New insights on the role, pathogenesis, and treatment of osteoporosis and bone erosions in rheumatoid arthritis

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Summary

Bone erosions and osteoporosis are a main problem of Rheumatoid Arthritis and even in the biologic era are unsolved problems. Many hypothesis have been formulated since today on the pathogenesis of osteoporosis and bone erosions, and a new rising hypothesis is that osteoporosis and bone erosions are part of an unique pathology of bone. Our review summarizes the state of the art on osteoporosis in RA and discusses its clinical implications in terms of risk of bone erosions.

KEY WORDS: rheumatoid arthritis; osteoporosis; bone erosions; bone metabolism; synovitis.

Introduction

Fracture is the final event due to osteoporosis and it points out the real bone health status. The higher incidence of fractures in patients with Rheumatoid Arthritis (RA) is an indirect evidence of impaired bone health. This high incidence was found both at non-vertebral and vertebral sites and was related to total hip low BMD (1, 2). In RA patients the overall prevalence of osteoporosis evaluated with Dual X-Ray Absorptiometry (DXA) varies between 29% at lumbar spine and 36% at femoral neck and this prevalence significantly increased with disease duration (3, 4). Moreover, osteoporosis in RA was found at digital X-ray radiogrammetry (DXR) (5, 6) and with more innovative techniques like high-resolution peripheral quantitative computed tomography (HR-pQCT) at the hands and radius or tibia of patients with RA (7, 8). RA is an independent risk factor for osteoporosis and osteopenia (9, 10). Bone erosion is the main problem of RA and is associated with deformities and disabilities. Erosion mainly affects periarticular cortical bone and it results from unpaired bone resorption and formation (11). Even in the biological era. It is an unsolved problem and lot of hypothesis on the pathogenesis of bone erosions have been formulated since today. Is clear that the main trigger of periarticular bone erosions is inflammation but osteoclasts seem to play an important roles (11). A new hypothesis is that alterations of bone quantity and microstructure could be not only a secondary complication of RA but also an important “first hit” to the development of erosions.
Our mini-review summarizes the state of the art on osteoporosis in RA and discusses its clinical implications in terms of risk of bone erosions.

Osteoporosis: an independent determinant of bone erosions in RA

Higher Sharp score is known as an independent risk factor for osteoporosis and new vertebral fractures in patients with RA (1, 12), but also the opposite might be true! We found a strict inverse association between total hip BMD and erosions score; the lower was total hip BMD, the higher was the erosions score (13). Erosions in RA affect periarticular cortical bone (7, 11). Recently, Zhu and Kocijan reported alterations in density and microstructure of cortical bone in patients with RA. Their results showed that cortical bone is affected both with reduced thickness and increased porosity (7, 8). Moreover, Simon et al. demonstrated that osteoporosis in RA doesn’t concern only iuxta-articular sites but affects the intra-articular bone; furthermore postmenopausal state leads to bone loss at intra-articular sites. The same group also demonstrate the existence of cortical micro-channels in the bare area of joints of RA patients, these micro-channels.
RA disease duration is directly related with bone loss at lumbar spine and hip (9). A recent meta-analysis on randomized double-blind controlled clinical trials showed that patients over 50 years, naïve to treatment, have higher erosion score, independently of disease activity and duration (14). We think that higher osteoporosis prevalence might be the link between higher aggressiveness and age in RA. As a matter of fact, age is the most important risk factor of osteoporosis, both in male and female. Many other factors are related with higher risk of erosions in RA, including disease activity, cigarette smoking, alcohol consumption, hypovitaminosis D, low Body Mass Index (BMI), corticosteroids use and aging (1); all of these are well known risk factors for osteoporosis too! Therefore, we could speculate that the correlation with bone erosions might also be mediated by osteoporosis (Figure 1).
On the other hand, the described protective effect of obesity on radiographic joint damage (15, 16) might be due to the well known positive correlation between BMI and BMD.

New actors in the pathogenesis of RA-related osteoporosis and bone erosions

It has long been known the pathogenetic role of pro-inflammatory cytokines, such as IL1, IL6 and TNFα.
Recently, Parathyroid hormone (PTH) serum level has been found higher in patients with RA and was related to bone erosions (13). Indeed, primary hyperparathyroidism is related to a decline in BMD at cortical sites (17). This finding could explain the direct correlation of PTH with bone erosion in RA (13).
Another actor of bone loss in RA is Dkk1, a physiological inhibitor of Wnt system. The Wnt system is involved in osteoblasts differentiation, therefore Dkk1 is the master regulator of bone formation (18). Dkk1 is up regulated during the late phase of osteoblasts differentiation and was detected higher in many bone-remodeling conditions including RA (19-22). Dkk1 serum levels were also found higher in RA patients with bone erosions (18, 22), negatively correlated with hip BMD and strictly related to PTH in RA, as observed in other conditions (17, 23, 24). So PTH appears an important determinant of Dkk1 serum levels, as inflammation (21), and in particular IL6 (25). In summary, PTH and Dkk1 might act together in the genesis of bone loss and articular erosions (Figure 1).
ACPA are major risk factors in poor clinical outcome and for articular bone destruction (26-29). The latter is independent of inflammation status and disease activity. ACPA can affect cortical bone even in the preclinical phase, reducing cortical thickness (30). Recent studies showed that ACPA and high levels of RF are associated with systemic bone loss in patients with RA (27, 31). Moreover, In RA patients a strong and specific association between ACPA and serum markers for osteoclast-mediated bone resorption was found (32). Interestingly, human osteoclasts have been described to express enzymes promoting protein citrullination, and a specific N-terminal citrullination of vimentin was induced during osteoclast differentiation (32). Affinity-purified human autoantibodies against mutated citrullinated vimentin (MCV) not only bound to osteoclast surfaces, but also led to robust induction of osteoclastogenesis and bone resorptive activity (32). Moreover adoptive transfer of these purified human MCV autoantibodies into mice induced osteoclastogenesis and osteopenia (32). ACPA have a negative titer-dependent effect on BMD at femoral sites, mainly constituted by cortical bone (31). ACPA-positive patients, especially if at high titer, should undergo bone investigations and be treated with bone protecting agents. Disease-modifying anti-rheumatic drugs lowering ACPA titer might have positive effects on systemic bone mass.
RF is another important element associated with early onset of erosions and poor clinical response (33). Systemic BMD in patients with early RA is reduced in relation with ACPA positivity and high RF levels (27). Solomon et al. found an association between RF and total hip bone mineral density (BMD) but not with lumbar spine BMD (34). In conclusion, both ACPA and RF are associated with poor cortical density and higher cortical porosity and this association seems to increase susceptibility to erosions in RA patients (Figure 1).

Effects of biological disease modifying anti-rheumatic drugs (bDMARDs) on RA-related osteoporosis

Tumor Necrosis Factor inhibitors (TNFi) have change the history of RA treatment. TNFi are known to well inhibit the progression of both clinical and radiographic progression of RA. TNFi have been proved to reduce Dkk1 serum levels (24) but the effect on bone turnover markers (BTMs) is uncertain (35). Kim et al. showed that non-vertebral fracture in-

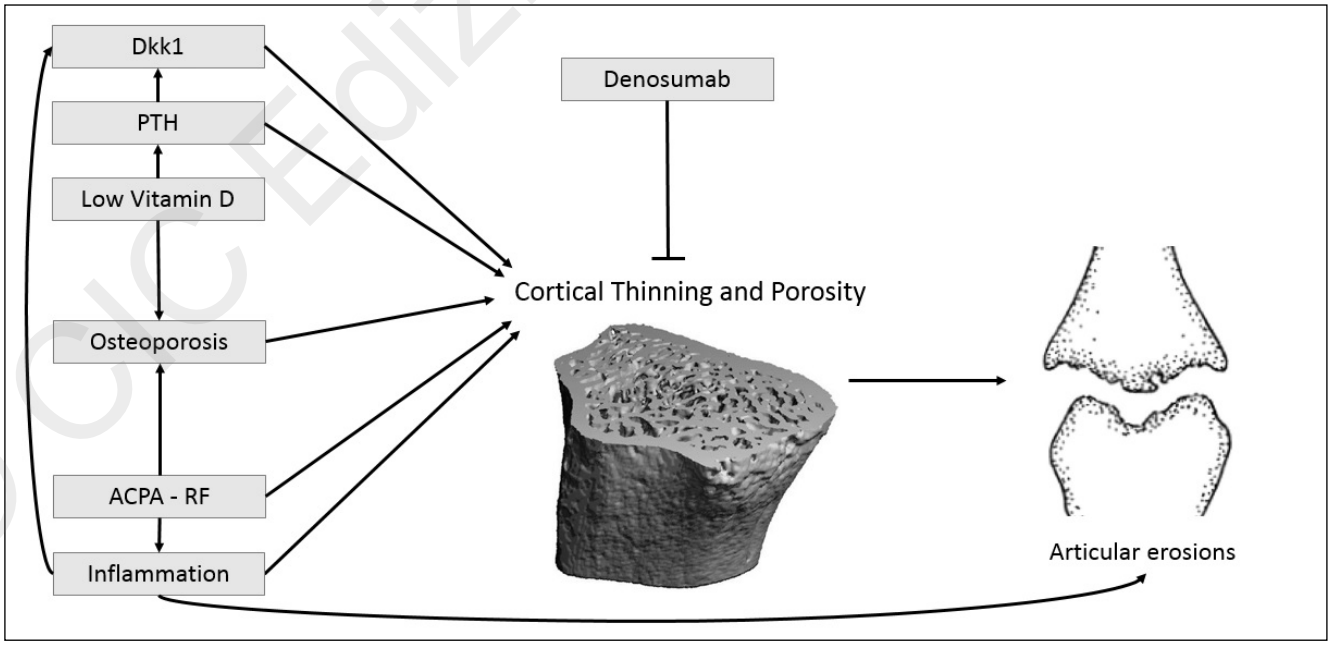

Figure 1 - Not only inflammation but also metabolic pathogenesis of bone erosions. Direct and indirect mechanism of impaired cortical bone leading to erosions in rheumatoid arthritis.

cidence is similar among TNFi users and conventional disease modifying anti-rheumatic drugs (cDMARDs) users (36). The latter evidence, joint to the large uncertainty in the results that TNFi have on BTMs and BMD (35, 37), increased the need of a better designed study on bone and TNFi. Indeed, despite great results achieved, some patients treated with TNFi, even in clinical remission, experience radiographic progression of the disease. One of the possible explanation resides in the observed raise of PTH during TNFi treatment (24) that might blunt the positive effect that these drugs exert on Dkk1 (24, 38). Moreover, PTH has been related to higher erosion score and to a plenty of bony unfavorable effects (13, 22, 39). It would be intriguing to assess the effect of large doses of vitamin D in patients treated with TNFi. Vitamin D would lower PTH (40) and eventually hump down Dkk1.

Tocilizumab (TCZ) an anti-IL-6 monoclonal antibody showed to lower CTX serum levels (41); another study showed an increase in P1NP serum levels while CTX levels remained stable, these results it would probably resides in the lowered Dkk1 (42). Overall TCZ seems to have a favorable effect on BTMs. These latter findings might explain the positive effect of TCZ on BMD (43).

Rituximab (RTX) is a monoclonal antibody directed against the molecule CD20 that blocks the activity of B lymphocytes. Two studies demonstrated the predictable drop in the RANKL serum levels after CD20 inhibition, with a favorable related effect on erosions (44, 45). Salvin et al. reported, in few patients with RA, an improvement in bone mineral density after RTX treatment (46).

Abatacept (ABT), a fusion protein of cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) and immunoglobulin G1, selectively modulates the CD80/CD86:CD28 costimulatory signal required for full T-cell activation. Only one human study has been made on ABT and its role on BMD. Tada et al. showed that ABT increase the femoral neck BMD, a cortical site (47). This evidence is in accordance with previous similar evidences on mice (48, 49).

Unfortunately, the overall results with biological therapy on bone damage is unsatisfactory. It would be especially important keeping in consideration corticosteroid use during biologic treatment, since the percentage of patients who stop glucocorticoids post-initiation of any biological treatment is around 30-40% (50-52).

Effects of osteoporosis treatment in RA

Bisphosphonates (BPs) are a milestone of the treatment of osteoporosis, and these drugs showed efficacy also in patients with bone fragility and RA (53). In 2006 Jarret et al. showed, in 39 RA patients, a beneficial effect of zoledronic acid on erosion score (54). However this encouraging result, the use of amino-bisphosphonates (N-BPs) is causative of an acute phase response that is linked to the activation of γδ T cells (in particular their major subpopulation of Vδ2 T cells) (55-58); this particular side effect raise some interest since Mo et al. suggest that Vδ2 T cells are involved in the pathogenesis of RA (59, 60). In this scenario TNF-α mediated chemotaxis of peripheral Vδ2 T cells could play a role also in some of the immunoeffects of N-BPs and it could be true the other way around (61).

Better result in preventing and even healing erosions have been achieved with denosumab, a fully human monoclonal antibody against the receptor activator of nuclear factor-κB ligand (RANKL). RANKL is essential for the formation, function, and survival of osteoclasts. Denosumab is a well-known, effective agent for increasing BMD, both at trabecular and cortical sites (62, 63) and has been showed to prevent metacarpal bone loss in patients with RA, and to improve cortical porosity (64, 65) (Figure 1). Two double-blind placebo controlled clinical trials showed that denosumab inhibits the progression of bone erosions and systemic bone loss in RA (66, 67). The trials proved the hypothesized importance of cortical osteoporosis in the developing of bone erosions (68, 69). Recently denosumab has been proved even to heal bone erosions in RA in combination with both cDMARDs (70) and bDMARDs (71).

Teriparatide (TPD) showed encouraging results in animal models of RA in term of healing erosions (72) and on BTM in RA patients (73). A randomized controlled trial of TPD in tumor necrosis factor inhibitor-treated patients with RA was recently published. This trial was designed to prove that TPD could heal bone erosions (74);it is not surprising that did not produce the expected result since the known partial effect of TPD on cortical bone (75).

SOST is another important physiological Wnt inhibitor. SOST is secreted by osteocytes and its serum levels are inversely related with mechanical load. SOST was found to be higher during immobility and in post-menopausal women (76, 77). A few studies are available on SOST in RA; many of these are on animal models of RA. Wehmeyer et al. found a considerable overexpression of SOST in the synovial tissue of patients with RA (78). Other studies are needed to reveal the role of SOST in RA and its relation with bone health, in particular by providing for the coming of SOST inhibitor, romosozumab.

Conclusions

We think that the bone deserves more consideration in RA pathogenesis and consequences. Recent evidences show that low-BMD and factors affecting BMD are related to erosions and there is an increasing demand in bone health pointed studies in RA. Unfortunately, all major clinical trials, on both cDMARDs and bDMARDs, lack of data about the bone health (79-90). This lack could lead to a significant bias toward the evaluation of treatment efficacy in preventing bone erosions. In RA, BMD is affected mainly at cortical sites, such as total hip, distal forearm and hand; and so lumbar spine BMD cannot be used to predict the risk of fractures in RA (91), but evidences show that cortical BMD is a reliable tool for predicting bone erosions (13, 34, 92-94). A recent study found a strict inverse association between total hip BMD and erosions score; the lower was total hip BMD, the higher was the erosions score (13). Low BMD is related to many of negative prognostic factors in RA and all of these seem to jointly act affecting bone health. Protocols of clinical trials on cDMARDs and bDMARDs have never included a cheap densitometry. The latter is an important lack; in the future, cortical bone health and systemic osteoporosis should be investigated by clinicians when evaluating a patient with RA, for example performing total hip or distal forearm densitometry or DXR at least, if pQCT is not available. We also think that osteoporosis treatments deserve more attention in the management of RA, in order to achieve also a better control of bone erosions.

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