

# Effects of beta-blockers on fracture risk

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## Abstract

Laboratory studies make clear that the sympathetic nervous system does impact on bone cell and tissue function. However, these effects are inconsistent between models, possibly reflecting sympathetic effects at different levels, from the central nervous system through to the bone cells. Observational studies of the use of  $\beta$ -blockers are confounded by the indications for which these drugs are prescribed, and by other medications that are commonly co-prescribed with them. These data are inconsistent, although a recent meta-analysis did conclude that  $\beta$ -blocker use was associated with a significant decrease in fracture risk. However, the more recent studies cast doubt on this finding, and the limited data regarding fractures in randomized controlled trials certainly do not support this conclusion. Therefore, there is not an adequate evidence base to support using  $\beta$ -blockers as a treatment for osteoporosis, nor can they be regarded as a discriminating risk factor for fracture assessment. Until there are definitive randomized, controlled trials of  $\beta$ -blockers, which include fracture as an endpoint, it is unlikely that the current confusing situation will be resolved.

**Keywords:** Sympathetic Nervous System, Adrenergic Receptors, Osteoporosis, Osteoblast

## Adrenergic effects on bone cells

The possibility that the sympathetic nervous system might play a role in skeletal metabolism is suggested by the presence of  $\beta$ -adrenoreceptors in bone, first demonstrated in osteoblasts some years ago<sup>1,2</sup>. These were subsequently shown to be of the  $\beta^2$  sub-type<sup>3</sup>, though Kellenberger also found  $\beta_1$  and  $\beta_3$  in some cell preparations<sup>4</sup>.

Consistent with this,  $\beta$ -agonists have been shown to exert a number of effects on bone, including stimulation of production of bone-active cytokines such as interleukin-6, interleukin-11, and prostaglandin  $E_2$ <sup>5-7</sup> in osteoblast-like cells. However, adrenergic agonists also directly stimulate osteoblast expression of both receptor activator of NF $\kappa$ B-ligand (RANKL) and osteoprotegerin, the former being a  $\beta$ -agonist effect whereas stimulation of osteoprotegerin is mediated by  $\alpha$ -adrenoreceptors<sup>6</sup>. Thus  $\beta$ -agonists stimulate osteoclastogenesis both by direct actions on osteoblasts and

via stimulation of local cytokine production<sup>6</sup>. Consistent with these cell culture findings, norepinephrine has been shown to increase bone resorption in bone organ culture, and propranolol to have the opposite effect<sup>3,8</sup>.

## Animal studies of sympathetic nervous system effects on bone

Some animal studies are consistent with the *in vitro* data suggesting predominant effects on bone resorption, such as the recent demonstration that propranolol reduces osteoclast markers, but does not affect serum osteocalcin in ovariectomized mice<sup>9</sup>. However, others have found effects of  $\beta$ -agonists or antagonists on indices of osteoblast activity, though these findings are sometimes contradictory. Minkowitz<sup>10</sup> has demonstrated increased mineral apposition rates in the femurs of propranolol-treated rats, but others have shown positive effects of  $\beta$ -agonists on osteoblasts<sup>11</sup> or bone mass<sup>12,13</sup>. Levasseur<sup>14</sup> has shown positive effects of propranolol on bone density in tail-suspended rats, which could be mediated by effects on either formation or resorption.

Reflecting these inconsistencies, sympathectomy produces variable effects on bone turnover *in vivo*<sup>15-17</sup>. Some of this variability might be contributed to by a shifting balance between the direct and indirect effects of adrenergic agonists and antagonists on bone, the latter including regulatory

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pathways such as parathyroid hormone, though these effects are also inconsistent<sup>18,19</sup>.

A further way to gain insights into the effects of the sympathetic nervous system on bone metabolism is to study animals in which the various  $\beta$ -adrenoreceptor sub-types have been knocked out. For example, the  $\beta$ -agonist, isoproterenol, stimulates both bone formation and resorption leading to bone loss in wild-type mice, but this does not occur in  $\beta_2$ -receptor knockout mice<sup>20</sup>. However, deletion of both the  $\beta_1$ - and  $\beta_2$ -receptors reduces bone size, cortical thickness and total body bone mineral content, but does not change trabecular bone density<sup>21</sup>. When all three adrenergic receptors are knocked out<sup>22</sup>, total body bone mineral content, cortical thickness and trabecular bone volume are higher than in wild-type animals, possibly contributed to by an increase in fat mass. These findings indicate that each of the adrenergic receptors has a different impact on bone, and that some of these effects might be indirect (e.g., by way of effects on soft tissue composition).

Greater attention has been focused on sympathetic nervous system effects on bone recently, because of the demonstration that the central nervous system can play an important regulatory role in skeletal homeostasis. Thus, Ducy<sup>23</sup> has shown that bone formation and bone mass in mice are responsive to intracerebroventricular administration of leptin, and Baldock<sup>24</sup> has complemented this with the demonstration that neuropeptide Y signaling in the hypothalamus also has profound effects on these end points. These observations were extended by Takeda<sup>25</sup>, who concluded that the central effects of leptin were mediated by the sympathetic nervous system, ultimately acting through  $\beta_2$ -adrenergic receptors on osteoblasts which negatively regulate the proliferation of these cells. These studies further demonstrated that the systemic administration of  $\beta$ -agonists resulted in decreased bone formation and bone loss in mice, while the administration of propranolol, a non-selective  $\beta$ -blocker, had the opposite effects. This has led to the suggestion that  $\beta$ -blockers may be a potential therapy for osteoporosis.

### Effects on bone turnover in humans

We have recently explored the role of  $\beta$ -blockade on skeletal metabolism in a randomized, placebo-controlled trial, comparing the effects on bone turnover markers of propranolol 160 mg/d and placebo over 3 months in 41 normal postmenopausal women<sup>26</sup>. Serum osteocalcin declined by almost 20% in the first 2 weeks of propranolol treatment, and this effect increased over time ( $p < 0.0001$ ). A very similar effect has been reported in a cross-sectional study of  $\beta$ -blocker users<sup>27</sup>. Other osteoblast markers, procollagen type-I N-terminal propeptide and total alkaline phosphatase activity, were not significantly changed by propranolol. Urine free deoxyypyridinoline declined 10% ( $p = 0.019$ ) in the  $\beta$ -blocker group, but serum C-terminal telopeptide of type I collagen did not change significantly. Thus, this study provided no evidence that  $\beta$ -blockers stimulate bone formation; if anything, propranolol reduces osteoblast activity. It was also found to influence renal function and fluid balance, effects that might indirectly affect bone metabolism.

### Effects on bone density in humans

Clinical studies of  $\beta$ -blockers are complicated by differences between the users of these drugs and the populations with which they are compared. For instance, in the Study of Osteoporotic Fractures users had significantly greater weight, more thiazide use, more estrogen use, less glucocorticoid use, more statin use, and more hypertension than non-users, and they smoked less<sup>28</sup>. Similar differences are likely to exist in other studies of these drugs, since they reflect the reasons these agents are prescribed in the first place (e.g., hypertension, ischemic heart disease), and also the conditions in which they are contraindicated (e.g., obstructive airways disease). This makes interpretation of cross-sectional studies very problematic.

With these caveats in mind, we studied bone density both cross-sectionally and longitudinally using data from the Study of Osteoporotic Fractures<sup>28</sup>. Total hip bone density was 1.0% higher in the  $\beta$ -blocker users ( $p = 0.02$ ), but adjustment for weight eliminated this difference. Further adjustment for age, estrogen use, thiazide use, glucocorticoid use, and smoking, all of which were significantly different between groups, resulted in virtual identity of the means for hip density. Similar results were found at the os calcis, there being a 1% difference between groups before any adjustment, which was no longer significant after adjustment for weight. Further adjustment for the cluster of factors listed above reduced the between groups difference even more. In subjects in whom bone density was re-measured after a mean follow-up of 4 years, bone loss was not different between the groups, whether or not the data were adjusted for co-variables. When selective and non-selective  $\beta$ -blockers were considered separately, the findings for both the cross-sectional and longitudinal data were essentially the same.

These results have been confirmed by Levasseur<sup>29</sup> using data from the EPIDOS study, another prospective study in normal older women. They reported that bone density in those using  $\beta$ -blockers was 2% higher than non-users, but this difference was no longer present following correction for confounding factors. Rejnmark also reported no association between bone density and  $\beta$ -blocker use in a cohort of normal Danish women<sup>27</sup>. In contrast, Bonnet<sup>30</sup> found differences in density of  $\sim 2\%$  in a case series of  $\beta$ -blocker users, and these were apparently unaffected by adjustment. The latter finding is surprising, since there were differences between users and non-users in statin and thiazide use, and the users tended to be heavier, though not statistically significantly so. In this study,  $\sim 40\%$  of subjects were using hormone therapy and  $\sim 15\%$  other osteoporosis treatments, which might have affected the outcome.

### Effects on fractures – Observational studies

There have now been several observational studies, which have assessed the associations between fractures and  $\beta$ -blocker use. These are set out in the Table. The small case-control

Study	Cases/Controls or Cohort Size	Mean Age (case/control or cohort)	% Female	Fracture Type	Odds Ratios or Relative Hazard (95%CI)	Adjustments, matching and restrictions
<i>Case-Control</i>						
Jensen, 1991	200/200 <sup>a</sup>	81/81	82	Femoral neck	0.85 (0.35-2.12)	Age, sex, nursing home, number of hospital admissions
Rejnmark, 2004	163/978	50	100	Appendicular skeleton and vertebral	3.3 (1.1-9.4)	Age, sex, years postmenopausal, previous fracture, weight, physical activity, energy intake, calcium and vit D, alcohol, smoking, use of medications, BMD, serum creatinine, serum vit D, serum bone ALP, serum osteocalcin, urinary OHP/creatinine
Pasco, 2004	569/775	70/70	100	Any	0.68 (0.49-0.96)	Age, sex, weight, height
Schlienger, 2004	30601/120819	Not stated	60	Any	0.77 (0.72-0.83)	Age, sex, GP, years in database, smoking, BMI, number of GP visits, medications
Rejnmark, 2006	124655/373962	43/43	52	Any	0.91 (0.88-0.93)	Co-morbidities, medications, social status
De Vries, 2007 UKGPD	22247/22247	>80	76	Femur	0.82 (0.74-0.91)	Osteoporosis, falls risk, co-morbidities, medications, BMI
De Vries, 2007 PHARMO	6763/26341	~ 80	73	Femur	0.87 (0.80-0.95)	Co-morbidities, medications
<i>Cohort</i>						
Levasseur, 2005	7598	81	100	Non-vertebral	1.2 (0.9-1.5)	Age, sex, health status
Reid, 2005	8412	77	100	Any	0.91 (0.79, 1.05)	Age, sex, weight, medications, smoking
Schoofs, 2005	7892	>55	Not stated	Arm, hip and pelvis	0.67 (0.46-0.97)	Age, sex, BMD, BMI, cardiovascular disease, hypertension, medications
Gage, 2006	14564	80	55	Vertebral, wrist, hip	0.84 (0.70-1.00)	Age, sex, race, falls risk, co-morbidities, medications
<sup>a</sup> Control drawn from nursing home Modified after Wiens <sup>36</sup>						

**Table.** Case-Control and Prospective Cohort Studies of  $\beta$ -Blocker Use and Fractures.

study of Jensen<sup>31</sup>, published in the early 1990s, showed no significant association between femoral neck fractures and  $\beta$ -blocker use. Subsequently, Rejnmark<sup>27</sup> reported a somewhat bigger study of similar design, and found a statistically significant *increase* in clinical and vertebral fractures associated with  $\beta$ -blocker use. This study was carried out in a cohort of normal older women (the Danish Osteoporosis Prevention Study). Analyses on duration of treatment showed that those treated for more than eight years had a greater fracture risk than those treated for less than this period of time (odds ratios of 5.3, and 2.4, respectively).

A similar study was reported by Pasco<sup>32</sup> in women from a population cohort in Australia. They found a 32% *decrease*

in risk of fracture in those using  $\beta$ -blockers. There was a substantial difference in weight between  $\beta$ -blocker users and non-users, but adjustment for this and for other factors, surprisingly had little effect on the observed difference in fracture risk.

Rejnmark<sup>33</sup> has now revisited this issue using computerized registers of drug use from Denmark, and relating these to fracture records. In this case-control study, fracture in the year 2000 was the outcome, and drug use during the previous five years was the exposure. Analysis included 125,000 cases of fracture and 374,000 gender-matched controls. Crude odds ratios for any fracture were 1.02 (95% CI 1.00-1.05), for hip fracture 1.00 (0.94-1.07), for spine fracture 1.07 (0.95-

1.22), and for forearm fracture 1.00 (0.94-1.06). However, after adjustment for drug use, medical history and socioeconomic factors,  $\beta$ -blocker use was associated with a significantly reduced odds ratios for any fracture or for hip fracture (both 0.91). The authors concluded that  $\beta$ -blocker use was associated with reduced risk of fracture, but this interpretation is entirely dependent on the appropriateness of the adjustment procedures.

Two groups have used the United Kingdom General Practice Database to assess this issue, with somewhat different outcomes. Schlienger<sup>34</sup> matched 30,000 fracture patients aged 30 to 79 with 121,000 controls. While the endpoint was any fracture, the most frequent fractures were those of the hand and forearm (42%), and of the foot (15%). The odds ratio for current use of  $\beta$ -blockers only was 0.77 (95% CI 0.72-0.83) and for combined use of  $\beta$ -blockers and thiazides was 0.71 (95% CI 0.64-0.79). Data were adjusted for BMI and the use of a number of other specific medications. They concluded that current  $\beta$ -blocker use was protective against fractures, and that this effect was possibly additive to that of thiazides.

More recently, de Vries<sup>35</sup> revisited this database, identifying 22,000 cases with a first femoral fracture and a similar number of matched controls. The odds ratio of fracture in  $\beta$ -blocker users was 0.82 (95% CI 0.74-0.91). However, this risk reduction was not associated with the cumulative dose of  $\beta$ -blocker, the lipophilicity of the agent used, or the  $\beta$ -receptor specificity of the drugs. The protective effect of  $\beta$ -blockers was only present among patients with a history of use of other anti-hypertensive agents as well (odds ratio 0.72, 95% CI 0.64-0.83) whereas in patients using  $\beta$ -blockers only, the odds ratio was 0.97 (95% CI 0.82-1.14). In those using other anti-hypertensive agents, there is no dose-response relationship with the use of  $\beta$ -blocker, and fracture risk was apparently reduced even in those who had only just started these drugs. de Vries provides no explanation for why their analysis of the United Kingdom General Practice Database differs from that of Schlienger, but each has identified a different cohort and studied different fracture endpoints.

The de Vries paper also reported a similar analysis of almost 7,000 cases and 26,000 controls from the Dutch PHARMO Record Linkage System, producing essentially the same results. The similarity of these findings from two completely independent databases suggests that the apparent reduction in fractures is unlikely to be related to the  $\beta$ -blocker itself and maybe attributable to drugs co-administered with  $\beta$ -blockers, or to other factors associated with their use. Reduced fracture risk and/or increased bone density have now been reported for a large number of cardiac medications<sup>36</sup> including ACE inhibitors<sup>33</sup>, calcium channel blockers<sup>33</sup>, statins<sup>37</sup>, fibrates<sup>37</sup>, nitrates<sup>38</sup> and thiazide diuretics<sup>39</sup>, so the possibility that these agents are confounding the findings is likely. In addition, other differences between users and non-users, as described above for the Study of Osteoporotic Fractures cohort, may contribute to differences in fracture rates. Failure of some studies to adjust for

all these potential confounders could account for the apparent discrepancies between them.

These case-control studies have been complemented by several cohort studies. In the EPIDOS cohort of 7,600 women (mean age 80 years at recruitment),  $\beta$ -blocker use was associated with a hazards ratio for fracture of 1.2 (95% CI 0.9-1.5) after follow-up of 3.6 years<sup>29</sup>. Our own analysis of the Study of Osteoporotic Fractures database<sup>28</sup> showed no significant effect on the unadjusted risk of any fracture (hazard ratio 0.92, 95% CI 0.81-1.05) or on risk following adjustment for a number of factors (see table), though after more extensive adjustments (including measures of frailty) borderline statistical significance was reached (hazard ratio 0.87, 95% CI 0.7-1.00). Wrist (431) and non-spine (2,031) fractures showed downward trends in risk, which were non-significant with or without adjustment. However, the hazard ratio for hip fracture was significantly reduced whether or not it was adjusted for potential confounders (0.66-0.76). One potential difficulty with calculating hazard ratios for hip fracture over a long period of follow-up near the end of life is that the risk of fracture climbs steeply during the follow-up period, and this violates the assumptions of constant risk over time which underpins the proportional hazards model. This might account for the different findings between hip fractures and other fractures in this analysis. A recent report in abstract form from the Rotterdam Study<sup>40</sup>, a population-based cohort of men and women over 55 years, found no change in the risk of non-vertebral fracture but a reduction of upper arm, hip and pelvis fractures in long term  $\beta$ -blocker users (hazard ratio 0.67, 95% CI 0.46-0.97). Vertebral fracture risk was unaffected (odds ratio 0.83, 95% CI 0.49-1.41). A recent prospective cohort study of American Medicare beneficiaries<sup>41</sup>, found that  $\beta$ -blocker use was associated with an odds ratio of 0.84 for fracture of the spine, hip or wrist (95% CI 0.70-1.00).

The converse of studying effects of  $\beta$ -blockers on fractures is to study those of  $\beta$ -agonists. de Vries et al. have recently reported such a population-based case-control study (6,763 cases), again using the Dutch PHARMO database<sup>42</sup>. Patients using higher doses of  $\beta$ -2 agonists had increased risk of hip/femur fractures (OR 1.94) but this reduced after adjustment for disease severity (OR 1.46; 95% CI, 1.02-2.08), and was non-significant after exclusion of oral glucocorticoid users (OR 1.31; 95% CI, 0.80-2.15). Risk of hip/femur fracture was similar between users of  $\beta$ -2 agonists, inhaled glucocorticoids and anti-cholinergics. Thus, they concluded that severity of the underlying disease, rather than the use of  $\beta$ -2 agonists, may play an important role in the etiology of fractures in patients using these drugs.

## Effects on fractures – Randomized studies

A potential source of human data relating to the bone effects of  $\beta$ -blockers, not subject to the biases inherent in an observational study, is the incidence of fractures (captured as adverse events) in randomized controlled trials of  $\beta$ -

blockers. We have recently analyzed data pooled from nine randomized controlled trials of a non-selective  $\beta$ -blocker (carvedilol) in the management of congestive heart failure<sup>28</sup>, a diagnostic group with a high risk of fracture. From a total subject population of 5,865, 2.0% of placebo-treated subjects experienced a fracture, compared with 2.3% of those randomized to carvedilol (RR 1.15, 95% CI 0.81-1.64). Data on falls were not available. This meta-analysis did not provide any evidence to support the hypothesis that  $\beta$ -blockers reduce fracture numbers.

## Conclusions

Laboratory studies make clear that the sympathetic nervous system does impact on bone cell and tissue function. However, these effects are inconsistent between models, possibly reflecting sympathetic effects at different levels, from the central nervous system through to the bone cells. Observational studies of the use of  $\beta$ -blockers are confounded by the indications for which these drugs are prescribed, and by other medications that are commonly co-prescribed with them. These data are inconsistent, although a recent meta-analysis did conclude that  $\beta$ -blocker use was associated with a significant decrease in fracture risk<sup>36</sup>. However, the more recent studies cast doubt on this conclusion and the limited data regarding fractures from randomized controlled trials certainly do not support this conclusion. Therefore, there is not an adequate evidence base to support using  $\beta$ -blockers as a treatment for osteoporosis, nor can they be regarded as a discriminating risk factor for fracture assessment. Until there are definitive randomized, controlled trials of  $\beta$ -blockers, which include fracture as an endpoint, it is unlikely that the current confusing situation will be resolved.

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