

How drugs decrease fracture risk: Lessons from trials

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Abstract

In women with osteoporosis, each 1% improvement in spine BMD (by DXA) is expected to reduce vertebral fracture risk by about 4%. However, randomized trials of antiresorptive agents show that 1 to 6% improvements in spine BMD reduce vertebral fracture risk by 35 to 50%. Less than 20% of the decreased spine fracture risk produced by alendronate or raloxifene be explained by improvement in spine BMD. The discrepancy is even greater during the first year or two of treatment when 1 to 4% improvements in BMD are associated with 65-68% decreases in spine fracture risk. Bisphosphonates continue to increase BMD but the reduction in fracture risk wanes to 20 to 45%. DXA underestimates the change in bone density of spinal trabecular bone and this might explain part of the discrepancy between expected and observed reductions in spine fracture risk. Even more accurate measurement of BMD would not explain the rapid onset and later waning of effect despite gradually increasing BMD. The biomechanical effects inhibiting bone resorption could explain the early onset but not the waning effectiveness. The waning effectiveness of antiresorptives raises concerns that prolonged inhibition of remodeling may weaken bone by allowing microdamage to accumulate. The effect of drugs on nonspine fracture risk is more complex and cannot be predicted from changes in DXA BMD. For example, Beck showed that long-term users of estrogen increase section modulus vs. nonusers with a net increase in section modulus and predicted femoral neck strength despite losing about 0.4% per year in femoral neck BMD. PTH reduces spine fracture risk and this effect is more completely explained by improvement in spine BMD. This suggests that sustaining the increased BMD produced by PTH may maintain long-term reductions in fracture risk.

Keywords: Osteoporosis, Antiresorptive, Estrogen

The standard paradigm held that drugs would reduce fracture risk by improving bone density (BMD). This was first questioned by the finding, in the randomized trial of sodium fluoride by Riggs and colleagues, that fluoride substantially improved bone density without decreasing the risk of fractures. Subsequently, large trials of antiresorptive drugs have observed reductions in risk of vertebral fractures that were much greater than could be accounted for by the modest effects of those drugs on BMD¹⁻⁴. In particular, the MORE trial found that raloxifene reduced the risk of vertebral fractures by about 40% even though it improved spine bone density by only 1-2%². This led us (and others) to conclude that bone density did not play an important role in the reduction of risk of fractures observed during treatment with antiresorptive drugs.

To describe the role of improvement in BMD in the reduction in fracture risk observed in trials, we conducted a meta-analysis of all trials available as of the beginning of 2001. We plotted the relationship between change in spine BMD during the trials and reduction in risk of vertebral fracture after 3-4 years of treatment (Figure 1). We used data from the placebo groups of the Fracture Intervention Trial and from the Study of Osteoporotic Fractures to describe the association between BMD and risk of vertebral fractures. This allowed us to compare the expected reduction in risk of fracture, based on changes in spine BMD, with that observed reduction.

We found that trials of antiresorptive drugs demonstrated that increases in BMD during various treatments were associated with a decreased risk of fractures. Indeed, the relationship between improvement in BMD and reduction in risk of vertebral fractures was very similar to the relationship between BMD and risk of vertebral fractures observed in FIT and SOF. We found that among women with osteoporosis, each 1% improvement in spine BMD (by DXA) is expected to reduce vertebral fracture risk about 4%. However, there

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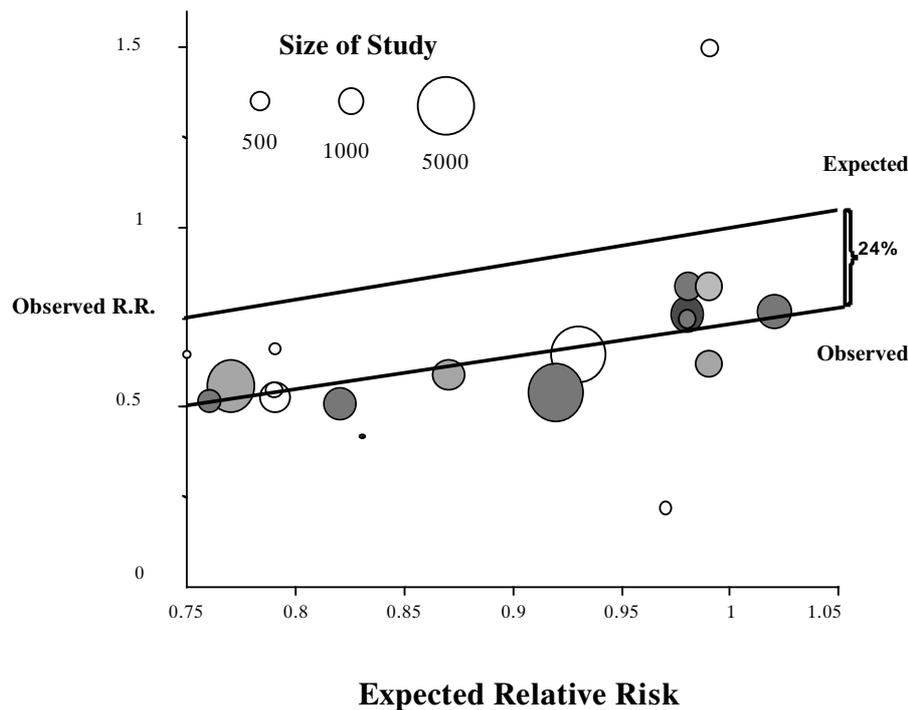


Figure 1. Meta-analysis of trials that measured spine BMD and assessed risk of vertebral fracture. Linear regression of the change in BMD vs. reduction in risk of fractures is plotted as the observed relationship. This analysis indicates that each 1% gain in BMD reduces risk 4%. In addition, treatment with an antiresorptive drug added an additional ~24% reduction in risk of vertebral fracture. Cummings and Black (submitted).

was an additional decrease in fracture risk that could not be explained by improvements in BMD. Specifically, treatment with an antiresorptive drug was associated with a 20 to 25% reduction in risk of vertebral fractures in addition to the reduction in risk attributable to improved BMD.

The discrepancy between change in BMD and reduction in risk of vertebral fracture is even greater during the first year or two of treatment when 1 to 4% improvements in BMD are associated with 65-68% decreases in spine fracture risk. Bisphosphonates continue to increase BMD but the reduction in fracture risk wanes to 20 to 45%.

Thus, a drug that increased spine BMD by 3% would be predicted to reduce fracture risk over 3 to 4 years by about 12% based on improvement in BMD, plus another 20-25% due to other processes, a total risk reduction of 42 to 47%.

An alternative theory is that reduction in bone resorption produces an immediate reduction in bone resorption and that this confers improvements in bone strength by reducing the number and depth of resorption pits.

DXA underestimates the change in bone density of spinal trabecular bone and this might explain part of the discrepancy between expected and observed reductions in spine fracture risk. Even more accurate measurement of BMD would not explain the rapid onset and later waning or constancy of effect despite gradually increasing BMD. The biomechanical effects inhibiting bone resorption could explain the early onset but not the waning effectiveness.

The effect of drugs on nonspine fracture risk is more complex and cannot be predicted from changes in DXA BMD. Long-term use of antiresorptive treatments may alter the macroscopic structure of bone in a way that is not captured by changes in BMD. We have previously found that long-term (>10 year) use of estrogen therapy was associated with >50% reduction in risk of hip and wrist fracture that could not be explained by improvements in BMD. Beck has recently shown that that long-term users of estrogen lost 0.4% of femoral neck BMD but during the same period experienced significant improvements in section modulus and predicted bone strength (Figure 2)⁵.

Thus, it appears that drugs reduce fracture risk by inhibiting bone resorption with immediate mechanical benefits. Long-term use may increase section modulus in a way not detected by densitometry.

PTH-induced formation of new bone. The effect of PTH on the risk of vertebral fracture is more consistent with the theory that the drug works by improving BMD. This suggests, too, that combinations of PTH and antiresorptive drugs should have synergistic effects on fracture risk⁶.

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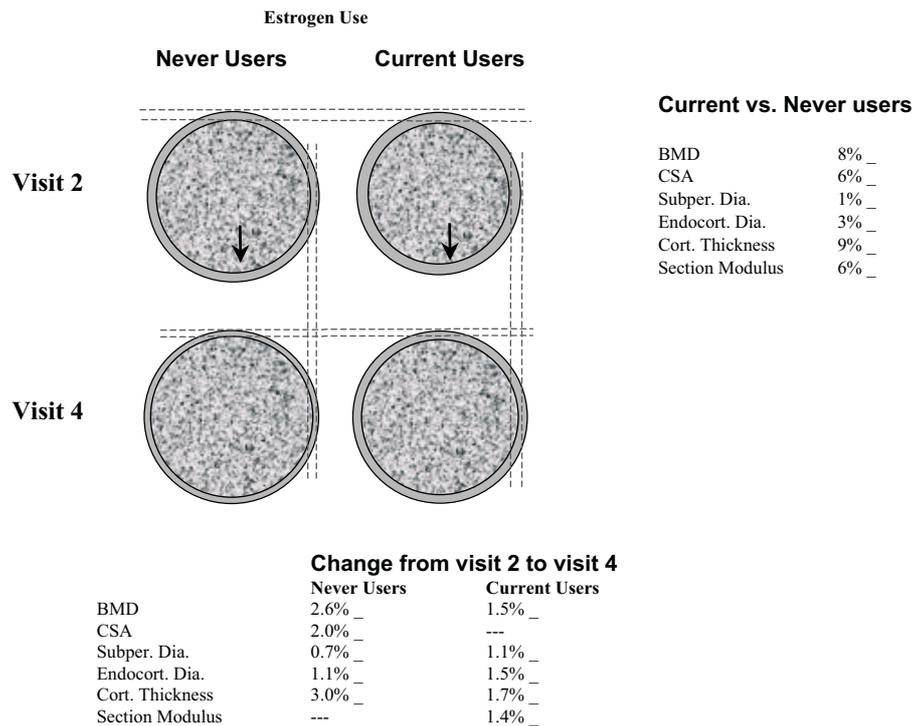


Figure 2. Estrogen users had and maintained higher bone density, thicker cortices, wider bone diameter, and greater section modulus in the femoral neck than did never users. Based on analyses of serial DXA scans of the proximal femur about 4 years apart in older women participants in the Study of Osteoporotic Fractures⁵.

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