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COMMENTARIES

Bisphosphonates and Denosumab: Do They Thicken Bone Cortices, and Can These Changes Be Assessed by High-resolution pQCT?

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A randomized controlled study in postmenopausal women with low bone mineral density (BMD) recently evaluated the effects of alendronate (ALN; 70 mg weekly), denosumab (60 mg sc q6m) and placebo for one year by using high-resolution peripheral computed tomography (HR-pQCT; XtremeCT, Scanco, Switzerland). This is the first published study using this technique to evaluate drug effects on volumetric BMD (vBMD), and trabecular and cortical bone microstructure. Results indicate that both drugs significantly improve cortical vBMD and thickness at both the distal radius and tibia, some of these effects being greater with denosumab. This *Commentary* reviews the evidence for an improvement of cortical bone (micro)structure with antiresorptives and the potential and limitations of HR-pQCT to evaluate these changes, as also discussed by the authors in their paper.

Antiresorptive agents, such as bisphosphonates (BPs) and the recently developed RANKL antagonist, denosumab, decrease fracture incidence by increasing BMD – which partly reflects an increase in the mean degree of mineralization – and by preventing the decay of bone (micro)-structure. Whereas areal BMD (aBMD) changes predict only a small proportion of the reduction in fractures with BPs, iliac crest bone biopsies sometimes have shown a preservation of trabecular number, a decrease of trabecular separation, and an increase of trabecular bone volume compared to placebo after a few years of treatment (1-3). However, only sequential bone biopsies can truly address the issue of an increase versus a decrease in structural units. Sequential bone biopsies obtained in a small number of women treated with risedronate for up to 5 years further demonstrate that trabecular bone parameters are stable over time (4). Although a proper improvement of cancellous bone volume and/or connectivity over baseline has not been unequivocally demonstrated with antiresorptives, by decreasing eroded surfaces and bone remodeling (as evaluated by MS/BS and BFR), these agents allow refilling of the remodeling space and potentially eliminate a number of stress risers on trabecular surfaces. In turn, these effects are expected to improve cancellous bone strength, such as in vertebrae. 2D and 3D analyses (the latter by micro-CT) of iliac crest bone biopsies generally have failed to demonstrate a significant improvement of cortical thickness with BPs vs. placebo. Only cross-sectional bone biopsies from a subgroup of women treated with zoledronate and concomitantly exposed to other anti-resorptives such as HRT or raloxifene (stratum 2 of the HORIZON pivotal study) have shown some significant improvement of cortical thickness by 3D micro-CT compared to placebo (3). In the repeated biopsies study of risedronate, cortical

thickness non-significantly increased by 6% over time, as evaluated by conventional histomorphometry. On another side, a recent analysis of cortical porosity by 3D micro-CT on iliac crest bone biopsies showed that, after 5 years, risedronate reduced by about 2.5% the surface of cortical bone occupied by pores below 500 microns compared to baseline (5). If a similar phenomenon happened at the hip or radius, it would be expected to increase vBMD of the cortical compartment and could potentially increase its apparent cortical thickness by reducing the number of pores opening up onto the endocortical surface.

Comparison of ALN and Denosumab in Human and Animal Models

Recent comparisons of ALN and denosumab in postmenopausal women have established that the latter increases aBMD at all sites more than ALN (6;7). This further improvement has been observed particularly at the radius, where positive gains of aBMD have not typically been observed with BPs. Taken together with a faster and more profound inhibition of bone turnover by denosumab (at least compared to an oral BP), these observations raise the possibility that inhibiting RANKL might not only further inhibit the erosion depth at each basic multicellular unit (BMU; note that it is unclear whether BPs actually reduce the erosion depth), but also prevent the appearance of new resorption sites more broadly than BPs (*i.e.*, by inhibiting osteoclast differentiation), thereby reducing the remodeling space more effectively. To support this hypothesis, studies in ovariectomized (OVX) monkeys indicate that one year of denosumab as well as transitioning from ALN to denosumab (6 months each) improved volumetric bone mineral content (vBMC) at the distal radius metaphysis more than one year of ALN (8). At the femur diaphysis, cortical vBMC was highly correlated with bone strength (peak load in bending). Peripheral QCT data from OVX monkeys treated for 16 months with denosumab also suggest that this drug prevents the loss of cortical thickness at diaphyseal sites. These studies in monkeys have also shown that denosumab, and to a lesser extent ALN, by inhibiting Haversian bone remodeling, have the ability to reduce intracortical porosity, as evaluated by histomorphometry at the tibia diaphysis and the rib (9). Moreover, in OVX mice expressing a humanized form of RANKL (so that they become responsive to denosumab), a comparison with ALN has shown that denosumab increases cortical thickness at the distal femur and vertebrae more than ALN (10). Together these data raise the possibility that denosumab might improve cortical bone (micro)structure in a way not previously achieved with BPs. Whether this happens in postmenopausal women, however, remained to be investigated, but this has been made possible recently by the development of HR-pQCT.

Evaluation of Bone Microstructure by HR-pQCT

HR-pQCT (Xtreme CT, Scanco, Switzerland) enables the simultaneous acquisition of a stack of 110 parallel CT slices with a nominal resolution of only 82 microns (voxel size), starting approx. 1 cm and 2.2 cm from the endplate of the radius and tibia, respectively, and extending proximally over 0.9-1 cm. The total volume of interest (VOI) is separated into a cortical and trabecular region using a threshold of one-third of the apparent cortical bone density (Dcort, mg HA/cm^3) to define the cancellous bone region. In addition to the volumetric densities in these two compartments, HR-pQCT provides a measure of trabecular number (TbN) by evaluating the mean 3D distance between the mid-axes of trabeculae. The other measures of trabecular microstructure, *i.e.*, bone volume fraction (BV/TV), thickness (TbTh), and separation (TbSp), are all derived from the above and therefore are not independent of the apparent Tb bone density or number. TbTh in particular cannot be measured directly by HR-pQCT because of the limited resolution of this technique, *i.e.*, not greater than the mean trabecular thickness, and partial volume effects. Cortical thickness (CTh) is obtained by dividing the cortical volume by the outer bone surface (*i.e.*, the cortical area by the perimeter of each slice). Because the boundary between the cortical and

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cancellous region is defined by a drop in mineral density, as explained above, changes in the degree of bone mineralization, particularly at the endocortical region, are likely to affect the evaluation of CTh. Moreover, CTh varies quite substantially even within the small VOI, particularly at the radius metaphysis where the VOI is closer to the end-plate and the cortex becomes quite thin in the more distal slices (Fig. 1). The corollary of this observation is that finite element analysis (FEA), which can be applied on HR-pQCT measures simulating an axial compression test to predict bone strength in the trabecular and cortical compartments, indicates that the contribution of the cortical compartment to carry load decreases from more than 80% proximally to less than 60% more distally (11). Because changes in cortical thickness are not necessarily uniformly distributed within the VOI (which the mean CTh will ignore), their impact on bone strength may vary quite substantially whether they occur mostly proximally or distally. The large heterogeneity of the cortical thickness in the VOI also implies that this value is highly dependent on the strict location of the measurement, which poses the problem of repositioning the scanning region in longitudinal studies. Of note, whereas the CV of repeated measures is low for volumetric densities and CTh (≤1%), it is in the range of 3-5% for TbN and the derived parameters.

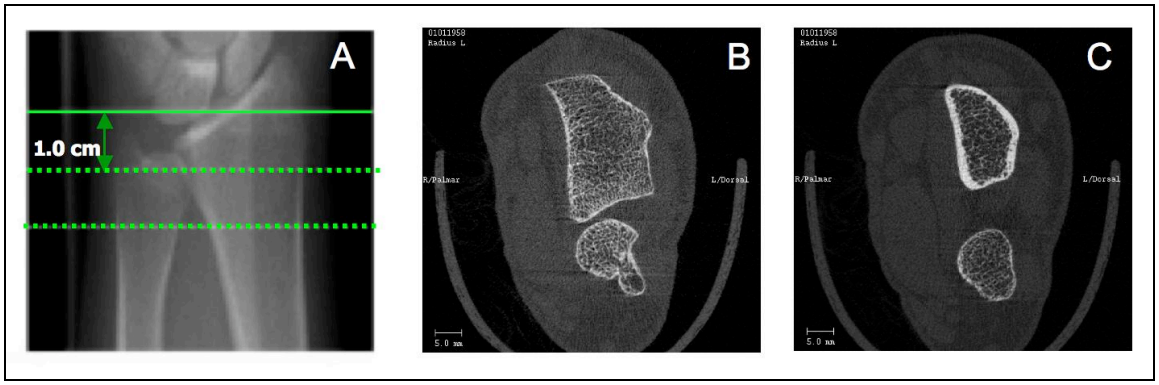

Fig. 1. A. An HR-pQCT scanning region at the distal radius (between dotted lines). B. Microstructure in the more distal portion of the radius scanning region – note that the cortex is thin and its boundaries with the trabecular compartment are ill-defined. C. Microstructure in the more proximal portion of the radius scanning region (8.64 mm from slice B, same subject).

Effects of ALN and Denosumab by HR-pQCT

The study by Seeman *et al*. (12) now shows that in postmenopausal women (mean age 60.6 yrs.) with moderately low bone mass (T-score of -2.4 at the spine and -1.3 at the hip), vBMD decreases over one year in both the cortical and trabecular bone compartments of the distal radius (-1.5 and -2%, respectively), less so at the distal tibia – a weight-bearing site. These changes were prevented by ALN and denosumab and, in cortical bone, there was actually a small net gain of vBMD with the latter that was significantly greater than with ALN. This observation is in keeping with the results in OVX monkeys summarized above. More surprisingly, CTh, which did not significantly change from baseline at the distal radius and increased by about 1-1.5% at the distal tibia in the placebo group, increased by 2% and 3% at the radius and by nearly 5% at the tibia with ALN and denosumab, respectively (non-significant for the difference between active treatments). In turn, the calculated polar moment of inertia (PMI), an index of bone strength at the distal radius, significantly improved with both agents, more significantly so with denosumab.

As thoroughly discussed by the authors, this apparent increase of CTh by 3% or more with anti-resorptives might be explained by a reduction in cortical porosity (particularly with denosumab, as seen in monkeys, see above), which would increase the cortical volume (and area) and thereby the apparent CTh (as computed by the Scanco).

Moreover, the suppression of new bone remodeling sites at endocortical surfaces will increase the bone density so that the boundary for cortical/trabecular separation is moved (see above). Eventually, an increase in the measured CTh could be explained by an increase in tissue mineral density, so that the density of voxels on the endocortical surface is increased, again moving the cortical/trabecular boundary inward. It is intriguing that such changes of CTh have not usually been observed on iliac crest bone biopsies with ALN and other BPs (see above), although this might be due to the limited power of (mostly) cross-sectional bone biopsy studies available so far. On another side, the correlation between microstructural parameters evaluated by HR-pQCT at the distal radius and micro-CT on iliac crest bone biopsies is poor (13), so different things might happen at different skeletal sites. Conceptually, a true thickening of the cortex can only result from an expansion of the periosteum and/or endosteum, which by nature cannot be achieved with any anti-resorptive. However, by improving cortical bone microstructure, mineral density, and, in the case of denosumab, the PMI, this study demonstrates that anti-resorptives will improve cortical bone strength.

Conflict of Interest: Dr. Ferrari reports that he receives research support from Amgen and Merck Sharp & Dohme, and is an advisory committee member and lectures occasionally at conference symposia for the Alliance for Better Bone Health (sanofi aventis/P&G), Amgen, Merck Sharp & Dohme, Eli Lilly, Servier, and Novartis.

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References

1. Boonen S, Haentjens P, Vandenput L, Vanderschueren D. Preventing osteoporotic fractures with antiresorptive therapy: implications of microarchitectural changes. *J Intern Med*. 2004 Jan;255(1):1-12.

2. Recker R, Masarachia P, Santora A, Howard T, Chavassieux P, Arlot M, Rodan G, Wehren L, Kimmel D. Trabecular bone microarchitecture after alendronate treatment of osteoporotic women. *Curr Med Res Opin*. 2005 Feb;21(2):185-94.

3. Recker RR, Delmas PD, Halse J, Reid IR, Boonen S, García-Hernandez PA, Supronik J, Lewiecki EM, Ochoa L, Miller P, Hu H, Mesenbrink P, Hartl F, Gasser J, Eriksen EF. Effects of intravenous zoledronic acid once yearly on bone remodeling and bone structure. *J Bone Miner Res*. 2008 Jan;23(1):6-16.

4. Borah B, Dufresne TE, Ritman EL, Jorgensen SM, Liu S, Chmielewski PA, Phipps RJ, Zhou X, Sibonga JD, Turner RT. Long-term risedronate treatment normalizes mineralization and continues to preserve trabecular architecture: sequential triple biopsy studies with micro-computed tomography. *Bone*. 2006 Aug;39(2):345-52.

5. Borah B, Dufresne T, Nurre J, Phipps R, Chmielewski P, Wagner L, Lundy M, Bouxsein M, Zebaze R, Seeman E. Risedronate reduces intracortical porosity in women with osteoporosis. *J Bone Miner Res*. 2010 Jan;25(1):41-7.

6. Brown JP, Prince RL, Deal C, Recker RR, Kiel DP, de Gregorio LH, Hadji P, Hofbauer LC, Alvaro-Gracia JM, Wang H, Austin M, Wagman RB, Newmark R, Libanati C, San Martin J, Bone HG. Comparison of the effect of denosumab and alendronate on BMD and biochemical markers of bone turnover in postmenopausal women with low bone mass: a randomized, blinded, phase 3 trial. *J Bone Miner Res*. 2009 Jan;24(1):153-61.

7. Kendler DL, Roux C, Benhamou CL, Brown JP, Lillestol M, Siddhanti S, Man HS, San Martin J, Bone HG. Effects of denosumab on bone mineral density and bone turnover in postmenopausal women transitioning from alendronate therapy. *J Bone Miner Res*. 2010 Jan;25(1):72-81.

8. Ominsky MS, Smith SY, Vlasseros F, Samadfam R, Kostenuik PJ. Transition from alendronate to denosumab in ovariectomized cynomolgus monkeys

maintained or improved cortical and trabecular bone mass, without altering the linear relationship between bone mass and bone strength. *J Bone Miner Res*. 2008 Sep;23(Suppl 1):S22.

9. Ominsky MS, Jolette J, Smith SY, Vlasseros F, Samadfam R, Kostenuik PJ. Transition from alendronate to denosumab resulted in further reductions in local and systemic bone turnover parameters and reduced cortical porosity in ovariectomized cynomolgus monkeys. *J Bone Miner Res*. 2008 Sep;23(Suppl 1):S61.

10. Ferrari SL, Pierroz D, Bonnet N, Dwyer D, Stolina M, Kostenuik P. Comparison of denosumab and alendronate in combination with PTH in ovariectomized knockin mice expressing humanized RANKL. *J Bone Miner Res*. 2007 Sep;22(Suppl 1):S37.

11. Boutroy S, Van Rietbergen B, Sornay-Rendu E, Munoz F, Bouxsein ML, DeImas PD. Finite element analysis based on in vivo HR-pQCT images of the distal radius is associated with wrist fracture in postmenopausal women. *J Bone Miner Res*. 2008 Mar;23(3):392-9.

12. Seeman E, Delmas PD, Hanley DA, Sellmeyer D, Cheung AM, Shane E, Kearns A, Thomas T, Boyd SK, Boutroy S, Bogado C, Majumdar S, Fan M, Libanati C, Zanchetta J. Microarchitectural deterioration of cortical and trabecular bone: Differing effects of denosumab and alendronate. *J Bone Miner Res*. 2010 Mar 10. [Epub ahead of print]

13 Cohen A, Dempster DW, Müller R, Guo XE, Nickolas TL, Liu XS, Zhang XH, Wirth AJ, van Lenthe GH, Kohler T, McMahon DJ, Zhou H, Rubin MR, Bilezikian JP, Lappe JM, Recker RR, Shane E. Assessment of trabecular and cortical architecture and mechanical competence of bone by high-resolution peripheral computed tomography: comparison with transiliac bone biopsy. *Osteoporos Int*. 2010 Feb;21(2):263-73.