

Bone Loss in Ankylosing Spondylitis: Can We Put the Puzzle Together?



Ankylosing spondylitis (AS) raises the paradox of a disease characterized by new bone formation at sites of chronic inflammation and the association of reduced bone mass and increased fracture risk. For several years it has been established that bone mineral density (BMD) loss occurs early in the AS disease course and is associated with inflammation correlated with increased bone resorption^{1,2}. Recent reports confirm reduction of BMD at the hip and femoral neck³, and a vertebral fracture rate of 0.4% at a mean age of 50 ± 9 years, occurring after 2 decades of disease, with possible neurological complications⁴.

In this issue of *The Journal*, Karberg and colleagues⁵ report that bone loss is more frequently detected in AS patients with syndesmophytes. Their study confirms reduction of BMD in a cohort of AS patients. Bone loss was apparent using different devices and techniques and at different sites of evaluation [dual energy x-ray absorptiometry (DEXA) at the lumbar spine and femur, dual energy quantitative computerized tomography (CT) at the lumbar spine, and peripheral quantitative CT at the forearm]. The results with different techniques were not correlated. Their findings concur with our ultrasound measurements at the calcaneus¹, whereas Jansen, *et al*⁶ using quantitative ultrasound of the heel were able to identify AS patients with osteoporosis associated fracture.

Karberg, *et al* found that DEXA at the femoral neck was the most sensitive method for evaluating osteopenia and osteoporosis in AS, even in patients without syndesmophytes. This method and site were also felt to be the most accurate in AS for British rheumatologists⁷. Measurement at the femur avoids bias represented by entheses ossification (namely syndesmophytes) in posteroanterior lumbar spine assessment. Syndesmophytes have no distorting effect on BMD measured by lateral DEXA⁸.

Reduction of BMD was greater in AS patients with syndesmophytes; and although, as expected, these patients exhibited a longer duration of disease, there was no correlation between BMD and disease duration; moreover, in the presence of syndesmophytes more patients were seen to

have decreased BMD, even those with short disease duration. Recently, Lange⁹ confirmed decreased bone density even at the initial stage of AS and continuing into the advanced stages; this was observed not only in the spine but also at the femoral neck. It would be interesting to add to the results of Karberg by quantifying syndesmophytes (using the modified Stoke AS Spine Score, for instance) to look for a correlation between BMD reduction and syndesmophyte score. A correlation would underline the responsibility of an (un)coupling process between bone decrease (resorption) and syndesmophyte formation. This would allow a new interpretation of these observations, which is still under debate.

In AS, the pathological process begins at the entheses: local inflammation is followed by ligament ossification involving potentially proinflammatory cytokines [interleukin 6 (IL-6), tumor necrosis factor- α (TNF- α), IL-1] and growth factors [transforming growth factor- β (TGF- β), insulin-like growth factor (IGF)]. These local phenomena are difficult to investigate due to the poor accessibility of the entheses. Bone loss is evident adjacent to areas of entheses inflammation, but, as a systemic disease, there is also evidence of bone loss at clinically uninvolved sites like femoral neck in the study of Karberg.

WHAT UNDERLYING PHYSIOPATHOLOGICAL MECHANISMS LEAD TO BONE LOSS IN AS?

The available puzzling data originate from studies evaluating systemic modifications of factors involved at different stages of bone loss.

Bone histomorphometric studies are scant. Szejnfeld, *et al* studied 16 patients with AS: osteopenia was found in 14 patients, mineralization defect in 10, and osteomalacia in 3 patients¹⁰. Moreover, there was a positive correlation between measures of osteomalacia (osteoid volume, mineralization lag time) and disease duration, and a negative correlation between disease duration and resorption (eroded surface, bone osteoclast interface), suggesting a biphasic mechanism.

Low BMD in AS is associated with increased biochemi-

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cal markers of bone turnover, especially resorption, such as deoxypyridinoline (DPD); in fact DPD levels have been found to be correlated in AS with inflammation assessed by erythrocyte sedimentation rate or C-reactive protein (CRP)^{1,3}. The latter may reflect severity and evolution of disease and therefore be compatible with accelerated syndesmophyte formation, irrespective of disease duration, as in the study reported by Karberg. However, the authors did not find a correlation between DPD and clinical or biological activity of the disease, as assessed by Bath AS Disease Activity Index and CRP. This apparent discrepancy can be explained: serum levels of biological markers reflect the situation at a given timepoint, whereas radiological features such as syndesmophytes or BMD values reflect the cumulative influence of the disease over time.

Other factors may be involved. Genetic factors have been suspected, and there is evidence that vitamin D receptor gene may contribute to BMD differences, bone metabolism, and inflammation processes in AS¹¹. The role of reduced physical activity in AS patients with syndesmophytes is discussed in the article by Karberg, and is probably not predominant. Hormones may also play a part. Franck, *et al*³ demonstrated a positive correlation between BMD at the femoral neck and free testosterone serum levels in AS men and free estradiol serum levels in AS women.

Cytokines represent a link between local and systemic inflammation on the one hand, and bone resorption and BMD reduction on the other. IL-6 and TNF- α , which are involved in AS inflammation, are osteoclast activators¹², whereas consistent modification of growth factor (TGF- β , IGF) serum levels have not been demonstrated^{1,13}. Finally, the RANK-RANK ligand system and its natural inhibitor osteoprotegerin (OPG) may represent the key point in bone-cytokine interrelation. Franck³, *et al* found significantly lower serum OPG levels in AS patients compared to controls; this finding was unrelated to age, suggesting a lack of this resorption antagonist in AS. Further investigation in this area might include soluble RANK ligand levels and correlation with biological inflammation.

IL-17 (and its receptor) is a good candidate for the missing piece of the puzzle¹⁴. IL-17 is a T cell cytokine exhibiting proinflammatory properties by triggering expression of inflammatory effectors that promote osteoclastogenesis and bone destruction. IL-17 may enhance chemotactic factors (granulocyte macrophage-colony stimulating factor, monocyte chemotactic protein, IL-8) that promote neutrophil recruitment and activation, which can exert both bone protective and destructive effects. *In vivo* bone erosion mediated by overexpression of IL-17 has been shown to occur through alterations in the RANKL/OPG ratio¹⁵.

Bone loss in AS appears to be multifactorial and perhaps involves different mechanisms at different stages of disease. Nevertheless, and beyond hypotheses, BMD reduction in AS is a reality that should be taken into account in the management of these patients, particularly since the advent of

new therapeutic opportunities (anti-TNF agents) able to improve both disease activity and BMD¹⁶.

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