects of age, weight, and lifestyle factors. Further analysis revealed that the association between BB use and BMD was mainly found in non-selective BB.

BB use and fracture

Between 1989 and 2008, 229 (18%) men and 641 (29%) women had sustained a low-trauma fracture. The majority of fractures were hip fracture (44 men and 133 women) and clinical vertebral fracture (97 men and 264 women). As expected [17], advancing age, lower BMD, lower body weight, shorter height, lower BMI, lower dietary calcium intake, lower physical activity and smoking were each significantly associated with a higher fracture risk in both sexes (Table 2). Alcohol use was significantly associated with lower risk of hip fracture in women only.

Table 1
Baseline characteristics of participants by beta-blocker use and gender.

	Men			Women		
	Beta-blocker users	Non-users	*P* value	Beta-blocker users	Non-users	*P* value
N (%)	262 (20.4)	1023 (79.6)		411 (18.7)	1792 (81.3)	
Age (years)	68.6 (5.7)	69.0 (7.0)	0.3868	68.7 (6.4)	68.7 (8.0)	0.8637
Weight (kg)	84 (14)	81 (14)	0.0051	70 (14)	67 (14)	0.0002
Height (cm)	174 (6)	173 (7)	0.2438	160 (6)	160 (6)	0.6525
BMI (kg/m^2)	28 (4)	27 (4)	0.0122	27 (5)	26 (5)	0.0001
BMD (g/cm^2)						
Lumbar spine	1.318 (0.209)	1.245 (0.215)	<0.0001	1.109 (0.218)	1.055 (0.199)	<0.0001
Femoral neck	0.955 (0.147)	0.919 (0.150)	0.0005	0.829 (0.138)	0.809 (0.142)	0.0094
Smokers (*n*, %)	159 (61)	604 (59)	0.6286	111 (27)	536 (30)	0.2438
Alcohol users (*n*, %)	181 (69)	682 (67)	0.4573	153 (37)	762 (43)	0.0494
Physical activity (METs)	33 (5)	33 (6)	0.3976	31 (3)	31 (3)	0.7747
Dietary calcium intake (mg/day)[a]	614 (426, 819)	648 (435, 901)	0.0936	589 (398, 831)	675 (465, 905)	0.0001
Any fractures (*n*, %)	28 (10.7)	201 (19.7)	0.0007	94 (22.9)	547 (30.5)	0.0021
Hip fractures (*n*, %)	5 (2.1)	39 (4.5)	0.0889	18 (5.4)	115 (8.5)	0.0602
Vertebral fractures (*n*, %)	10 (4.1)	87 (9.6)	0.0062	41 (11.5)	223 (15.2)	0.0713

Values are means (SD), unless otherwise specified.
[a] Median (Q1, Q3). METs: metabolic equivalents.

Men on BB had 51% lower odds of fracture (OR: 0.49; 95% CI: 0.32–0.75), but the association was mainly found in any fracture and clinical vertebral fracture (Table 3). The association was significant after adjustment for age and BMD, or propensity score with (OR 0.54; 95% CI: 0.34–0.86) and without BMD. In women, BB use was also significantly associated with reduced fracture risk either before (OR: 0.68; 95% CI: 0.53–0.87) or after adjusting for covariates (OR 0.71; 95% CI: 0.54–0.93).

Further analysis revealed that the association between BB use and fracture risk was mainly driven by the effect of selective BB use, not non-selective use. In men, selective BB use was associated with a 63% reduction in the odds of fracture (0.37, 95%: 0.33–0.84), which is virtually identical to the reduction observed in non-selective BB (0.37; 95% CI: 0.13–1.05) but the association was not statistically significant. In women, selective BB use was also significantly associated with reduced fracture risk (OR: 0.68; 95% CI: 0.51–0.91), but again the association was not observed in non-selective BB users. This pattern was maintained after adjusting for propensity score and BMD in both men and women. The association remained statistically significant after adjusting for thiazides diuretics and other anti-hypertensive drugs (data not shown). In both genders, BB use accounted for ~0.7% variance of fracture liability after adjusting for other clinical risk factors.

Discussion

The association between BB use and fracture has been controversial, with conflicting findings having been reported in the literature. In this population-based study, by using a longitudinal design and propensity score approach, we have shown that the use of beta-blockers was associated with higher BMD, and most importantly, with a reduced fracture risk. The association between BB use and fracture risk which was independent of age, BMD, BMI and other covariates. The association was consistently found in men and women. The present study's findings add to the growing *in vivo* and *in vitro* evidence that BB has pleiotropic effects on cardiovascular disease and bone health.

Previous studies on the association between BB and fracture yielded inconsistent results [22–24], but the underlying reasons for those discrepancies are not clear. In observational studies, the distribution of potential confounders was not even among BB users and non-BB users, because individuals in the exposure (e.g. BB use) and control groups were not randomized. As a result, variation of fracture prevalence could relate to different age groups, ethnicities [25], dietary calcium intakes, sun light exposure and physical activity. In addition, self-report of BB treatment may introduce a potential recall bias, which may misclassify exposure and control groups. Finally, the point estimate of fracture risk may be influenced by diverse fracture sites from different studies [22,23,26]. In this study, we used the method of propensity scores [20], which mimics the randomized controlled trial and therefore making the results more reliable.

The underlying mechanism of relationship between BB and fracture risk is still unknown. However, a partly relevant mechanism may be the leptin-sympathetic nervous system pathway. In animal models, leptin deficiency results in a low sympathetic tone, and genetic or pharmacological ablation of adrenergic signaling leads to leptin-resistance and high bone mass. Similarly, BB as anti-

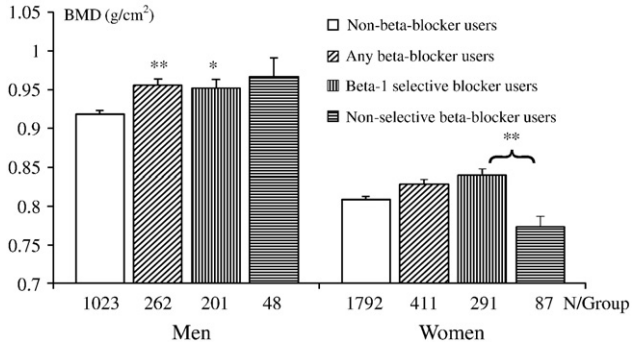

Fig. 1. Femoral neck BMD in beta-blocker users and non-users stratified by gender. *P* values were adjusted for propensity score. Significant difference at *$P<0.05$ **$P<0.01$.

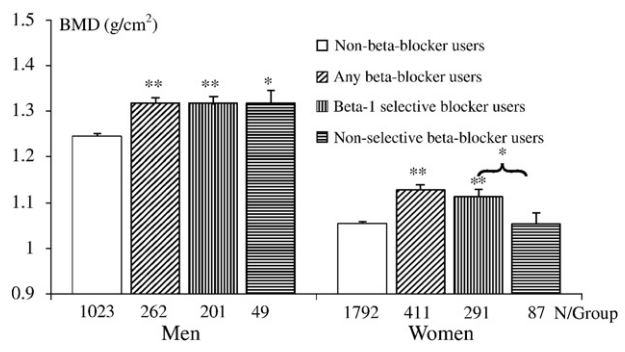

Fig. 2. Lumbar spine BMD in beta-blocker users and non-users stratified by gender. *P* values were adjusted for propensity score. Significant difference at *$P<0.05$ **$P<0.01$.

Table 2
Association between risk factors and fracture for men and women: univariate analysis.

Variables	Unit of change*	Men**			Women**		
		Any fracture	Hip fracture	Vertebral fracture	Any fracture	Hip fracture	Vertebral fracture
Age (years)	7	**1.81 (1.55, 2.11)**	**2.27 (1.69, 3.06)**	**1.78 (1.43, 2.22)**	**1.55 (1.42, 1.69)**	**2.39 (2.04, 2.79)**	**1.62 (1.44, 1.82)**
Weight (kg)	−14	**1.48 (1.26,1.73)**	**2.08 (1.44, 2.99)**	**1.84 (1.44, 2.35)**	**1.35 (1.22, 1.49)**	**3.11 (2.39, 4.04)**	**1.44 (1.24, 1.67)**
Height (cm)	6	**0.79 (0.69, 0.90)**	**0.74 (0.56, 0.96)**	**0.69 (0.57, 0.83)**	**0.85 (0.78, 0.93)**	**0.61 (0.51, 0.73)**	**0.79 (0.70, 0.90)**
BMI (kg/m^2)	−5	**1.44 (1.19, 1.74)**	**2.22 (1.42, 3.48)**	**1.72 (1.29, 2.30)**	**1.26 (1.15, 1.39)**	**2.43 (1.90, 3.12)**	**1.30 (1.13, 1.50)**
LSBMD (g/cm^2)	−0.21	**1.69 (1.44, 1.98)**	**1.88 (1.36, 2.62)**	**2.24 (1.76, 2.85)**	**1.86 (1.66, 2.09)**	**2.64 (2.08, 3.35)**	**2.50 (2.10, 2.98)**
FNBMD (g/cm^2)	−0.14	**1.84 (1.59, 2.15)**	**3.93 (2.74, 5.64)**	**2.28 (1.83, 2.85)**	**2.01 (1.81, 2.25)**	**4.47 (3.47, 5.76)**	**2.21 (1.90, 2.58)**
Smokers (Y/N)		**1.34 (1.00, 1.81)**	0.79 (0.43, 1.44)	**2.96 (1.76, 4.95)**	**1.22 (1.00, 1.48)**	1.06 (0.72, 1.56)	1.28 (0.97, 1.69)
Alcohol users (Y/N)		1.08 (0.80, 1.47)	0.65 (0.35, 1.20)	1.35 (0.85, 2.16)	0.88 (0.73, 1.06)	**0.54 (0.37, 0.80)**	0.87 (0.66, 1.13)
PA (METs)	5	**0.82 (0.70, 0.96)**	0.88 (0.64, 1.22)	**0.73 (0.57, 0.94)**	**0.75 (0.63, 0.89)**	**0.35 (0.23, 0.53)**	**0.67 (0.51, 0.88)**
DCI (mg/day)	300	**0.79 (0.69, 0.91)**	**0.55 (0.38, 0.79)**	**0.82 (0.67, 1.00)**	**0.91 (0.84, 0.98)**	**0.85 (0.72, 0.99)**	0.95 (0.85, 1.05)

Abbreviations: LSBMD: Lumbar spine BMD; FNBMD: Femoral neck BMD; PA: physical activity; DCI: Dietary calcium intake.
Bold-faced values indicate statistical significance at $P<0.05$.
* Values are approximately 1 SD.
** Values are odds ratio (95% confidence interval).

sympathetic agents, have been postulated to increase bone mass via the same pathway, which acts locally through beta-2 adrenergic receptors on bone osteoblasts [12]. In addition, the production of other bone-active cytokines (e.g. PTH, RANKL and interleukin-11 etc.) [27–29] can be stimulated by beta-agonists, and bone resorption can be inversely decreased by beta-antagonists. Furthermore, there is evidence that propranolol increases cross-linking of type 1 collagen in other tissue [30], enhancing its tensile strength. Taken together, *in vivo* and *in vitro* results suggest that BB use has a beneficial effect on bone health.

Regardless of the mechanisms involved, the present study's findings have several major clinical implications at the population level. The data suggest that the use of BB over the past few decades may have contributed to a plateau of reduction in osteoporotic fractures. This could be expected to be of considerable importance, particularly in North America where obesity and associated high blood pressure have been increasing. Indeed about half of the hypertensive population is post-menopausal women [7], who are at high risk of osteoporosis and fracture. Hence the relatively common concomitant use of widely used and well tolerated BB, plus thiazide diuretics, could have reduced fracture risk by 29% [31] and the public health implications of which are immense. Recent recommendations have supported the use of thiazide diuretics as baseline treatment for hypertension, while beta-blockers are less commonly recommended [31–33] in the US, Europe and Asia. Other agents, such as angiotensin converting enzyme inhibitors and receptor blockers, and calcium-channel blockers, have not been suggested to have a protective effect in our present study (data not shown). Hence the gradual drift away from thiazide–BB combination therapy and towards these often "non-protective" agents could be expected to result in a clinically significant increase in osteoporotic fractures.

This study's findings should be interpreted within the context of a number of strengths and limitations. The participants of the present study were well-characterized, community-dwelling elderly population, whose bone health has been monitored continuously for almost 20 years. Moreover, the number of fractures, including hip fractures, was sufficient to provide relatively reliable confidence intervals for the estimates. The use of propensity score to minimize confounding factors in a non-randomized setting [20,21] is an advantage of this study. However, as in all observational studies, bias or unknown confounders cannot be completely ruled out as alternative explanations. Hypertension is commonly associated with overweight and obesity [34]; these conditions may protect against fractures. Nevertheless, as noted previously, this protection was not seen with other anti-hypertensive agents and the effect remained after adjustment for body weight. In addition, the vertebral fracture considered in this study was symptomatic; yet typically less than one-third of vertebral deformity fractures are recognized [35]. Individuals with high blood pressure would be more likely to have radiographs for other purposes and thus could have more fractures identified incidentally. This could be expected to bias against finding a reduction of fractures in the hypertensive group as noted here. Due to incomplete data, the study did not formally examine the effects of dose and duration of BB use, and this could be a potential weakness. However, a subgroup analysis on 91 men and 156 women with complete data, we found no significant association between dose and duration of BB use and fracture risk. Finally, as with all observational studies, the present results must be interpreted as evidence of association, not a cause-and-effect relationship and unknown confounders which cannot be completely ruled out.

In summary, in this large prospective study in elderly men and women, the use of BB was associated with a significantly increased BMD and reduced fracture risk. Given the high prevalence of osteoporosis and hypertension in the general population, this finding raises the possibility that these anti-hypertensive agents may materially affect fragility fracture risk in many populations with high incidence of hypertension, such as those of the US, Europe and Japan. Moreover, if this effect and effect size are correct, a shift away from these agents in combination could be expected to lead to more than a doubling of all types of osteoporotic fractures. The public health implications of such an outcome demand a rapid and careful

Table 3
Association between BB use and fracture risk in men and women: results of multivariate analysis.

Models	Men			Women		
	Any fracture	Hip fracture	Vertebral fracture	Any fracture	Hip fracture	Vertebral fracture
Unadjusted	**0.49 (0.32, 0.75)**	0.45 (0.18, 1.16)	**0.40 (0.21, 0.79)**	**0.68 (0.53, 0.87)**	0.62 (0.37, 1.03)	0.72 (0.51, 1.03)
Adjusted for age and BMD	**0.55 (0.36, 0.86)**	0.45 (0.15, 1.33)	**0.47 (0.24, 0.94)**	**0.75 (0.58, 0.98)**	0.94 (0.54, 1.63)	0.82 (0.57, 1.19)
Adjusted for propensity score without BMD	**0.50 (0.32, 0.78)**	0.53 (0.20, 1.38)	**0.40 (0.20, 0.82)**	**0.66 (0.51, 0.86)**	0.69 (0.41, 1.16)	0.71 (0.49, 1.04)
Adjusted for propensity score with BMD	**0.54 (0.34, 0.86)**	0.50 (0.17, 1.51	**0.47 (0.23, 0.97)**	**0.71 (0.54, 0.93)**	0.90 (0.51, 1.56)	0.80 (0.55, 1.17)

Values are odds ratio (95% confidence interval).
Bold-faced values indicate statistical significance at $P<0.05$.

examination of other large carefully studied study groups to confirm or refute these findings.

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