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COMMENTARY

Improvement of bone strength with teriparatide: hip as well as spine?

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Commentary on: Poole KE, Treece GM, Ridgway GR, Mayhew PM, Borggrefe J, Gee AH. Targeted regeneration of bone in the osteoporotic human femur. PLoS ONE 2011; **6**:e16190 and Keaveny TM, McClung MR, Wan X, Kopperdahl DL, Mitlak BH, Krohn K. Femoral strength in osteoporotic women treated with teriparatide or alendronate. Bone 2012; **50**:165–170.

Introduction

Intermittent parathyroid hormone (PTH) is still the only approved osteoporosis drug with anabolic effects on bone. In treatment-naïve postmenopausal osteoporotic women, teriparatide (TPTD) has been shown to increase spine and hip bone mineral density (BMD), and to decrease vertebral fractures by 65% and non-vertebral fractures by 35% over 18 months.[1] In glucocorticoid-induced osteoporosis, TPTD has also shown greater BMD gain and reduction in vertebral fractures compared with alendronate (ALN) over 3 years.[2] Yet TPTD has not directly been proven to decrease the incidence of hip fractures. Actually, studies in which women on bisphosphonates were switched to TPTD have shown a transient decrease of areal bone mineral density (aBMD) at the femur neck and/or total hip, before returning to baseline after 1–2 years.[3–6] This transient decrease in hip BMD could be explained by an acceleration of bone turnover leading to some decrease in the degree of tissue mineralization (previously increased with anti-resorptives), by the formation of new, and thereby relatively less mineralized, bone and/or (primary) osteons, as well as by an increase in intracortical porosity. Moreover, although it is clear that intermittent PTH exerts most of its bone-forming effects at remodeling surfaces,[7] it remains uncertain whether TPTD at the dose of 20 μg daily exerts clinically significant effects on modeling surfaces, particularly at the periosteum.[8] Whether and how TPTD increases cortical thickness and improves hip strength, therefore, remains a matter of contention. In this context, the recent development of novel imaging and segmentation techniques based on computed tomography (CT) scans of the spine and hip in conjunction with finite element analyses (FEA) has allowed to estimate the effects of intermittent PTH on bone strength. Although these techniques are not yet validated surrogates for fractures, they provide some valuable information on the effects of TPTD, particularly in women previously treated with anti-resorptives for whom there is no randomized controlled trial directly examining fracture end-points.

TPTD Versus ALN Effects on Vertebral and Femur Strength in Treatment-Naïve Women

Few studies provide a direct comparison of intermittent PTH regimen with anti-resorptives. In a head-to-head study (Forteo Alendronate Comparator Trial (FACT)) of TPTD (20 μg per day) versus ALN (10 mg per day) in postmenopausal women with osteoporosis, BMD gain after 18 months was significantly greater with TPTD at spine (aBMD +10.3 vs +5.5% and vBMD +19.0 vs +3.8%, respectively, $P<0.01$) but not at the hip.[9] In a subset ($n=53$) with quantitative computed tomography (QCT) measurements of the spine, both treatment had positive effects on the estimated vertebral compressive strength, as evaluated by FEA of QCT scans.[10] However, the estimated compressive strength increased significantly more with TPTD compared with ALN at both 6 months (+13 vs + 4.9%) and 18 months (+21 vs +3.7%). The increase in anteroposterior bending stiffness was also significantly greater with TPTD compared with ALN. Moreover, TPTD showed a significant increase in estimated strength/density ratio and a further improvement between 6 and 18 months, which was not observed with ALN, suggesting a progressive restoration of trabecular bone structure at this site with TPTD.

The hip QCT FEA results from the FACT study have been recently published.[11] In a subset of 48 women in whom hip CT scans were obtained at baseline, 6 and 18 months, the only statistically significant difference between the two treatments was for the change of trabecular volumetric bone mineral density (vBMD), which was greater with TPTD than ALN (+4.6 vs 0% at 18 months). However, the peripheral (cortical) vBMD slightly but significantly decreased with TPTD (−1%), whereas it remained unchanged with ALN. When forces simulating a sideways fall were applied to generate estimates of femoral strength, this increased more with TPTD versus ALN (+5.4 vs 0.9% at 18 months), but the difference was not significant, pertaining to the limited number of observations and wide range of changes in either group. Changes in estimated femoral strength

were best predicted by changes in trabecular vBMD in TPTD-treated women ($r^2 = 0.79$), and by changes in peripheral (cortical) vBMD in ALN-treated women ($r^2 = 0.62$).

The PATH study also showed greater aBMD and vBMD gain at spine, but not hip, with PTH(1-84) compared with ALN in treatment-naïve osteoporotic postmenopausal women, but failed to demonstrate additive effects of PTH(1-84) combined with ALN.[12] In that study, hip QCT was obtained in 162 subjects. FEA analysis mimicking a sideways fall indicated similar changes in estimated hip strength with both treatments (PTH +2.1%, ALN +3.6%) after 1 year.[13] Treatment with PTH resulted in decreased density (−1.3%) and mass (−6.2%) of the cortical bone and increased density (+2.6%) of the trabecular bone compartment. Hence, the improvement of estimated hip strength with PTH was attributed to its trabecular bone effects, contrarily to ALN in which effects were equally distributed between the trabecular and cortical bone compartments.

In summary, these studies indicate that in treatment-naïve women, PTH (TPTD) improves trabecular bone mass, structure and estimated strength, and this more prominently at the spine than the hip, whereas it may decrease cortical vBMD (at the hip).

TPTD Effects on Vertebral and Hip Strength in Women Previously Treated with Anti-Resorptives

The OPTAMISE (open-label) study reported greater early increases in biochemical markers of bone turnover and spine vBMD when 12 months of TPTD treatment was preceded by 2 years or more of risedronate versus ALN treatment.[5] FEA analysis of L1 QCT scans in 171 subjects indicated that the mean increase in stiffness was greater in the prior risedronate group than the prior ALN group (24.6±3.2% vs 14.4±2.8%, respectively; $P < 0.007$). Similarly, vertebral failure load increased by 27.2±3.5% in the prior risedronate group versus 15.3±3.1% in the prior ALN group ($P = 0.004$).[14]

EUROFORS is an observational study of osteoporotic women receiving TPTD (20 μg per day) for 2 years, of whom a vast majority was recently switched from anti-resorptives (principally ALN).[3,6] In a subset of 44 patients (mean age 68), FEA of high-resolution CT (multidetector CT) spine images was used to test vertebral strength in both compression and bending.[15] TPTD induced a progressive increase in the estimated maximal force and stiffness, +20% at 1 year and up to +29% at 2 years, that is, similar to the effects observed in women not switched from anti-resorptives (above). In a separate analysis of hip QCT, TPTD was shown to increase hip cortical area (+4%), but not total area, arguing against a major effect on bone geometry (periosteal extension).[16] However, this result has to be tempered by the still relatively low spatial resolution of this technique. Moreover, whereas trabecular vBMD increased progressively up to 5% at 2 years, cortical vBMD significantly decreased for the duration of the observation (−2% at 2 years). Although FEA analysis of hip strength from this study is not available, estimates of the femoral neck bending and buckling strength (as derived from neck geometry, bone mass distribution and cortical thickness) suggest a significant improvement after 2 years of TPTD treatment.

Hence these results confirm that TPTD improves vertebral, and to a lesser extent hip, estimated strength, including in women previously on anti-resorptives, although it decreases cortical vBMD probably as a result of increased cortical porosity.

TPTD Effects on Hip Cortical Thickness

Poole *et al.*[17] recently reported a new approach to analyze hip cortical thickness in the QCT subset of EUROFORS subjects described above. Their technique derives from neuroimaging statistical analyses to infer thickness maps from dense, spatially correlated data. First they confirmed that the cortex of osteoporotic women is thinner (1 mm or less) in the superior:anterior portion of the femur neck and the intertrochanteric region. Then they showed that the percentage increase in cortical thickness with TPTD could be mapped to those same regions (up to +8%), particularly the head-neck junction and infero-medial portion of the intertrochanteric region. Considering, however, the large range of cortical thickness in various areas of the proximal femur, that is, from <1 mm to 4+ mm as evaluated in this study, a greater percent change in the thinner cortex could represent a similar amount of newly formed bone in this area as in the other, thicker, cortical areas. Although the former could lead to a disproportionate increase in femur neck strength at sites of greatest bone fragility, it does, therefore, not necessarily mean that the effects of TPTD on bone geometry are not uniform.

Conclusions

There is no doubt that new bone formation with TPTD, by improving trabecular bone thickness and connectivity, greatly increases vertebral bone strength, as predicted from FEA analyses in both treatment-naïve and previously treated (with anti-resorptive) women, and as demonstrated by a marked reduction in vertebral fractures. Recent analyses clearly indicate that TPTD also improves trabecular vBMD, as well as cortical area and/or thickness of the proximal femur. However, it simultaneously decreases cortical vBMD and does not seem to change hip geometry by an expansion of the cortical diameter, but rather by endocortical apposition. Hence, the induced changes in estimated hip strength, as predicted by FEA, are smaller than for vertebrae, and probably no better than ALN. As the latter has been demonstrated to decrease the incidence of hip fractures by 30–40%, one might infer that similar changes of hip strength with TPTD could lead to similar effects on the risk of hip fracture. However, the distribution of changes in bone mass as well as the structural changes at the hip markedly differ between the two treatments. Hence, it remains unclear whether an ~5% gain in predicted femoral strength with TPTD will exert clinically significant effects on the reduction of hip fractures.

Conflict of Interest

S Ferrari serves as a paid consultant for Eli Lilly, AMGEN, GSK and MERCK.

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