Aging Clinical and Experimental Research
https://doi.org/10.1007/s40520-023-02432-9

REVIEW

Chronic arthritides and bone structure: focus on rheumatoid arthritis—an update

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Received: 8 April 2023 / Accepted: 1 May 2023

Abstract
Normal bone remodeling depends of a balance between bone forming cells, osteoblasts and bone resorbing cells, the osteoclasts. In chronic arthritides and some inflammatory and autoimmune diseases such as rheumatoid arthritis, there is a great constellation of cytokines produced by pannus that impair bone formation and stimulate bone resorption by inducing osteoclast differentiation and inhibiting osteoblast maturation. Patients with chronic inflammation have multiple causes that lead to low bone mineral density, osteoporosis and a high risk of fracture including circulating cytokines, impaired mobility, chronic administration of glucocorticoids, low vitamin D levels and post-menopausal status in women, among others. Biologic agents and other therapeutic measures to reach prompt remission might ameliorate these deleterious effects. In many cases, bone acting agents need to be added to conventional treatment to reduce the risk of fractures and to preserve articular integrity and independency for daily living activities. A limited number of studies related to fractures in chronic arthritides were published, and future investigation is needed to determine the risk of fractures and the protective effects of different treatments to reduce this risk.

Keywords Rheumatoid arthritis · Inflammation · Bone · Osteoporosis · Fractures · Bone mass

Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune disease occurring more frequently in women. RA affects approximately 1% of the overall population and is characterized by persistent synovitis which causes destruction of the cartilage and bone, eventually leading to joints disability, deterioration in quality of life, lack of independence and labor capacity loss [1, 2].

The goal of management in chronic inflammatory arthropathies, is to control the disease activity, reduce symptoms, slow the progression of structural damage and

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Published online: 24 May 2023

whenever it's possible, prevent further complications as irreversible bone destruction. Loss of bone mineral density in the course of inflammatory arthropathy is a well-recognized phenomenon. Inflammation is associated with different deleterious outcomes affecting both bone and general health of the patient. The objective of this article is precisely to review the mechanisms involved in bone loss and the clinical and therapeutic implications that the clinician should consider as part of the comprehensive management of patients with inflammatory arthropathies, using rheumatoid arthritis as a model [3, 4]. Search strategy included key words such as: chronic arthritides, osteoporosis, fractures, chronic inflammation, low bone mineral density. We included meta-analysis, reviews, original series related to chronic arthritides, osteoporosis, fractures and low bone mineral density.

Pathophysiology of bone structural damage

Chronic inflammatory manifestations in RA are driven by a constellation of cytokines such as IL-1, IL-6, IL-17, IL-23 and tumor necrosis factor (TNF-α) released from the inflamed synovium that leads to enhanced osteoclastic activity. In adults, prior to menopause and aging, bone turnover is tightly coupled and, bone resorption and bone formation processes are balanced and in a state of equilibrium. In inflammatory joint diseases, this balance is lost and there is enhanced osteoclastic activity and decreased osteoblastic activity [5]. Also, there is often an inverse relationship between inflammatory activity levels and bone mineral density. Understanding this process provides a rational for therapeutic interventions [6, 7].

The bone remodeling cycle is a process in which there is activation of osteoclasts from precursors, resorption, a reversal and a bone formation phase mediated by osteoblasts. Bone mass is maintained in adults through repeated resorption of mature bone by osteoclasts and formation of new bone at site of resorption. This remodeling cycle is constant and replace approximately 10% of bone mass yearly in humans [8, 9].

Osteoclasts are essential mediators of bone resorption under physiological conditions. In the RA synovium there are immune cells with phenotypic features of osteoclasts included in resorption lacunae at the bone synovial interface. Both the pannus and the inflammatory synovium are sources of myeloid precursors and immunomodulatory and proinflammatory factors that stimulate osteoclastogenic activity. Macrophage lineage cells can differentiate into osteoclasts induced by factors produced in RA synovium particularly the receptor activator for nuclear factor κB ligand (RANK-L) and macrophage colony-stimulating factors (M-CSF). The synovium adjacent to the resorption sites has been shown to be an abundant source of RANK-L [5, 7, 10].

Another crucial player, that will be discussed later on is the Wnt system and its regulators. The Wnt system, and its inhibitors sclerostin (SOST) and Dickkopf-1 (DKK1), can precisely regulate the RANK-L/Osteoprotegerin (OPG) ratio, which, as we previously mentioned, is crucial for balancing bone resorption/apposition [11]. For instance, in multiple myeloma, the overproduction of DKK1 causes increased bone resorption and decreased bone formation [12]. (See Fig. 1) This makes DKK1 an exemplary regulator of bone turnover. Interestingly, changes in DKK1 levels have been linked to disturbances in the bone turnover coupling. In diseases such as multiple myeloma and rheumatoid arthritis,

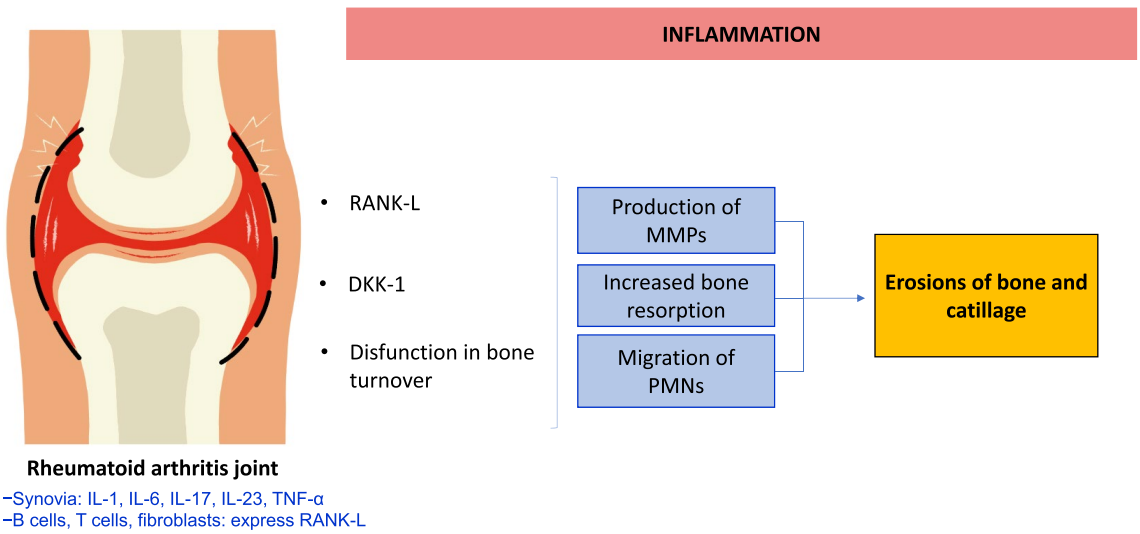

Fig. 1 Rheumatoid arhthritis and bone damage. *IL* interleukin, *RANK-L* receptor activator for nuclear factor κB ligand, *DKK-1* Dickkopf-1, *MMPs* metalloproteases, *PMN* polymorphonuclear cells

DKK1 is overexpressed, leading to bone destruction and erosions [2, 13, 14]. In contrast, in ankylosing spondylitis, diffuse idiopathic skeletal hyperostosis (DISH), and fibrodysplasia ossificans progressive, DKK1 serum levels are below average, causing uncontrolled apposition of calcified tissue in both skeletal and non-skeletal areas [15, 16]. It is worth noting that TNF-α, a crucial cytokine in the pathogenesis of bone loss in chronic arthritides, significantly increases DKK1 expression [17].

Several studies and publications highlighted the importance of therapeutic regimens (biologic and non-biologic agents) in patients with RA to control inflammation and ameliorates bone impairment. In patients with RA, lymphocytes T, B and synovial fibroblasts express RANK-L protein, RANK-L precursors and tartrate-resistant acid phosphatase (TRAP). Osteoblasts and RANK-L are required for osteoclasts differentiation and function. Denosumab 60 and 180 mg demonstrated to decrease modified Sharp erosion score with a significant inhibition of erosions at both doses at 12 months [3, 18–21]. Although the mechanism of bone impairment associated to RA is well known, it is still not always possible to prevent it, even with appropriate initial treatment. As a matter of fact, many patients with RA experience radiographic progression despite being in clinical remission. This unmet need of RA will be discussed forward in this paper.

Animal models and joint damage

Animal models have shown that blockade of osteoclasts represents a logical approach to prevent bone resorption in RA. RANK-L knockout mice have an absence of osteoclasts and despite marked synovial inflammation and pannus formation these mice do not develop significant bone erosions compared to control mice [22].

This fact highlights the concept that osteoclasts play an instrumental role in the pathogenesis of focal bone erosions in RA. In addition to increased resorption, there is a decreased bone formation at the erosion sites in active RA indicating uncoupled bone remodeling. Importantly, when joint inflammation is reduced by treatment, a partial restoration of bone formation may occur. Osteoblast differentiation involves both Wnt ligands and bone morphogenetic proteins (BMPs) to induce of bone formation. SOST and DKK1 are inhibitors of the classical canonical Wnt/β-Catenin signaling pathway, blocking the interaction between the receptor complex consisting of low-density lipoprotein receptor-related protein 5 and 6 (LRP5/6), Frizzled and Wnt, resulting in a degradation of β-Catenin and inhibition of bone formation. An antibody to SOST has been shown to increase bone mass in animal models and humans as well as fracture repair [4, 5, 7, 23].

Synovial fibroblasts are a very rich source of DKK1, and TNF-α is an important inducer [19, 24–26] Diarra et al. provided insights into the mechanism for the suppression of bone formation and repair in RA using animal models. They found inflamed synovial tissues in animals expressed high levels of DKK1. The author also showed that treating arthritic animals with anti-DKK1 antibody resulted in a marked inhibition in focal articular bone resorption. This effect was attributed to an increase in the production of OPG, a potent inhibitor of RANK-L [27].

Autoantibodies related to bone erosion

Two phases have been recognized in the pathogenesis of bone loss in patients with RA. An autoimmune phase induced by environmental factors such as smoking and environmental pollution [28]. During this phase patients may develop rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA) over 10 years before clinical manifestation of the disease [1]. Additionally, an inflammatory phase possibly induced by an infection or other environmental triggers may lead to a chronic inflammatory state that can affect multiple organs including bone [29].

RA patients have an increased fracture rate that includes both vertebral, non-vertebral and hip fractures due to not only trabecular but also cortical bone loss in RA patients [1]. Bone structure damage includes reduced trabecular bone volume, cortical bone thickness, increased cortical porosity and overall reduced volumetric BMD. Interestingly, these findings have been seen in ACPA-positive non arthritic individuals compared to ACPA-negative controls. Several observations support that bone metabolism is altered before the onset of clinical manifestations of RA. ACPA-positive patients are at risk for developing severe bone erosions with extensive resorption of the trabecular network. Bone loss is strongly associated with ACPA positivity in RA. Higher ACPA titers correlate with increased systemic osteopenia, suggesting that ACPA might contribute to bone loss either directly or increasing systemic inflammation [6]. Llorente et al. described that ACPA was associated with baseline bone mass independently of disease activity suggesting a direct effect of ACPA on bone [30]. This was further confirmed in patients without clinical signs of RA who displayed signs of bone loss in metacarpal bone [31].

Complexes of ACPA and RF induce robust cytokine production from human macrophages. TNF-α induces TRAP positive in the absence of RANK-L through the induction of the NF-kB pathway, TNF-α induces RANK expression by osteoclast precursors and TNF-α and RANK-L cooperate to induce osteoclast formation in a TNF receptor associated factor 6 (TRAF-6) independent pathway through TRAF-3 signaling. IL-6 is also a powerful molecule to induce

osteoclast differentiation. In aggregate ACPA titer has been shown to aggravate bone impairment with eventually the development of osteoporosis and fractures in patients with RA [32–36].

Other autoantibodies associated to bone damage

Some proteins resulting from posttranslational modified protein epitopes (PTM) are capable of triggering an autoimmune response in a healthy individual, through processes other than citrullination. Some examples are the autoantibodies against carbamylated protein (anti-CarP), acetylated proteins, malondialdehyde, malondialdehyde-acetaldehyde and other post-translated modified epitopes, which has gained more clinical interest in the last decade [37]. Anti-CarP are also associated with higher disease severity and increased bone erosion in RA subjects, although more research is needed to know the participating mechanisms [37–39].

A recent study evaluated the presence of anti-acetylated peptide antibodies (AAPA) in 531 patients with RA and other inflammatory diseases, and 99 healthy controls. The authors found that 60% and 68.7% of patients with early RA and stablished RA respectively presented AAPA positivity, while it was detected in 7.1–30.6% of patients with other inflammatory pathologies. AAPA was present in 40% of RA seronegative patients and in 22% of healthy controls were positive for AAPA. This demonstrates the highly prevalence of AAPA in RA independently of the presence of RF [40].

Fc gamma receptors family (FcγRs) possess four different classes known as FcγRI, FcγRIIB, FcγRIII and FcγRIV, that differ in their IgG binding capacity and downstream signaling pathways [41]. Osteoclasts share many features with macrophages and both express FcγR with FcγRI, FcγRIIB and FcγRIIIA being upregulated during human ex vivo osteoclastogenesis. This suggests that FcγR regulate osteoclastic activity and bone resorption. The positive effects of FcγR signaling on osteoclastogenesis suggest that autoantibodies or autoimmune complexes could directly enhance osteoclastic activity and osteoclast—mediated bone loss in patients with RA [1].

Affinity purified autoantibodies against citrullinated vimentin from RA patients, but not ACPA-depleted serum IgG were able to enhance osteoclastogenesis and bone resorption in ex vivo osteoclastogenesis assays [42]. This effect occurs on direct binding of autoantibodies to osteoclasts and their precursors resulting in the release of the pro-inflammatory cytokine TNF-α. Bone marrow edema in subchondral bone in RA predicts the development of bone erosions. Synovial inflammation induces bone loss by triggering an imbalance between bone resorption and formation. The synovial inflammatory tissue instructs T cells to produce M-CSF and RANK-L which induce osteoclastogenesis. RANK-L is highly expressed in the synovial membrane of patients with RA leading to osteoclastic differentiation and activation. Denosumab, a human RANKL monoclonal antibody, increases lumbar spine BMD and reduces vertebral and non-vertebral fracture rates in postmenopausal women with osteoporosis but also protects patients with RA from bone erosions by arresting osteoclastic formation and activation. TNF-α, IL-1β, IL-6 are involved in the osteoclastic activation leading to bone loss in RA and TNF-α blocks bone formation by production inhibition of osteoblast differentiation such as DKK1 and sclerostin in addition to enhance osteoclast differentiation. Therefore, blocking these cytokines can suppress bone erosions in addition to inhibit inflammation. IL-17 is one of the major drivers of RANK-L production by fibroblasts in the synovial pannus [7, 32]. Besides the direct action of autoantibodies on osteoclastogenesis, the release of inflammatory cytokines by macrophages upon antibody stimulation has been identified to enhance osteoclast differentiation and function. Lack of balance between pro and anti-inflammatory cytokine activities drives the induction of chronic inflammation and joint damage. Macrophages play an instrumental role in the cytokine production in the joints of patients with RA and are a major source for most of the main mediators of disease, such as TNF-α and IL-6 but also other cytokines involved in the disease process such as IL-1β, IL-8 and chemokine (C–C motif) ligand 2 (CCL2) [7].

Inflammation and bone impairment

During the last three decades, many studies have shown that besides the joint inflammation and destruction, bone mass and mineral density is lower in patients with RA when compared with healthy controls and the risks of osteoporosis and fractures are clearly increased [6, 43–45]. Most epidemiological studies provide a fracture risk increased by 1.5 to twofold among patients with RA compared to general population In the United States. Data from the National Data Bank for Rheumatic Diseases indicated that osteoporosis fractures are the third cause of mortality in RA [46, 47]. Compared to non-arthritic age matched group the risk of sustaining any clinical fracture in the RA group was 1.49 (1.26 vs. 1.75 $p < 0.001$). The risk of sustaining a hip fracture significantly increased in the RA group (2.03 vs. 4.51 ($p < 0.001$) [48].

Highly sensitive C-reactive protein (CRP) level is a predictor of the risk of fracture that is underlying the role of systemic inflammation. Studies of RA and fractures are listed in Table 1. Some studies showed alterations in bone mineral density, geometry and microarchitecture among

Table 1 Studies showing the relationship between chronic arthritides and bone involvement

Autor	Primary objective	Patients (*N*)	Intervention	Results	Conclusion
Huusko TM [70]	To evaluate the impact of RA on the incidence of hip fractures	Patients (517)	None	29 (5.6%; 95% CI 3.8 to 8.0) of the patients with hip fracture had RA. There were 15 (52%) cervical hip fractures and 14 (48%) trochanteric fractures among the patients with RA	Patients with RA are at increased risk of osteoporotic hip fractures
Cohen SB [20]	To evaluate the effects of Dmab on structural damage in patients with RA receiving MTX treatment	PBO (75) Dmab 60 mg (71) Dmab 180 mg (72)	PBO vs Dmab 60 mg and Dmab 180 mg for 6 months. Primary endpoint: change from baseline in the magnetic resonance imaging (MRI) erosion score at 6 months	At 6 months the increase in the MRI erosion score from baseline was lower in the 60 mg Dmab group (mean change 0.13; $p=0.118$) and significantly lower in the 180 mg Dmab group (mean change 0.06; $p=0.007$) than in the placebo group (mean change 1.75)	Addition of twice-yearly injections of Dmab to ongoing MTX treatment inhibited structural damage in patients with RA for up to 12 months, with no increase in the rates of adverse events as compared with placebo
Aeberli D [50]	To assess 3D bone geometry and density at the epiphysis and shaft of the third metacarpal bone of female RA patients in comparison to healthy controls using pQCT	RA patients (50) Controls (100)	None	RA patients had 12% to 19% lower trabecular BMD ($p\leq0.001$) at the distal epiphyses of radius, tibia and metacarpal bone. At the shafts of these bones (radius, tibia and metacarpal bone), RA patients had 7% to 16% thinner cortices ($p\leq0.03$). CSA at the metacarpal bone shaft of patients was larger (between 5 and 7%, $p<0.02$), and relative cortical area was reduced by 13%. Erosiveness by Ratingen score correlated negatively with trabecular and total BMD at the epiphyses and shaft cortical thickness of all measured bones ($p<0.04$)	Reduced trabecular BMD and thinner cortices at peripheral bones, and a greater bone shaft diameter at the metacarpal bone suggest RA specific bone alterations
Wright NC [48]	To examine the relationship between arthritis and fracture	Women were classified into 3 groups at baseline: Non-RA (83,295) OA (63,402) RA (960)	None	Compared to the non-arthritis group, the risk of sustaining any clinical fracture in the OA group was HR 1.09 (95% CI 1.05, 1.13; $p<0.001$) and HR 1.49 (95% CI 1.26, 1.75; $p<0.001$) in the RA group. The risk of sustaining a hip fracture was not statistically increased in the OA group (HR 1.11; 95% CI 0.98, 1.25; $p=0.122$) compared to the non-arthritis group; however, the risk of hip fracture increased significantly (HR 3.03; 95% CI 2.03, 4.51; $p<0.001$) in the RA group compared to the nonarthritic group	The increase in fracture risk confirms the importance of fracture prevention in patients with RA and OA

Table 1 (continued)

Autor	Primary objective	Patients (*N*)	Intervention	Results	Conclusion
Abdel Meguid MH [71]	To correlate IL-6 serum level with activity, severity, early development of OP, and early structural bone damage in RA patients	RA (40) Controls (20)	None	There was an inverse significant correlation between IL-6 and T-score ($r=-0.78$, $p=0.0001$). The low T-score was more marked in the group of patients receiving GC treatment, compared with group not on steroid therapy	Blocking IL-6 using IL-6 inhibitors and anti-RANK-L therapy may be effective in inhibiting the inflammatory process and preventing the bone complications of RA disease
Takeuchi T [18]	To evaluate efficacy and safety of three different regimens of Dmab on Japanese patients with RA	RA (350) receiving: Dmab 60 mg: every 6 months (Q6M:85) every 3 months (Q3M:82) every 2 months (Q2M:85) PBO (88)	Patients were randomly assigned to: Dmab 60 mg every 6 months (Q6M), every 3 months (Q3M) or every 2 months (Q2M) during 12 months compared with PBO	Dmab significantly inhibited the progression of bone erosion at 12 months compared with the PBO. The mean changes of the modified Sharp erosion score at 12 months from baseline were 0.99, 0.27 (compared with placebo, $p=0.0082$), 0.14 ($p=0.0036$) and 0.09 ($p<0.0001$) in the placebo, Q6M, Q3M and Q2M, respectively	Addition of Dmab to MTX has potential as a new therapeutic option for patients with RA with risk factors of joint destruction
Yue J [72]	To compare the bone healing effects of Dmab and ALE in female RA patients by HR-pQCT	Patients (40) Dmab 60 mg ALE 70 mg	Patients were randomized in a 1:1 ratio to receive either subcutaneous Dmab (60 mg) once or oral ALE (70 mg) weekly for 6 months	BMD of the erosion margin significantly increased only after treatment by Dmab (19.75 mg/cm^3; $p<0.05$) and 25.44 mg/cm^3; P 5 0.51 for ALE. $p<0.05$ for between-group differences. Width, depth, and volume of erosion significantly decreased in the Dmab group (20.23 mm, 20.16 mm, 20.91 mm^3, respectively; all $p<0.01$), whereas these parameters significantly increased in the ALE group (0.19 mm, 0.32 mm, and 1.38mm^3, respectively; all $p<0.01$; between-group differences, $p<0.01$ for all)	Dmab can induce partial repair of erosions in patients with RA, while erosions continued to progress in patients treated with ALE. Combining Dmab with DMARDs may be considered for RA patients with progressive bone erosions
Hasegawa T [73]	To elucidate the additional efficacy of Dmab used concomitantly with bDMARDs on suppressing radiological progression in RA	Dmab + bDMARDs (40) bDMARDs (40)	None	After 12 months, the increase in modified Sharp erosion scores was significantly less in the Dmab + bDMARDs group than in the bDMARDs group (0.16 vs 0.64, $p=0.038$	Compared with treatment by bDMARDs alone, concurrent use of Dmab and bDMARDs in RA patients was efficacious ininhibiting structural damage without increasing adverse events
Simon D [52]	To define normal sex- and age-dependent values of intra-articular bone mass and microstructures in the metacarpal heads of healthy individuals by HR-pQCT and test the effect of RA on these parameters	RA (106) Healthy controls (108)	None	RA patients showed significant ($p<0.001$) loss of intra-articular total (263.0 ± 44.8), trabecular (171.2 ± 35.6), and cortical bone (610.2 ± 62.0) compared with sex- and age-adjusted controls	Postmenopausal state and RA led to significant decrease of intra-articular bone

Table 1 (continued)

Autor	Primary objective	Patients (*N*)	Intervention	Results	Conclusion
Clynes M [74]	To investigate associations between RA, RA medications and BMD, falls and fractures, using UK Biobank data	RA (502,543) Women (3849) Men (1643) were found to have a diagnosis of RA	None	RA was associated with lower eBMD (men: $\beta -0.244$, 95% CI $-0.378, -0.110$ $p<0.001$; women: $\beta -0.217$, 95% CI $-0.297, -0.138$ $p<0.001$) and a reported fall in the last year (men: OR 1.54, 95% CI 1.26, 1.87 $p<0.001$; women:OR 1.36, 95% CI 1.19, 1.56 $p<0.001$) and fracture in women (OR 1.76, 95% CI 1.43, 2.16 $p<0.001$). GC therapy in men ($\beta -0.934$, 95% CI $-1.565, -0.304$ $p=0.004$) and DMARD use in both sexes (men: $\beta -0.437$, 95% CI $-0.761, -0.112$ $p=0.008$; women: $\beta -0.243$, 95% CI $-0.421, -0.065$ $p=0.007$), but not biologic therapy, were associated with a lower eBMD with RA	RA was associated with lower eBMD, increased falls and fracture. GC and DMARD therapy, but not biologic therapy, were associated with lower eBMD
Hong WJ [75]	To examine the incidence rate and risk factors of osteoporotic vertebral fracture in RA patients with new-onset CVD and evaluate the effects of medications on such fracture risk	RA total patients (30,505) CVD (1267) Non-CVD (1267)	None	The aHR of developing osteoporotic vertebral fracture was 1.47-fold greater in CVD group than in non-CVD group (95% confidence interval 1.19–1.81, $p<0.001$). Both the age > 40 years and female gender were significant risk factors for developing osteoporotic vertebral fracture in CVD patients. Using patients not taking medication as a reference group, the aHR of osteoporotic vertebral fracture was significantly lower in those receiving statins (0.50), low-dose GC (0.57), or HCQ (0.12)	The risk of osteoporotic vertebral fracture was significantly increased in RA-CVD patients, particularly women above 40 years of age, and could be reduced by statin therapy. However, the protective effect of low-dose GC or HCQ on osteoporotic vertebral fracture risk needs further validation

Table 1 (continued)

Autor	Primary objective	Patients (*N*)	Intervention	Results	Conclusion
Jin S [51]	To evaluate bone microarchitecture, geometry, and volumetric BMD among patients with RA in mainland China using HRpQCT	RA (81) Healthy controls (81)	None	Trabecular area at distal radius showed a positive correlation with disease duration ($p=0.012$) and functional disability ($p=0.044$), while ever use of HCQ had negative association with it ($p=0.028$). At distal tibia, trabecular area was correlated with advanced age ($p=0.004$). The cortical area was negatively correlated with advanced age and low BMI at both sites. Trabecular vBMD at the distal radius was negatively related to advanced age ($p=0.010$), female sex ($p=0.005$), low BMI ($p=0.009$), and disease duration ($p=0.010$). Cortical vBMD was negatively associated with age ($p<0.001$), disease duration ($p=0.001$), and activity ($p=0.049$). Treatment with HCQ was associated with higher total vBMD at both bone sites. Patients with RA had significantly larger total and trabecular bone area, increased cortical bone perimeter, and lower total and cortical vBMD at the distal radius. They also had lower total vBMD and thinner cortical bone at the distal tibia Current treatment with GCs was correlated with decreased cortical vBMD and higher porosity at both bone sites. They also had decreased trabecular number, increased trabecular separation, and inhomogeneity at distal tibia. No correlations were observed with regards to dose or duration of GC	Patients with RA have reduced BDM and impaired microarchitecture in both trabecular and cortical bone compared with healthy individuals. Alterations at the distal tibia and distal radius were similar, supporting the systemic influences of RA on the bone. Traditional risk factors for OP as well as RA-related factors are correlated with bone impairment. Patients with fragility fractures have more severely compromised bone parameters than those without

RA Rheumatoid arthritis, *PBO* placebo, *Dmab* denosumab, *MRI* magnetic resonance imaging, *BMD* bone mineral density, *CSA* total cross-sectional area, *OA* osteoarthritis, *IL-6* interleukin-6, *OP* osteoporosis, *GC* glucocorticoid, *ALE* alendronate, *HR-pQCT* high-resolution peripheral quantitative computed tomography, *bDMARDs*: biological disease-modifying antirheumatic drugs, *eBMD* estimated bone mineral density, *CVD* cardiovascular disease, *aHR* adjusted hazard ratio, *HCQ* hydroxychloroquine

Table 1 was adapted from references [18, 20, 48, 50, 51, 70–75]

patients with RA compared to healthy individuals which may impair bone strength and lead to increased risk of fractures. Compared with controls, patients with RA had significantly larger bone area and lower total and trabecular vBMD at both distal radius and tibia. Lower cortical bone thickness was also shown at distal tibia assessed by HRpQCT techniques [49, 50] (See Table 1).

Compared to patients with RA and without fractures, patients with fragility fractures showed lower trabecular and cortical vBMD, thinner cortical bone, impaired trabecular microstructure and a trend of declined bone strength. Advanced age, low BMI, female sex, disease duration and activity were associated with decreased vBMD and impaired microstructure [51].

Simon et al. performed a cross sectional study to define normal sex and age dependent values of intra articular bone mass and microstructure in the metacarpal heads of healthy individuals by HR-pQCT and the effect of RA on these parameters. Human cadaveric metacarpal heads were used to define intra articular bone. Total, cortical and trabecular bone densities as well as microstructural parameters were compared between the different ages and sexes in healthy individuals and between metacarpal heads, the radius and between healthy individuals and RA patients [52].

This cadaveric study allowed exact definition of the intraarticular and intracapsular bone margins. These data were applied in measuring intra-articular and radial bone parameters in 214 women and men (108 healthy controls, 106 RA patients). Correlations between intra-articular and radial bone parameters were good ($r = 0.51$ to 0.62, $p < 0.001$). In contrast to radial bone, intra-articular bone remained stable until 60 years of age (between 297 and 312 mg HA/cm^3) but decrease significantly ($p < 0.001$) in women thereafter (237.5 ± 44.3) with loss of both cortical and trabecular bone. RA patients showed significant ($p < 0.001$) loss of intra-articular total (263 ± 44.8), trabecular (171.2 ± 35.6) and cortical bone (610.2 ± 62) compared with sex and aged- adjusted controls [52].

Pathological bone metabolism in RA

The incidence of osteoporosis in patients with RA is approximately twice as high as that of the general population of similar age. RA patients have a 1.3-fold increased risk of femoral fractures and 2.4-fold increased risk of spinal fractures [43, 45, 53, 54]. Osteoporosis is a comorbidity found in 40–50% of patients with RA. Factors contributing to this high incidence are: postmenopausal status, inflammation, high levels of proinflammatory cytokines produced by pannus, deteriorated cortical bone quality, impaired mobility, GC, nutritional deficiency and low vitamin D levels [55].

The prevalence of vertebral fractures ranges from 8 to 50%; the risk of fracture, despite the site, is always higher in RA patients than in the general population. In a large case–control study of 30,262 patients with RA, using the British General Practice Research Database, the increased risk of fracture compared to the general population was most marked at the hip (RR: 2.0, 95% CI 1.8–2.3) and spine (RR: 2.4, 95% CI 2.0–2.8) [6, 56].

In the Women's Health Initiative prospective study (WHI) the risk of sustaining any clinical fracture comprising self-reported spinal fracture in the RA group was 1.49 (1.26, 1.75) when compared to the non- arthritis group ($p < 0.001$) [46, 48]. Moreover, the risk of sustaining a hip fracture significantly increased in the RA group (3.03, 2.03, 4.51) ($p < 0.001$) [48]. A Canadian nested-case control study conducted using Quebec physician billing and hospital discharge data found that the incidence rate of non-vertebral osteoporotic fractures is 11/1000 person-years in the population of RA patients aged 50 years and more [46]. In another large study conducted based on a health database on both sexes aged more than 18 years comparing 92,827 RA to 921,715 non-RA controls, the incidence rate of fracture at any of the four sites (wrist, humerus, hip and pelvis) among RA patients was 9.6 per 1000 person-years and 1.5 times higher than that of non-RA patients (6.3 per 1000 person-years) particularly in those patients receiving GC [46].

Epidemiological studies on the frequency of fractures in RA populations can be observational, case-controlled, conducted on databases or prospective. Most of them provide a fracture risk increased by 1.5 to 2.0-fold among patients with RA compared to the general population [6, 44–46]. Patients with RA are at high risk of vertebral fractures. However, the prevalence of spine fractures varies according to the population included (age, women alone or both sexes, etc.), the way to assess fractures (VFA of Rx) and the source of data (cohort, registry, randomized trial).

Risk factors independent from inflammation

Many patients with RA receive GC during flares. It is well known that GC suppresses osteogenesis through initiation of apoptosis of osteoblasts, inhibition of Wnt signaling pathways and regulation of microRNA expression in osteoblasts and osteocytes. On the other hand, excessive GC also suppress the OPG expression and promote bone resorption [7, 57]. Fracture incidence in RA patients exposed to GC is twice as it is among non-exposed patients. However, some controversy still remains on the true harmfulness of short-term, and low dose treatment with GC in active RA. These controversies are based on the established benefits of GC in controlling disease activity, improving mobility, that may counterbalance the deleterious effects on GC on bone. So

far, the most disseminated FRAX version is not able to discriminate between long and short-term users or between high and low GC doses. For this reason, in some national guidelines FRAX is not included to stratify patients' risk and in others is included only in the GC dose adjusted version [58–60].

In a large cross-sectional study including patients previously or currently exposed to GC at doses ≤ 5 mg/day of prednisone did not seem to be associated with negative effects on bone mineral density. Higher daily GC dosages lost their negative association with BMD after adjustment for confounding factors. In patients with RA GC doses > 7.5 mg daily seemed to be negatively associated with BMD only in combination with moderate or high disease activity. GC should be used in an optimum dose with both benefit and harm in mind to achieve remission and to support bone health in patients with chronic inflammatory rheumatic diseases [61].

Another risk factor to take into account is the concomitant use of proton pump inhibitors (PPIs), which are the most commonly prescribed medication for patients with RA along with GC [62]. In 2010, the FDA issued a warning about the potential risk of fracture associated to PPI's consumption, this warning was updated in 2011 [63]. The potential side effects of these drugs on bone health have been evaluated in the last years, and it's believed that the hypochlorhydria induced by the PPIs mechanism of action impairs calcium solubility and decrease its absorption, leading to secondary hyperparathyroidism and bone resorption. This impairs bone mineral density and increases the risk of fractures [64].

Abtahi et al. evaluated the association between concomitant use of oral GC and PPIs and the risk of osteoporotic fractures in 12,351 patients with RA. This study found that concomitant intake of oral GC and PPIs was associated with a 1.6-fold increased risk of osteoporotic fractures compared with non-use (adjusted HR: 1.60, 95% CI 1.35 to 1.89). In patients taking GC or PPI alone, there was a statistically difference from a 1.2-fold increased osteoporotic fracture risk associated [62].

Hypomagnesaemia is another effect well described in literature, which may cause an imbalance between osteoblastic and osteoclastic differentiation enhanced by the activity of the nitric oxide, reducing osteoblastic activity. Magnesium is also a cofactor for vitamin D-intermediates hydroxylation pathways and the lacking of this mineral might impair PTH secretion making organs as kidney and bone resistant to its action [65].

Hinson et al. found that chronic PPIs exposure was associated with mild hyperparathyroidism in elderly adults. Chronic PPI exposure was associated with statistically significantly higher PTH levels (65.5 vs. 30.3 pg/mL, $p < 0.001$; normal range 10–55 pg/mL) regardless of concurrent use of oral bisphosphonates [66].

Effects of RA treatment on bone metabolism and risks of fracture

Inflammatory cytokines such as TNF-α and IL-6 promote RANK-L expression in the synovial tissue in RA. RANK-L-independent osteoclast-like cells induced by TNF-α and IL-6 under RA condition have been found. Besides, TNF-α increases the expression of DKK1 which inhibits osteogenesis. These facts suggest that the treatment of RA with biological agents (bDMARD) and janus kinase (JAK) inhibitors have protective effects on bone metabolism [2, 32]. However, a recently published post hoc analysis from the ORAL surveillance study found that tofacitinib treatment (10 mg bid) was associated with a higher incidence of fragility fractures compared to TNF inhibitors [67]. Such result has been corroborated by another study that analyzed the World Health Organization (WHO) pharmacovigilance database and found a disproportion on the osteoporosis related adverse events reports for tofacitinib [68]. Nonetheless, Pawar and colleagued compared the risk of non-vertebral fractures risk among patients treated with tsDMARDs and bDMARDs and found no incremental risk in the latter population [69]. More studies related to biologic agents and fracture reduction in patients with RA are warranted.

Final remarks

Chronic rheumatic diseases include a wide spectrum of inflammatory conditions characterized by destruction of several skeletal structures. Bone tissue is commonly involved in many rheumatic diseases and osteoporosis and fractures are the most frequent disease and complications. Physicians should be aware of the increased risk of developing osteoporosis in these patients. These effects are induced by a constellation of cytokines produced by pannus and may be moderated using appropriate treatments such as biologic agents and antiosteoporotic drugs as bisphosphonates, denosumab and teriparatide.

Chronic administration of steroids at doses higher than 5 mg for more than 3 months imposes a greater risk to develop osteoporosis. It is very important to ensure an adequate calcium intake, keeping levels of vitamin D above 30 ng/mL and reaching remission of the arthritis as soon as possible, to maintain independence in activities of daily living and mobility. Finally, sarcopenia should be considered and avoided by performing active exercises programs.

Funding This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Declarations

Conflict of interest The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Statement of human and animal rights This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent For this type of study, formal consent is not required.

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