Comparing and contrasting the effects of strontium ranelate and other osteoporosis drugs on microarchitecture

FERRARI, Serge Livio

Abstract

Altered bone microstructure is a major component of osteoporosis and bone fragility. Whilst an important standard by which to diagnose and make treatment decisions for osteoporosis, the evaluation of bone mineral mass by dual-energy X-ray absorptiometry (DXA) at spine or hip is not sufficient for understanding the complex nature of bone microstructure nor to evaluate specific treatment effects on cancellous and cortical bone. Various alternatives to DXA have been developed, enabling the measurement of bone geometry and/or microarchitecture and/or bone strength including hip strength analysis, peripheral and central QCT, 3D analyses of iliac crest bone biopsies, and more recently HR-pQCT, which allows longitudinal assessment of bone microstructure at the distal radius and tibia. The efficacy of treatments for osteoporosis can be evaluated using these techniques. A true improvement of bone microstructure above baseline has not been demonstrated with anti-resorptive treatments; however, they may prevent the decay of cancellous bone and, potentially, cortical thinning. Anabolic agents such as parathyroid hormone (PTH) [...]
Comparing and contrasting the effects of strontium ranelate and other osteoporosis drugs on microarchitecture

S. Ferrari

Abstract Altered bone microstructure is a major component of osteoporosis and bone fragility. Whilst an important standard by which to diagnose and make treatment decisions for osteoporosis, the evaluation of bone mineral mass by dual-energy X-ray absorptiometry (DXA) at spine or hip is not sufficient for understanding the complex nature of bone microstructure nor to evaluate specific treatment effects on cancellous and cortical bone. Various alternatives to DXA have been developed, enabling the measurement of bone geometry and/or microarchitecture and/or bone strength including hip strength analysis, peripheral and central QCT, 3D analyses of iliac crest bone biopsies, and more recently HR-pQCT, which allows longitudinal assessment of bone microstructure at the distal radius and tibia. The efficacy of treatments for osteoporosis can be evaluated using these techniques. A true improvement of bone microstructure above baseline has not been demonstrated with anti-resorptive treatments; however, they may prevent the decay of cancellous bone and, potentially, cortical thinning. Anabolic agents such as parathyroid hormone (PTH) increase cancellous bone volume and cortical thickness; however, the improvement of cortical bone strength by PTH may be limited by an increase in cortical porosity. Strontium ranelate has been shown to improve not only the trabecular network but also cortical thickness, contributing to its anti-fracture efficacy at vertebral, non-vertebral, and hip sites.

Keywords Bone strength · Bone structure · Histomorphometry · HRqPCT · Microarchitecture

Introduction

Osteoporosis is a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue (which has been redefined as poor bone quality to reflect the properties of the bone material in addition to its microstructure), leading to bone fragility and an increased propensity to fractures. The evaluation of bone mineral mass (areal BMD, g/cm²) by dual-energy X-ray absorptiometry (DXA) at spine or hip is the standard by which to diagnose and make decisions about osteoporosis treatment. T-scores<−2.5 however are not sufficient to capture the whole population at risk, whence the need for new tools to evaluate fracture probability, such as FRAX [1]. Bone fragility can be better understood by examining the complex nature of bone microstructure, with its cortical and cancellous bone compartments that are distributed in different proportions at the various skeletal sites [2].

For many years only quantitative computed tomography (QCT), either centrally (spine, hip) or peripherally (wrist), was able to appreciate non-invasively losses in cortical and cancellous bone volumetric density (vBMD, g/cm³). It showed that trabecular bone loss is most prominent within the first 10 years after the menopause (~4%/year), while cortical vBMD declines more progressively (~1%/year), with these changes actually reflecting not only the loss of bone mineral but also of bone microstructure [3]. Hence, a decrease of cancellous vBMD can reflect a loss of trabeculae, i.e., a decrease of Tb number, as well as thinning and/or loss of connectivity of those trabeculae. Similarly, a decrease of cortical vBMD can reflect not only a lesser degree of mineralization within the boundaries of the periosteal and endocortical envelope but also endocortical erosions and/or intracortical (Haversian) bone remodeling leading to cortical...
porosity. Investigations on bone biopsies demonstrate that both trabecular and cortical bone microarchitecture contribute independently to vertebral fractures in men with osteoporosis [4]. In contrast to data reported in women, in men it is cortical porosity, and not cortical width, that is associated with vertebral fractures when compared with osteoporotic men without such fractures, suggesting that the cortical deficit is different in men and in women with fragility fractures. In post-menopausal women, vertebral fractures are associated with low vBMD and architectural decay of trabecular and cortical bone at the radius and tibia, independently of spine aBMD [5].

The contribution of microstructural changes in the cortical and trabecular bone compartments to bone fragility varies between skeletal sites. Hence, a sharp decrease of cancellous vBMD, reflecting a loss of trabeculae, is a strong determinant of the rapidly rising incidence of wrist and vertebral fractures in post-menopausal women, whereas trabeculae within the femur neck could contribute less than 10% to the axial compression strength of the hip [6]. In contrast, hip fractures will be prominently determined by loss of cortical bone vBMD and thickness, which will take many more years to become clinically manifest due to the lower remodeling surfaces on cortical than trabecular bone [6, 7]. From these observations, it clearly appears that current non-invasive evaluation of BMD, be it areal or volumetric, has limited value in understanding the actual changes in bone microstructure/quality that occur in the skeleton.

Evaluation of bone structure and strength

Attempts have been made to evaluate geometrical/structural parameters at the hip from DXA acquisitions by hip strength analysis (HSA). This approach, based on the distribution of apparent densities from side to side on the 2D planar image of the hip, has shown that fracture cases have a wider neck diameter, lower cortical thickness (CTh), and an increased buckling ratio, BR (outer radius/wall thickness) [7]. A recent study [8] reported greater changes in the cross-sectional area (CSA), section modulus (SM), CTh, and BR at both the narrow neck and intertrochanteric region from baseline to 2 years with alendronate (ALN) compared with risedronate (RIS), paralleling the differences observed in BMD gain between these drugs. Teriparatide (TPT) similarly improved CSA, SM, and BR compared with PBO [9]. HSA analysis in 483 post-menopausal osteoporotic women from the TROPOS study showed a 5% to 8% increase in CSA, SM, and CTh and a 3% reduction of BR in those treated with strontium ranelate (SR) for 5 years, while these structural parameters decreased by 2–3% and BR increased by 5% in the placebo (PBO) group (Table 1). Similar differences were seen in all three subregions analyzed (narrow neck, intertrochanteric, and shaft). Moreover, CSA and CTh remained different between SR and PBO after adjustment for BMD. HSA however is limited by the heavy assumptions underlying it, such as a cylindrical shape of the femur neck, the poor definition of edge margins between the cortical and medullary space, the large effects of even small differences in hip rotation from one examination to the other, and, most importantly, its dependence upon changes in bone mineralization/apparent density as influenced by various drugs [10].

As an alternative to DXA, QCT offers complete 3D information, high in plane resolution, and separate assessment of cortical and trabecular bone of the femur. Moreover, finite element analysis (FEA), which calculates bone strength from QCT data, strongly predicts in vitro femoral and vertebral breaking strength. The FEA strength-to-density ratio in particular can reveal when treatment increases strength beyond its BMD effects. Hence, consistent with its bone anabolic properties, teriparatide (TPT) was shown to increase the estimated vertebral strength and strength-to-density ratio over alendronate after 6 and 18 months [11]. At the hip, a recently developed structural analysis approach (QCT-PRO BIT®) showed an increase of cortical CSA, while total CSA remained unchanged, confirming that TPT induces endosteal but no periosteal growth. This analysis also showed a significant decline of hip cortical vBMD with PTH from 6 to 24 months, which could reflect both the endocortical apposition of under-mineralized new bone and/or increased cortical porosity [12].

Histomorphometry and 3D microstructure of bone biopsies

The gold standard to identify alterations in bone microstructure/quality and treatment effects thereon has long been (and remains) the histomorphometrical analysis of iliac crest bone biopsies, first by 2D conventional microscopy then by 3D micro-CT analysis of the biopsy cores. This approach allows one to assess not only the finest dimensions of the cancellous and cortical bone compartments but also the dynamic parameters of bone remodeling as evaluated by double-tetracycline labeling of bone surfaces. In this case, the mineral apposition rate (MAR), as evaluated by the distance between the two tetracycline labels, reflects the bone-forming activity of osteoblasts, whereas the mineralizing surface (MS/BS) and bone formation rate (BFR), which depend on the extent of single- and double-labeled surfaces, reflect the degree of bone turnover/remodeling. Hence, bone biopsies from patients treated with potent antiresorptives that markedly decrease the activation frequency, such as bisphosphonates.
(and even more prominently the RANKL inhibitor denosumab), show a significant reduction of MS/BS and BFR, whereas MAR is not necessarily reduced [13–15] (Table 2). However, the recently observed increase in MAR with ZOL could be an overestimation caused by discarding from analysis several bone biopsies with missing double labels. MAR was also 9–10% greater on both trabecular and endocortical bone surfaces in women treated with SR compared with PBO for 2 to 5 years [16]. In contrast, due to its mechanism of action, which differs from that of anti-resorptives, SR did not inhibit MS/BS or BFR (Table 2). PTH and PTH-derived molecules also tend to improve MAR, BFR, and the mean wall thickness—a hallmark of new bone formation—(compared with baseline) at trabecular and/or endocortical surfaces [17, 18]. In a head-to-head bone biopsy study of teriparatide vs SR for 6 months in post-menopausal women with osteoporosis, the only bone forming parameter to differ between the groups was the endocortical MS/BS (TPT, n=28, 17.2%; SR, n=21, 9.7%, p=0.052), whereas BFR and MAR were similar with both treatments at both trabecular and endocortical surfaces [19].

3D micro-CT analysis of paired bone biopsies in 12 post-menopausal women from the PBO group of a randomized control trial showed that Tb bone volume decreased by 20% and Tb number (TbN) by 13% within 1 year, while LS BMD declined by 3% [20], whereas no statistically significant deterioration occurred in the risedronate-treated group (n=14). After 3 years, risedronate fully prevented the reduction of Tb bone volume fraction (BV/TV, −27%), Tb thickness (TbTh, −20%), and TbN (−10%) observed in a subgroup of 11 women with high bone turnover receiving PBO [21]. Histomorphometrical analyses of cross-sectional bone biopsies from numerous randomized, controlled trials with bisphosphonates have also consistently reported a preservation of trabecular bone microstructure. For instance, alendronate (ALN) and zoledronic acid (ZOL) improved the 2D and 3D trabecular BV/TV and TbN after 3 years vs PBO [15, 22] (Table 1). In contrast, bisphosphonates have generally not shown a significant improvement of CTh over time. Contrasting with anti-resorptives, agents with anabolic properties, such as PTH/teriparatide and SR, improve not only the trabecular bone structure but also CTh [16, 18].

Table 1 Five-year relative changes (%) of hip strength analysis parameters at the intertrochanteric site

<table>
<thead>
<tr>
<th></th>
<th>Strontium ranelate (n=251)</th>
<th>Placebo (n=232)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cross-sectional area</td>
<td>9.05±10.65</td>
<td>−4.06±8.82</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CSMI</td>
<td>8.60±14.06</td>
<td>−4.81±14.63</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Section modulus</td>
<td>11.07±14.03</td>
<td>−4.72±14.77</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Endocortical diameter</td>
<td>−1.93±3.19</td>
<td>−0.01±3.59</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cortical thickness</td>
<td>10.27±11.57</td>
<td>−4.02±9.33</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Buckling ratio</td>
<td>−10.32±10.08</td>
<td>5.93±22.00</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Table 2 Bone histomorphometry in randomized, controlled trials of osteoporosis drugs

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Trabecular</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAR (µm/d)</td>
<td>0.63–0.70</td>
<td>0.59</td>
<td>0.60</td>
<td>0.53</td>
<td>0.62</td>
<td>0.57</td>
<td>0.56</td>
<td>0.57</td>
</tr>
<tr>
<td>BFR (µm³/µm²/d)</td>
<td>0.003–0.019</td>
<td>0.039</td>
<td>0.05</td>
<td>0.15</td>
<td>0.025</td>
<td>0.028</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>2D-BV/TV (%)</td>
<td>17.1</td>
<td>13.4</td>
<td>16.9</td>
<td>14.2</td>
<td>NA</td>
<td>NA</td>
<td>18.0</td>
<td>14.0</td>
</tr>
<tr>
<td>2D-TbN</td>
<td>1.19</td>
<td>1.07</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>1.9</td>
<td>1.85</td>
</tr>
<tr>
<td>3D-BV/TV</td>
<td>19.4</td>
<td>16.2</td>
<td>16.2</td>
<td>12.9</td>
<td>17.4</td>
<td>15.4</td>
<td>13.0</td>
<td>11.0</td>
</tr>
<tr>
<td>3D-TbN</td>
<td>1.46</td>
<td>1.31</td>
<td>1.36</td>
<td>1.22</td>
<td>1.30</td>
<td>1.14</td>
<td>1.31</td>
<td>1.26</td>
</tr>
<tr>
<td>Endocortical</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAR (µm/d)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>0.77</td>
<td>0.72</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>BFR (µm³/µm²/d)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>0.033</td>
<td>0.037</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>2D-CTh (mm)</td>
<td>NA</td>
<td>NA</td>
<td>0.624</td>
<td>0.511</td>
<td>NA</td>
<td>NA</td>
<td>1.008</td>
<td>0.753</td>
</tr>
<tr>
<td>3D-CTh (mm)</td>
<td>NA</td>
<td>NA</td>
<td>0.72 (0.79)b</td>
<td>0.63</td>
<td>0.727</td>
<td>0.615</td>
<td>0.92</td>
<td>0.74</td>
</tr>
</tbody>
</table>

MAR mineral apposition rate, BFR bone forming rate, BV/TV trabecular bone volume fraction, TbN trabecular number, CTh cortical thickness, ALN alendronate, ZOL zoledronic acid, SR strontium ranelate, TPT teriparatide, PBO placebo, NA not available

a At 5 or 10 mg/d for 2 and 3 years

b A subgroup with previous non-bisphosphonate treatment (data in parentheses)
(Table 2). At the clinically used dose, wider cortical thickness with these agents is most certainly explained by new bone formation at endocortical rather than periosteal surfaces. In the head-to-head bone biopsy study of TPT vs SR mentioned above [19], no significant differences in parameters related to bone structure (BV/TV, TbN, TbTh, CTh,...) were observed between the two treatments. However, cortical porosity was significantly greater with TPT than with SR (5.4% vs 4.1%, p=0.037), reflecting the induction of Haversian bone remodeling by TPT.

Non-invasive evaluation of bone microstructure

In order to evaluate longitudinal changes of cortical and cancellous bone microstructure in the appendicular skeleton from a larger number of subjects, high-resolution (micro-) CT and MRI technologies are being developed. Although these technologies do not yet allow the evaluation of microstructure centrally, i.e., at spine or hip, peripheral sites such as the distal radius and tibia are commonly analyzed. One of the first studies to evaluate the effects of an osteoporosis drug, namely calcitonin, on trabecular structure at the wrist (QUEST) [23] used MRI (spatial resolution 156 x 500 µm, i.e., 20 slices over a 1-cm volume of interest, VOI). It showed preservation of BV/TV with this treatment compared to PBO over 2 years. However, this study also illustrated that changes in cancellous bone vary tremendously from one small region (2.5 mm) to another within the VOI. Improved MRI technology and a trabecular pattern recognition algorithm led to serially volume-registered cross-sectional micro-MRI images of the distal tibia [24], which showed a 7% BV/TV gain in early menopausal women receiving estradiol compared with no HRT. Meanwhile, pQCT at this site showed a 2% to 3% gain of cortical thickness compared to a 6% loss without treatment.

The most rapidly spreading technology for the non-invasive evaluation of bone microstructure is high-resolution pQCT (Xtreme CT, Scanco, Switzerland), which enables the simultaneous acquisition of a stack of 110 parallel CT slices with a nominal resolution of only 86 µm (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 (Fig. 1). The total volume of interest is separated into a cortical and trabecular region using a threshold of one third of the apparent cortical bone density (Dcort, mg HA/cm³) to define the cancellous bone region. In addition to the volumetric densities in these two compartments, HR-pQCT provides an indirect measurement of TbN by evaluating the mean 3D distance between the mid-axes of trabeculae and of CTh by dividing the cortical volume by the outer bone surface (i.e., the cortical area by the perimeter of each slice). The other microstructural values provided, such as BV/TV, TbTh, and Tb separation (TbSp), are all derived from the above and therefore not independent of the apparent Tb bone density or number. Hence, the best correlated measures between MRI and HR-pQCT are TbN and CTh, although the latter appears systematically wider when evaluated by MRI [25]. Moreover, bone microarchitecture evaluated at the distal radius or tibia by HR-pQCT correlates rather poorly with 3D measures of iliac crest bone biopsies (R=0.5 or less) [26]. Trabecular thickness in particular cannot be measured directly by HR-pQCT because of partial volume effects. In addition, whereas the CV of repeated measures is low for...

Fig. 1  a X-ray of distal tibia shows location of the VOI between green lines for analysis of vBMD and microarchitecture by HR-pQCT. b 3D-image of bone microstructure at distal tibia in a 25-year-old woman with Crohn’s disease and a vertebral fragility fracture. In her case, aBMD by DXA was normal (T-sc. LS −1.0, FN −0.4), whereas BV/TV (10.8%) was in the lowest quintile of normal values for age/sex
volumetric densities and CTh (≤1%), it is in the range of 3–5% for TbN and the derived parameters.

Cross-sectional and some longitudinal studies have now shown the differences in bone microstructure at the distal radius between women and men, the latter having a greater BV/TV and TbTh whereas the former lose TbN and CTh and increase TbSp more rapidly than men with age [27–29]. Moreover, volumetric densities and CTh have been reported to be inversely correlated with menarcheal age in young women [30], which emphasizes the major role of gonadal steroids in bone microstructure. Lower total and trabecular bone density, BV/TV, TbN, and CTh predominantly at the distal radius (more than at distal tibia), has been reported in relation to both fragility fractures, including wrist fractures, in post-menopausal women[3, 31, 32] and to traumatic fractures of childhood/adolescence in young women. Although HR-pQCT parameters are significantly correlated with aBMD at the same site (ultra-distal radius) or a proximal site (hip vs distal tibia) (R values ranging from 0.2–0.3 to 0.7–0.8), some of the associations between poor trabecular microstructure and fractures remained significant after adjustment for aBMD [33].

This technique is now also being used to evaluate treatment effects on bone microarchitecture. In a randomized, double-blind, double-dummy, head-to-head comparison between ALN and SR in 88 post-menopausal osteoporotic women (mean age 64, FN T-score −3.8–3.9), changes of bone microarchitecture at distal radius and tibia were analyzed at 3, 6, 12, and 24 months. The expected changes occurred for bone turnover markers, i.e., a 58% and 35% decrease of sCTX and bALP, respectively, with ALN, and minimal opposite changes with SR (sCTX −6.6%, bALP +5%), as well as for BMD (LS +5.1% and +4.6; FN +3.6 and +2.7%, with SR and ALN, respectively). At the distal tibia, CTh increased significantly more with SR than ALN at 1 year (+5.4 vs +1.3%, p=0.045). Significant differences were already detectable after 3 months, i.e., a time when deposition of SR in newly formed bone is still probably minimal and unlikely to influence the apparent bone density. Moreover, cortical vBMD remained similar between the two treatments (758 and 749 mg HA/cm³). After 1 year, trabecular BV/TV was also significantly greater with SR compared to ALN (2.2% vs 0.8%, p<0.05), although as explained above BV/TV is directly dependent on the trabecular vBMD. Note that the distal radius microstructural parameters were uninterpretable because of motion artifacts during data acquisition.

Conclusions

Studies of bone microstructure using iliac crest bone biopsies and, more recently, non-invasive techniques such as high-resolution MRI and pQCT highlight the major changes occurring after menopause, most prominently the loss of trabecular number and cancellous bone volume and the more progressive loss of cortical thickness. Altered bone microstructure in turn is a major component of osteoporosis and bone fragility. Anti-resorptives may prevent the decay of cancellous bone and, potentially, cortical thinning, although a true improvement of bone microstructure above baseline has never been demonstrated with these drugs. In contrast, bone-building agents such as PTH/teriparatide promote new bone formation at both trabecular and endocortical surfaces, resulting in a net increase of cancellous bone volume and cortical thickness and an improvement of bone strength, as estimated by FEA and other analyses of QCT acquisitions in vertebrae and the hip. However, the improvement of cortical bone strength by PTH/teriparatide may be limited by an increase in cortical porosity. SR on the other hand has been shown to improve not only the trabecular network but also cortical thickness by a variety of methods, including HSA, 3D microstructural analyses of iliac crest bone biopsies, and, most interestingly, longitudinal assessment of bone microstructure at the distal tibia by HR-pQCT. In turn, these positive changes of bone (micro-)structure will contribute to SR anti-fracture efficacy at both vertebrae and non-vertebral sites, including in the oldest women.

Conflicts of interest S.F. receives speaker, consultant, and research fees from MSD and AMGEN and is a speaker and/or consultant for SANOFI and Warner Shillcol, Eli Lilly, Servier, and Novartis.

References


