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REVIEW

Microarchitecture in focus

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Introduction

Osteoporosis is a complex disease characterized by a decrease in bone mass and alterations of bone quality leading to increased bone fragility and fracture risk. The increasing worldwide incidence of osteoporosis requires the use of effective treatments. The aim of antiosteoporotic treatments is to improve bone strength and thus to decrease the risk of fracture [1, 2]. Bone quality includes several aspects of bone composition and structure, including microstructure, bone turnover, the degree of mineralization, and the extent of microdamage. Bone quality is being given increased importance as recent observations demonstrate that traditional measures of bone density do not always predict fracture risk reliably [3].

At present, the major noninvasive measurement available for the diagnosis of osteoporosis is the measurement of areal bone mineral density (BMD) by dual-energy X-ray absorptiometry (DXA). Fracture risk prediction in the individual patient also relies mainly on BMD measurements. The diagnosis of osteoporosis measured by DXA, is a BMD of ≥2.5 standard deviations below the mean for young adults. However, many lines of evidence indicate that the decreased bone strength characteristic of osteoporosis is only partially accounted for by BMD and the remainder is dependent on material and structural properties of bone tissue, the bone microstructure [4–10]. Furthermore, the alterations in bone microstructure are not captured by BMD measurements. Measurements of BMD are useful in postmenopausal osteoporosis and other conditions of significant demineralization.

Knowledge of bone microstructure is a clue for understanding osteoporosis pathophysiology and improving its diagnosis and treatment; the response of microstructure parameters to treatment should allow assessment of the real efficacy of the osteoporosis therapy.

Assessment of bone microstructure

The gold standard for investigation of bone disease remains the histomorphometry or quantitative histology of iliac crest biopsies, which has greatly enhanced our understanding of normal bone microstructure, remodeling, and strength, as well as the effects on bone of various diseases and treatments for osteoporosis [11]. However, this technique is invasive, and thus longitudinal measurements of bone structure at the same location are difficult to follow up. In addition, bone biopsies are performed in regions of low load and low fracture prevalence [12].

Recently, there has been great interest in noninvasive imaging techniques that enable assessment of bone microstructure in vivo at weight-bearing and non-weight-bearing skeletal sites that may be affected by osteoporosis. As new products and methods have been developed, focusing more on bone fragility, it has been essential to develop effective and sensitive means to assess fracture repair [13]. New techniques are now available which are able to provide structural information about local and systemic skeletal health and the pathophysiology of bone fragility [13]. These include high-resolution magnetic resonance imaging (HR-MRI), micro-CT (μCT), and synchrotron radiation μCT [4, 14]. It has been demonstrated that microstructure

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parameters should be obtained by using several of the above-mentioned techniques. Micro-CT, micro-MRI, and synchrotron also allow the measurement in 3D of the trabecular microstructure in a nondestructive way on bone specimens [3]. In addition, the application of μCT to bone biopsy specimens has improved assessment of trabecular microstructure because the analysis is truly volumetric and encompasses the entire biopsy sample rather than being limited to several histological sections.

One recently developed noninvasive technique, HR-pQCT (Xtreme CT, Scanco Medical AG, Brüttisellen, Switzerland), can perform human in vivo measurements at peripheral sites including the radius and a weight-bearing site, i.e., the tibia. This technique yields 3D images of sufficiently high resolution (~82 μm). The standard HR-pQCT morphological measurement protocol includes a direct measurement of trabecular number (Tb.N), and derived measurements of bone volume ratio (BV/TVd), trabecular thickness (Tb.Th), trabecular separation (Tb.Sp), and cortical thickness (Ct.Th) [15, 16].

Treatment effects: from BMD…

Both anti-resorptive and anabolic interventions affect BMD. The majority of clinical studies on anti-resorptive agents, such as bisphosphonates, denosumab, selective estrogen receptor modulators, and estrogen have shown an increase in BMD that parallels the decreased risk of fracture [17–19]. Raloxifene and alendronate treatments have also been associated with a reduction in vertebral fracture, but the effect on BMD at the femoral neck and spine is less pronounced with treatment with raloxifene (+3%) than alendronate at the spine and trochanter (+8%) [17, 20–22]. However, it has been observed that improvement in spine BMD during treatment with anti-resorptive drugs accounted for a predictable but small part of the observed reduction in the risk of vertebral fracture [23].

In preclinical studies comparing determinants of bone strength, such as BMD, bone external dimensions, and trabecular bone morphology, BMD was systematically investigated and, independently of the laboratories performing the study or of the mammalian species investigated (pig, monkey, rat, mouse), predicted 50–75% of the variation in ultimate strength [1, 24, 25]. BMD measurements are therefore still useful for predicting bone strength.

Strontium ranelate has been shown to significantly increase bone mineral density at the lumbar spine, femoral neck, and total hip, which is significantly related to fracture risk reduction [26–28]. A post-hoc analysis of pooled data from the SOTI and TROPOS studies demonstrated that changes of BMD at the femoral neck after 3 years of treatment were predictive of vertebral fracture risk reduction, with each 1% increase in femoral neck BMD found to be associated with a 3% reduction in vertebral fracture risk. Changes in BMD thus explained 76% of the fracture risk reduction observed after 3 years of treatment [29]. An increase in femoral neck BMD after 1 year of treatment was also associated with a reduction in new vertebral fractures after 3 years of treatment (p=0.04). During 3 years of treatment, femoral neck BMD changes were also associated with hip fracture risk reduction [29] suggesting that femoral neck BMD assessment may be a more appropriate monitoring tool than lumbar spine BMD measurements in strontium ranelate-treated patients.

...to microstructure

A specific analysis of microstructure was performed on 41 bone biopsies obtained from patients participating in the SOTI and TROPOS studies and the biopsies were examined using three-dimensional μCT [11]. Compared with placebo (n=21), biopsies obtained from strontium ranelate-treated patients (n=20) demonstrated a significant increase in the number of trabeculae (+14%; p=0.05), decrease in trabecular separation (−16%; p=0.04) and an increase in cortical thickness (+18%; p=0.008). There was also a shift in trabecular structure from rod-like to plate-like configuration resulting in an improved trabecular structural model index and substantially stronger bone in strontium-treated compared with untreated patients (−22%; p=0.01) [11]. These changes in trabecular and cortical microstructure are likely to improve the biomechanical properties of bone and contribute to the anti-fracture efficacy observed with strontium ranelate.

In a recent head-to-head longitudinal study, the effects of strontium ranelate and alendronate on microstructure were compared. Eighty-eight women aged 50 or over with postmenopausal osteoporosis were randomized to SR 2 g/day or ALN 70 mg/week for 2 years. Microstructure of weight-bearing distal tibia bone was assessed by the aforementioned HR-pQCT after 3, 6, 12, 18, and 24 months of treatment. Baseline characteristics were similar in both groups: age, 63.7±7.4 years; lumbar and hip T-score, −2.7±0.9 g/cm^2 and −2.0±0.8 g/cm^2, respectively. After 1 year of treatment, BMD increases were similar to results from pivotal trials (L1–L4, +5.7% and +5.1%; total hip, +3.3% and +2.2%, in SR and ALN groups, respectively). For bone microstructure, mean increases of +5.3% (p<0.001) for C.Th, +2.0% (p=0.002) for BV/TV and +2.1% (p=0.002) for trabecular density were found in the SR group, compared to no change in the ALN group (1.3% p=0.130; 0.6% p=0.725 and 0.6% p=0.645, for corresponding variables, respectively), with thus a significant between-group differ-

ence in favor of SR (p=0.045, p=0.048 and p=0.035, for C.Th, BV/TV, and trabecular density, respectively). Improvement in microstructure was associated in the SR group with significant decrease in heterogeneity of trabecular network (−3.6±8.6%, p=0.007). This study demonstrated that strontium ranelate had significantly higher effects than alendronate on distal tibia microstructure including cortical and trabecular variables, in women with postmenopausal osteoporosis after 1 year of treatment [30]. Whether these changes translate into a commensurate reduction in fracture rate should be determined in the future.

Conclusion

BMD remains a good predictor of fracture risk, but many other factors contribute to bone strength, such as bone geometry, cortical thickness, and porosity as well as trabecular bone morphology. Advances in the assessment of bone quality in recent years have provided new insights into bone fragility in both untreated and treated bone disease. As an example, strontium ranelate treatment was associated with improved bone microstructure. The development of new technologies, which now allow in vivo noninvasive evaluation of bone, are important for the longitudinal monitoring of bone quality measurements and it can be envisaged that the HR-pQCT technique will be employed as standard protocol in the future for improved diagnosis and assessing the treatment effects of diseases such as osteoporosis.

Disclosure statement R.R. is a speaker for Amgen, Novartis, Danone, Merck, Roche, Servier, and is a member of the scientific advisory board of Amgen, Danone, Eli Lilly, Nycomed, Servier, Roche, Novartis.

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