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COMMENTARIES

Differential Effects of Strontium Ranelate, Bisphosphonates and Teriparatide on Bone Microstructure: Fact or Fiction?

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Commentary on: Rizzoli R, Laroche M, Kreig MA, Frieling I, Thomas T, Delmas P, Felsenberg D. Strontium ranelate and alendronate have differing effects on distal tibial bone microstructure in women with osteoporosis. *Rheumatol Int*. 2010 Aug;30(10):1341-8.

Macdonald HM, Nishiyama KK, Haney DA, Boyd SK. Changes in trabecular and cortical bone microarchitecture at peripheral sites associated with 18 months of teriparatide therapy in postmenopausal women with osteoporosis. *Osteoporos Int*. 2010 May 11. [Epub ahead of print]

In these two studies, high-resolution peripheral quantitative computed tomography (HR-pQCT) was used to investigate changes in peripheral bone microstructure in women treated with strontium ranelate, alendronate or teriparatide. In the first study, Rizzoli *et al*. investigated the effects of 12 months of treatment with strontium ranelate or alendronate on distal tibial structure in a randomized, double-placebo, controlled trial in 88 postmenopausal women with osteoporosis. Strontium ranelate therapy was associated with significant increases in cortical thickness, cortical area and trabecular density, whereas no significant changes were observed in women treated with alendronate. Macdonald *et al*. studied the effects of 18 months of treatment with teriparatide on bone microarchitecture and strength in the distal radius and tibia in 11 postmenopausal women, 10 of whom had received prior bisphosphonate therapy. Significant decreases in total bone mineral density (BMD) at the radius and cortical BMD at the radius and tibia were demonstrated, with a trend towards increased cortical thickness and porosity at both sites. There was also significant trabecular thinning at the radial site. However, these apparently adverse structural alterations were not associated with any reduction in bone strength, assessed using finite element analysis (FEA). The results of these studies thus imply distinct effects of the three drugs on cortical bone structure. This *Commentary* reviews the strength of the evidence for this conclusion.

Preservation or improvement of bone microarchitecture is one of the major mechanisms by which bone-protective interventions reduce fracture risk. In cancellous bone there is evidence that anti-resorptive agents prevent age-related structural deterioration (1), while anabolic agents (currently limited to parathyroid hormone (PTH) peptides) improve trabecular connectivity (2). Strontium ranelate has only weak effects on bone remodeling and effects on bone material properties may account for much of its beneficial effect on bone strength (3). Most of the evidence for the mechanism of action of all of these agents has been based on examination of cancellous bone in iliac crest biopsy specimens, using either conventional 2D histomorphometry or 3D analysis by microCT. In contrast, effects on cortical bone have received relatively little attention. Based on their effects on bone remodeling, anti-resorptive drugs would be expected to preserve cortical thickness by reducing endosteal resorption and to decrease cortical porosity; however, there is no known mechanism by which they could increase

cortical thickness, an effect that requires increased endosteal and/or periosteal bone formation. Conversely, PTH peptides have been shown to increase cortical thickness but may also increase cortical porosity, at least initially (4). The effects of strontium ranelate on cortical bone are more difficult to predict. The final effect on cortical bone strength of any drug will depend not only on structural changes, but also on alterations in the material properties of bone associated with treatment.

Whether using either bone histomorphometry or HR-pQCT, there are specific pitfalls associated with assessment of cortical bone microstructure (5). With increasing age the cortex becomes "trabecularized" as a result of intracortical and endocortical remodeling, so that cortical bone remnants are usually included in trabecular, rather than cortical bone measurements, leading to overestimation of trabecular bone volume and underestimation of cortical porosity (6). Changes in cortical bone vary between skeletal sites both in untreated and treated disease, so that changes at one site do not necessarily reflect those occurring elsewhere. Furthermore, within any one site of measurement cortical thickness and porosity may show substantial heterogeneity (7), a consideration that is also relevant to the estimation of bone strength by FEA using HR-pQCT. Limitations specific to HR-pQCT include insufficient resolution to detect smaller cortical pores, resulting in underestimation of porosity, and the effect of bone mineralization on attenuation, increased or decreased mineralization resulting in falsely elevated or low values, respectively, in cortical thickness and area. Finally, intracortical pores are usually included in the measurement of cortical area by HR-pQCT; since cortical thickness is derived from cortical area and perimeter, changes in porosity will affect both area and thickness measurements (8).

Interpretation of the effects of strontium ranelate on bone microstructure using HR-pQCT in the study of Rizzoli *et al*. (9) is particularly problematic because of the uptake of strontium by newly formed bone (10), which artefactually raises values for cortical area and thickness and trabecular density. In addition, the inclusion of intracortical pores in the measurement of cortical area in this study could influence the values obtained, as discussed above. Although the authors attempted to correct for the presence of strontium in bone, the possibility that this accounted for the apparent improvement in microstructure cannot be excluded. Indeed, since significant improvements in architecture were observed as early as three months after starting strontium ranelate, it appears to be the only plausible explanation, given that there were no significant changes in bone turnover markers in this treatment group at any point in time during the study. Increased calcium content of bone and reduced intra-cortical porosity may also have affected HR-pQCT measurements of microstructure in women treated with alendronate (11), although in this study no significant change in indices of microarchitecture was found in this group.

The effects of teriparatide therapy on cortical bone BMD in the study of Macdonald *et al*. (12) are consistent with the decrease in DXA-derived BMD previously reported in the radius and femoral neck (13). The potentially adverse biomechanical effect of increased cortical porosity may have been offset by small increases in cortical thickness (in this study measured after exclusion of intracortical pores and possibly underestimated as a result of hypomineralization of bone formed in response to teriparatide); the localization of changes in porosity within the cortex may also be relevant to effects on bone strength (14). Without prior bisphosphonate therapy in 10 of the 11 women the effects of teriparatide might have been greater, particularly with respect to worsening of cortical porosity (15). These considerations, together with the small sample size, reduce the certainty of any conclusions about effects of teriparatide on bone strength. Using HR-pQCT, Thomas *et al*. (16) also reported no significant change in bone strength in the tibia or radius in 10 postmenopausal women treated with teriparatide for 18 months, although in that

study no significant changes in bone structure in the radius were observed.

In the case of alendronate and teriparatide, the changes in bone microstructure reported in these two studies generally confirm previous reports and are consistent with their known mechanisms of action. Alendronate does not increase cortical thickness but probably reduces intracortical porosity (17;18). In contrast, teriparatide increases cortical thickness mainly, if not solely, by endosteal apposition and also increases cortical porosity, at least in the earlier stages of treatment. The finding that bone strength was preserved in teriparatide-treated women, while needing confirmation, is important because of potential concerns about adverse effects of the early increase in porosity on fracture risk at sites such as the hip and wrist. The effects of strontium ranelate on bone microarchitecture are less clear; it is difficult to reconcile the apparent improvements observed with the very modest changes in bone remodeling assessed by biochemical turnover markers. Because of the methodological limitations of HR-pQCT, the conclusion that strontium ranelate improves bone structure is precarious and, as acknowledged by the authors, requires further investigation.

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