Do beta-blockers and thiazides reduce fracture risk?

Schlienger RG, Kraenzlin ME, Jick SS, Meier CR. Use of β-blockers and risk of fractures. *JAMA* 2004;292(11):1326-32.

Background: There is evidence that 2 classes of antihypertensive drugs may improve bone mineral content. Animal studies have suggested that β-adrenergic blockers can increase bone formation by inhibiting the catabolic effect of the sympathetic nervous system on bone;[1] thiazide diuretics are felt to decrease urinary calcium excretion, thereby protecting against bone loss.[2] However, no studies have evaluated their effect in broad populations or their combined effect.

Methods: The investigators conducted a case–control study using a database of general practice patients. Cases were patients 30–79 years of age who had a fracture diagnosed between January 1993 and December 1999; excluded were those with a disorder known to affect bone metabolism (i.e., Paget's disease, osteoporosis, osteomalacia, cancer or alcoholism). For each case, up to 4 control patients were selected who were matched for age, sex, general practice attended and years in the database. The authors ascertained exposure to any β-blocker, thiazide or thiazide-like diuretic in both the case group (before fracture) and the control group by reviewing computerized prescription records. The analysis was adjusted for the use of other antihypertensive drugs and for drugs known to affect fracture risk (e.g., oral corticosteroids).

Results: The authors identified 30 601 cases and 120 819 control subjects. The most frequent fractures were of the hand or forearm and the foot. Compared with patients who used neither β-blockers nor thiazide diuretics, those who were using β-blockers only (≥ 3 prescriptions) were at decreased risk of fracture (adjusted odds ratio [OR] 0.77, 95% confidence interval [CI] 0.72–0.83), as were patients who were using thiazides only (≥ 3 prescriptions; adjusted OR 0.80, 95% CI 0.74–0.86) and patients taking both β-blockers and thiazides (≥ 3 prescriptions; adjusted OR 0.71, 95% CI 0.64–0.79). Data were adjusted for smoking, body mass index, number of practice visits, and use of calcium-channel blockers, angiotensin-converting-enzyme inhibitors, antipsychotics, antidepressants, statins, antiepileptics, benzodiazepines, corticosteroids and estrogens.

Commentary: Using a case–control design, which included a large number of male and female patients of a wide range of ages, the authors have provided indirect evidence to suggest that β-blockers and thiazide diuretics may decrease the risk of fracture by theoretically improving bone mineral content. Indeed, their study supports previous reports of a beneficial effect of β-blockers and thiazide diuretics in reducing fracture risk.[3,4]

The current study has several strengths, including its large sample, comprehensive adjusted analysis (by matching and statistical techniques) and random chart audits, which suggested that less than 1% of fractures were due to polytrauma. The study's limitations include a lack of exploration of the reasons for fracture, missed cases (patients who did not seek medical attention for asymptomatic compression fractures) and a nonlinear association between the duration of β-blocker usage and fracture risk. Although the findings of this observational study are encouraging, it is important to remember that large observational studies may be misleading (e.g., early evidence on hormone replacement therapy). A large randomized controlled trial is needed to confirm, or refute, the findings of this study.

Practice implications: There is insufficient evidence to recommend the use of β-blockers or thiazide diuretics as a treatment to decrease fracture risk. However, physicians should be aware that patients using β-blockers, thiazides or both may receive an additional benefit in reduction of fracture risk.

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References

1. Minkowitz B, Boskey AL, Lane JM, Pearlman HS, Vigorita VJ. Effects of propranolol on bone metabolism in the rat. *J Orthop Res* 1991;9:869-75.
2. Zawada ET Jr, Williams L, McClung DE, TerWee JA, Horning J, McNulty R, et al. Renal-metabolic consequences of antihypertensive therapy with diltiazem versus hydrochlorothiazide. *Miner Electrolyte Metab* 1987; 13(2):72-7.
3. Pasco JA, Henry MJ, Sanders KM, Kotowicz MA, Seeman E, Nicholson GC. Beta-adrenergic blockers reduce the risk of fracture partly by increasing bone mineral density: Geelong Osteoporosis Study. *J Bone MinerRes* 2004;19:19-24.
4. LaCroix AZ, Ott SM, Ichikawa L, Scholes D, Barlow WE. Low-dose hydrochlorothiazide and preservation of bone mineral density in older adults: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 2000; 133:516-26.

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