arthritis research&therapy

REVIEW

Osteoimmunology and osteoporosis

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Abstract

The concept of osteoimmunology is based on growing insight into the links between the immune system and bone at the anatomical, vascular, cellular, and molecular levels. In both rheumatoid arthritis (RA) and ankylosing spondylitis (AS), bone is a target of inflammation. Activated immune cells at sites of inflammation produce a wide spectrum of cytokines in favor of increased bone resorption in RA and AS, resulting in bone erosions, osteitis, and peri-inflammatory and systemic bone loss. Peri-inflammatory bone formation is impaired in RA, resulting in non-healing of erosions, and this allows a local vicious circle of inflammation between synovitis, osteitis, and local bone loss. In contrast, peri-inflammatory bone formation is increased in AS, resulting in healing of erosions, ossifying enthesitis, and potential ankylosis of sacroiliac joints and intervertebral connections, and this changes the biomechanical competence of the spine. These changes in bone remodeling and structure contribute to the increased risk of vertebral fractures (in RA and AS) and non-vertebral fractures (in RA), and this risk is related to severity of disease and is independent of and superimposed on background fracture risk. Identifying patients who have RA and AS and are at high fracture risk and considering fracture prevention are, therefore, advocated in guidelines. Local peri-inflammatory bone loss and osteitis occur early and precede and predict erosive bone destruction in RA and AS and syndesmophytes in AS, which can occur despite clinically detectable inflammation (the so-called 'disconnection'). With the availability of new techniques to evaluate peri-inflammatory bone loss, osteitis, and erosions, peri-inflammatory bone changes are an exciting field for further research in the context of osteoimmunology.

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Introduction

The concept of osteoimmunology emerged more than a decade ago and is based on rapidly growing insight into the functional interdependence between the immune system and bone at the anatomical, vascular, cellular, and molecular levels [1]. In 1997, the receptor activator of the nuclear factor-kappa-B ligand (RANKL)/RANK/osteoprotegerin (OPG) pathway was identified as a crucial molecular pathway of the coupling between osteoblasts and osteoclasts [2]. It appeared that not only osteoblasts but also activated T lymphocytes, which play a crucial role in the pathogenesis of rheumatoid arthritis (RA), and many other inflammatory cells can produce RANKL, which stimulates the differentiation and activation of osteoclasts [3]. These findings have contributed to the birth of osteoimmunology as a discipline.

Because of the multiple interconnections and interactions of bone and the immune system, bone is a major target of chronic inflammation in RA and ankylosing spondylitis (AS). Inflammation increases bone resorption and results in suppressed local bone formation in RA and locally increased bone formation in AS, causing a wide spectrum of bone involvement in RA and AS [4,5].

Osteoporosis has been defined as a bone mineral density (BMD) of lower than 2.5 standard deviations of healthy young adults and in daily practice is measured by dual-energy x-ray absorptiometry (DXA) at the spine and hip [6]. However, the bone disease component in RA and AS is much more complex, especially around the sites of inflammation. We reviewed the literature on the quantification of local and general bone changes and their relation to the structural damage of bone, disease activity parameters, and fracture risk in the context of osteoimmunology, both in RA and AS. We have chosen to focus on RA and AS since these inflammatory rheumatic diseases have the highest prevalence and since, in both diseases, characteristic but different types of bone involvement may occur.

Anatomical and molecular cross-talk between bone and the immune system

Multiple anatomical and vascular contacts and overlapping and interacting cellular and molecular mechanisms are involved in the regulation of bone turnover and the immune system, so that one can no longer view either

system in isolation but should consider bone and the immune system to be an integrated whole [4,5].

Anatomical connections

Bone, by virtue of its anatomy and vascularization, is at the inside and outside and is in direct and indirect and in close and distant contact with the immune system. At the inside, bones are the host for hematopoiesis, allowing bone and immune cells to cooperate locally. At the outside, bone is in direct contact with the periost, the synovial entheses within the joints at the periost- and cartilage-free bare area [7], the fibrous tendon entheses, the calcified component of cartilage and tendon insertions, and the intervertebral discs.

Until recently, it was thought, on the basis of plain radiographs of the hands, that there is only rarely a direct anatomical connection between bone marrow and joint space. Bone erosions have been found in hand joints of presumably healthy controls in less than 1% with plain radiology and in 2% with MRI [8]. However, exciting new data have shown that, with the use of high-resolution quantitative computer tomography (HRqCT), small erosions (<1.9 mm) in the metacarpophalangeal (MCP) joints can be found in 37% of healthy subjects without any signs or symptoms of RA, indicating that small erosions are not specific for RA [9]. Large erosions (>1.9 mm) were found to be specific for RA. Interestingly, 58% of erosions detected by HRqCT in healthy volunteers were not visible on plain radiographs [9]. In healthy controls, the erosions in the MCP joints were not randomly located but were located at the bare area and at high-pressure points adjacent to ligaments, which are erosion-prone sites in RA [10]. Bone erosions are also extremely common in healthy controls in the entheses [11] and in the vertebral cortices covered by periost and the intervertebral discs (in AS) [12]. The immune system, bone, and its internal and external surfaces not only are connected by these local anatomical connections but also are connected with the general circulation by the main bone nutrition arteries and locally with the periost (by its vasculature that perforates cortical bone) and within the bone compartment by attachments of fibrous entheses and the calcified components of cartilage and fibrocartilage up to the tidemark, which separates calcified from non-calcified components of cartilage and tendons [11].

Molecular connections

Bone cells exert major effects on the immune system. Bone cells interact with immune cells and play an essential role in the development of the bone marrow space during growth [13] and during fracture healing [14]. Osteoblasts play a central role in the regulation of renewal and differentiation of hematopoietic stem cells (HSCs) and of B cells in niches near the endosteum [15-17]. Metabolic pathways of the osteoblast which are involved in bone remodeling are also involved in the regulation of HSCs by osteoblasts, such as the calcium receptor, parathyroid hormone (PTH), bone morphogenetic proteins (BMPs), the Wnt signaling, and cell-cell interactions by the NOTCH (Notch homolog, translocation-associated (Drosophila)) signaling pathway [15-19]. On the other hand, multiple cytokines, chemokines, and growth factors of immune cells such as T and B cells, fibroblasts, dendritic cells, and macrophages directly or indirectly regulate osteoblast and osteoclast activity by producing or influencing the production of the RANKL/RANK/OPG pathway, tumor necrosis factor-alpha (TNFα), interferon-gamma (IFNγ), and interleukins (such as IL-1, IL-6, IL-15, IL-17, IL-18, and IL-23) and the Wnt signaling with involvement of Dikkoppf (DKK), sclerostin, and BMP [4,5,19-21].

In RA, bone loss and bone destruction are dependent on the imbalance between osteoclastogenic and anti-osteoclastogenic factors. T-cell infiltration in the synovium is a hallmark of RA. TH17 cells, whose induction is regulated by dendritic cells that produce transforming growth factor-beta, IL-6, and IL-23, secrete IL-17, which induces RANKL in fibroblasts and activates synovial macrophages to secrete TNFα, IL-1, and IL-6, which directly or indirectly (via fibroblasts producing RANKL) activate osteoclastogenesis [1]. Other direct or indirect osteoclastogenic factors include monocyte/macrophage colony-stimulating factor, IL-11, IL-15, oncostatin M, leukemia inhibitor factor, and prostaglandins of the E series (PGE) [22-24]. Inhibitors of osteoclastogenesis in RA include TH1 (producing IFNγ) and TH2 (producing IL-4) cells and possibly T helper regulatory (THREG) cells [1].

In AS, increased bone formation, as reflected by syndesmophyte formation in the spine, is related to decreased serum levels of DKK [25] and sclerostin [21], both inhibitors of bone formation, and to serum levels of BMP, which is essential for enchondral bone formation [26], and of CTX-II [27], which reflects cartilage destruction that occurs during enchondral bone formation in syndesmophytes [26-28]. There is, thus, increasing evidence that immune cells and cytokines are critically responsible for the changes in bone resorption and formation and vice versa, resulting in changes in bone quality in chronic inflammatory conditions. These conditions include RA, spondylarthopathies (SpAs) (AS, psoriatic arthritis, and inflammatory bowel disease), systemic lupus erythematosis, juvenile RA, periodontal diseases, and even postmenopausal osteoporosis [29]. We reviewed the literature on the quantification of bone involvement in RA and AS. For an in-depth discussion of the underlying metabolic pathways, a topic that is beyond

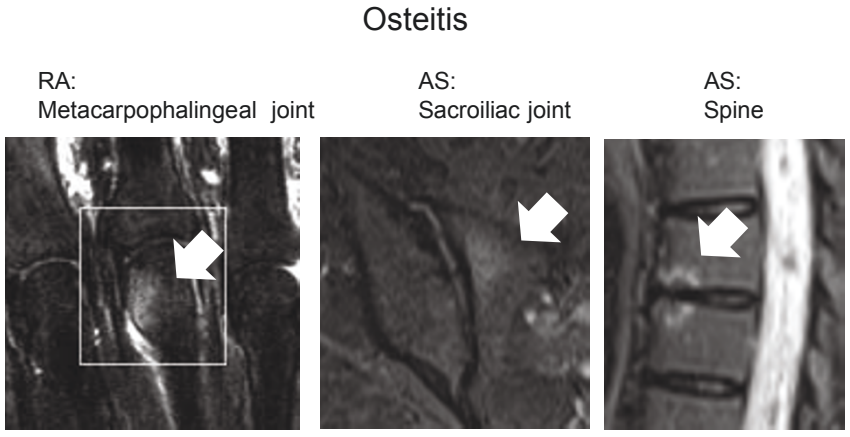

Figure 1. Osteitis in rheumatoid arthritis (RA) (in metacarpophalangeal joint) and in ankylosing spondylitis (AS) (in the sacroiliac joint and in vertebra).

the scope of this review, the reader is referred to other reviews [4,5].

Histology of bone in rheumatoid arthritis and ankylosing spondylitis

Bone resorption

Bone resorption is increased in RA and AS. In RA, this has been demonstrated histologically by the presence of activated osteoclasts in the pannus at the site of bone erosions [30,31], in the periarticular trabecular and cortical bone [32,33], and, in a general way, in sites distant from inflammation [34]. In AS, osteoclastic bone resorption has been demonstrated in the sacroiliac joints [35-37].

The introduction of MRI has shed new light on the involvement of subchondral bone and bone marrow in RA and AS (Figure 1). Periarticular MRI lesions have been described technically as bone edema (on short T inversion recovery (STIR), indicating that fatty bone marrow is replaced by fluid) and osteitis (on T1 after IV gadolinium) [38] and histologically as osteitis as inflammation has been demonstrated on histological examination of these lesions [33]. In joint specimens of patients with RA and with MRI signs of bone edema, histological correlates have been studied in specimens obtained at the time of joint replacement and have shown the presence of greater numbers of osteoclasts than in controls and in patients with osteoarthritis and the presence of T cells, B-cell follicles, plasma cells, macrophages, decreased trabecular bone density, and increased RANKL expression [33].

Osteitis is also a major component of AS [39-42]. Osteitis was described by histology of the vertebrae in 1956 [43] and occurs early in the disease and predicts the occurrence of bone erosions [39]. It has been shown that, as in RA, these lesions contain activated immune cells and osteoclasts [44,45]. In contrast to RA, these lesions differ in their location: in the vertebrae, the entheses, the periost of vertebrae and around the joints, the disco-vertebral connections, the intervertebral joints and the sacroiliac joints, and, to a lesser degree, the peripheral joints, mainly hips and shoulders (Figure 1) [46,47].

Bone formation

In spite of the presence of cells with early markers of osteoblasts in and around erosions in RA, bone formation is locally suppressed [48]. This uncoupling of bone resorption and bone formation contributes to the only rare occurrence of healing bone erosions [49] and results in persisting direct local connections between the joint cavity and subchondral bone and thus between synovitis and osteitis. In contrast, in AS, local peri-inflammatory bone formation is increased, resulting in healing of erosions, ossifying enthesitis, and potential ankylosis of sacroiliac joints and of intervertebral connections. The ossification of entheses and sacroiliac joints involves calcification of the fibrocartilage, followed by enchondral bone formation; that is, calcified cartilage is replaced by bone through osteoclastic resorption of calcified cartilage and deposition of bone layers on the inside of the resorption cavity with a very slow evolution and with prolonged periods of arrest [50].

Bone biomarkers

In patients with RA, markers of bone resorption are increased in comparison with controls [51]. Correlations between bone markers, bone erosions, and bone loss in RA varied according to study designs (cross-sectional or longitudinal), patient selection, and study endpoints (disease activity score, radiology, and MRI) [52]. Baseline markers of bone and cartilage breakdown (CTX-I and CTX-II) and the RANKL/OPG ratio were related to

short- and long-term (up to 11 years for RANKL/OPG) progression of joint damage in RA, independently of other risk factors of bone erosions [53,54]. Increased markers of bone resorption were related to increased fracture risk [49]. Studies on markers of bone formation in RA, such as osteocalcin, are scarce and show contradictory results, except low serum values in glucocorticoid (GC) users [55,56].

In AS, markers of bone resorption were increased [27,57] and were related to inflammation as measured by serum IL-6 [58]. Increased serum levels of RANKL have been reported [59] with decreased OPG [60,61], and RANKL expression is increased in peripheral arthritis of SpA [62]. Markers of bone formation (type I collagen N-terminal propeptide, or PINP) were related to age, disease duration, and markers of bone resorption (CTX-I) but not with low BMD in the hip or spine [63]. Markers of cartilage breakdown (CTX-II) were related to progression of the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) and the appearance of syndesmophytes [27].

Imaging of bone in rheumatoid arthritis and ankylosing spondylitis

Many methods, including histomorphometry, imaging (Figure 2), and biomarkers, have been used to study the effect of inflammation on structural and functional aspects of bone in RA and AS. Conventional radiology of the peripheral joints and the spine is used for identifying erosions, joint space narrowing, enthesitis, and syndesmophytes for diagnosis; assessment of disease progression; and standardized scoring in clinical trials, but it is estimated that bone loss of less than 20% to 40% cannot be detected on plain radiographs [64].

Methods that quantify changes in periarticular bone include radiogrammetry, digitalized radiogrammetry (DXR) [65], peripheral dual-energy x-ray absorptiometry (pDXA) [66], quantitative ultrasound (QUS) [67], high-resolution digital radiography [68], high-resolution peripheral qCT [9], and MRI [8], and methods that quantify changes in the vertebrae include DXA, qCT, MRI, and morphometry by vertebral fracture assessment on x-rays or DXA images [69] (Figure 2). At other sites of the skeleton, single x-ray absorptiometry, qCT, MRI, DXA, and QUS are available; of these, DXA is considered the gold standard [70]. Semiquantitative scoring of osteitis on MRI in the vertebrae has been standardized [40,42,71]. Local peri-inflammatory bone formation can be evaluated semiquantitatively in a standardized way on radiographs for scoring of syndesmophytes [41,42,72]. These techniques differ in regions of interest that can be measured, in the ability to measure cortical and trabecular bone separately or in combination, and in radiation dose, cost, and precision [64,73] (Table 1).

Periarticular bone loss and osteitis in rheumatoid arthritis

On plain radiographs of the hands, periarticular trabecular bone loss results in diffuse or spotty demineralization and blurred or glassy bone and cortical bone loss in tunneling, lamellation, or striation of cortical bone [74] (Figure 3). Quantification of bone in the hands has consistently shown that patients with RA have lower BMD than controls and lose bone during follow-up, depending on treatment (see below) [75-77]. Cortical bone loss occurs early in the disease, preferentially around affected joints and before generalized osteoporosis can be detected [51,78]. In studies using peripheral qCT at the forearm, trabecular bone loss was more prominent than cortical bone loss in RA patients using GCs [79,80].

Hand bone loss is a sensitive outcome marker for radiological progression. The 1-year hand bone loss measured by DXR predicted the 5- and 10-year occurrence of erosions in RA [73,81] and was a useful predictor of the bone destruction in patients with early unclassified polyarthritis [82]. Hand bone loss measured by DXR correlated with C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), disease activity score using 28 joint counts (DAS28), the presence of rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibody (anti-CCP), health assessment questionnaire (HAQ) score, disease duration, and Sharp score [66,83,84]. In the forearm and calcaneus, trabecular but not cortical periarticular bone loss measured by DXA in early RA correlated with ESR, CRP, RF, and HAQ score [80]. DXR correlated with hip BMD and the presence of morphometric vertebral fractures and non-vertebral fractures in RA [85]. DXR-BMD performed as well as other peripheral BMD measurements for prediction of wrist, hip, and vertebral fractures in the Study of Osteoporotic Fractures [86].

Periarticular osteitis is a frequent finding in RA (45% to 64% of patients with RA) and has remarkable similarities with periarticular bone loss in RA (Figure 1) [87]. Osteitis is found early in the disease process, is predictive of radiographic damage, including erosions and joint space narrowing, SF-36 (short-form 36-question health survey) score function, and tendon function, and is related to clinical parameters CRP and IL-6 in early RA and to painful and aggressive disease [87-94]. Scoring of MRI edema has been standardized by OMERACT (Outcome Measures in Rheumatoid Arthritis Clinical Trials) [88]. Osteitis is characterized by trabecular bone loss on histology [66,84-96], but no studies on the relation between osteitis and quantification of bone loss were found.

Generalized bone loss in rheumatoid arthritis

BMD is a major determinant of the risk of fractures, but the relationship between BMD and fracture risk is less

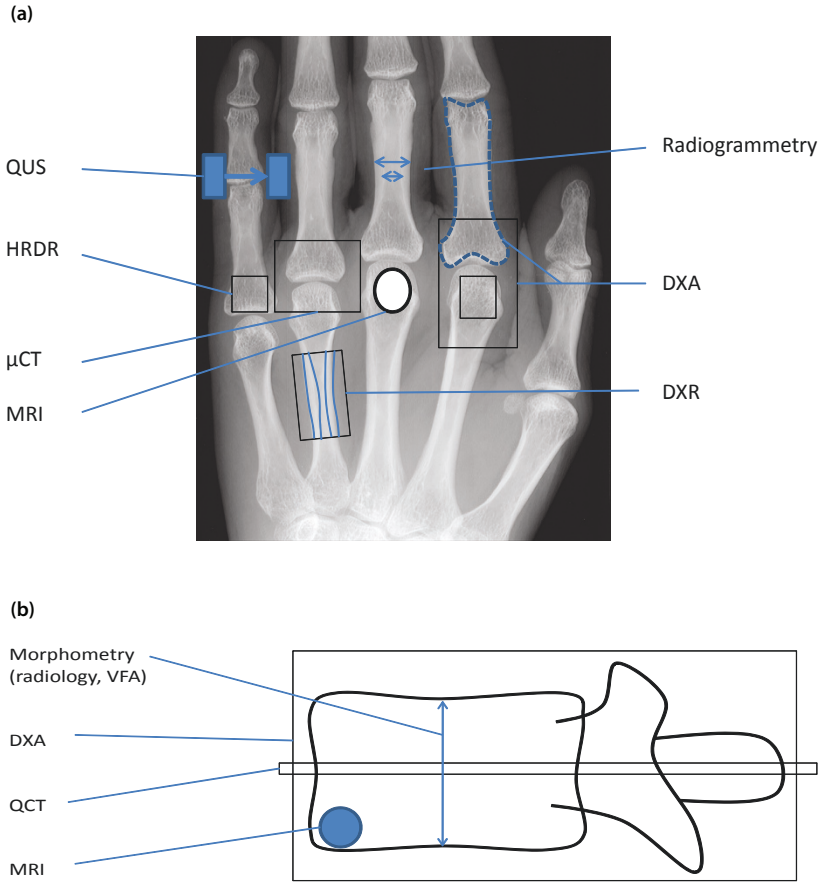

Figure 2. Methods to quantify bone changes in the hands and vertebrae. (a) Methods to quantify periarticular bone changes. **(b)** Methods to quantify vertebral bone changes. µCT, micro-computed tomography; DXA, dual-energy x-ray absorptiometry; DXR, digitalized radiogrammetry; HRDR, high-resolution digital radiology; MRI, magnetic resonance imaging; QCT, quantitative computer tomography; QUS, quantitative ultrasound; VFA, vertebral fracture assessment.

clear in RA than in postmenopausal osteoporosis, indicating that factors other than those captured by measuring BMD are involved in the pathophysiology of fractures in RA.

Patients with RA have a decreased BMD in the spine and hip and consequently have a higher prevalence of osteoporosis [56,97-101]. However, this was not confirmed in the Canadian Multicentre Osteoporosis Study (CaMos) [102]. In early untreated RA, BMD was related to longer symptom duration, the presence of RF [103] and anti-CCP [104], disease activity score [105], and the presence and progression of joint damage [106].

The interpretation of longitudinal changes in RA is complicated by the lack of untreated patients, and this limits our insights into the natural evolution of bone changes in RA to the above-mentioned studies. In one study with early untreated RA, bone loss was found in the spine and trochanter for a period of one year [107]. However, Kroot and colleagues [108] did not find bone loss over the course of a 10-year follow-up in RA patients treated with disease-modifying antirheumatic drugs, except when these patients were treated with GCs. Generalized bone loss was related to joint damage in some studies [109,110], but this relation disappeared after multivariate adjustment [111]. No correlation between BMD and the presence of vertebral fractures in RA patients treated with GCs was found [112].

Fracture risk in rheumatoid arthritis

In the largest epidemiological study, patients with RA were at increased risk for fractures of osteoporotic fractures (relative risk (RR) 1.5), fractures of the hip (RR 2.0), clinical vertebral fractures (RR 2.4), and fractures of the pelvis (RR 2.2) [113]. The risk of morphometric vertebral fractures was also increased [114,115]. In some but not all studies, the risk of fractures of the humerus (RR 1.9), wrist (RR 1.2), and tibia/fibula (RR 1.3) was increased [75,116,117].

The etiology of increased fracture risk in RA is multifactorial and superimposed on and independent of

Table 1. Techniques to assess hand bone damage in rheumatoid arthritis

	Studied features	Advantages	Disadvantages
CR	Bone erosion	Gold standard	Low sensibility
	Joint space narrowing	Easy accessibility Low cost High specificity	No evaluation of bone density Ionizing radiation
MRI	Bone erosion	Early detection of bone erosions	Expensive
	Bone edema	Prediction of erosive progression	Uncomfortable
	Synovitis	Monitoring bone change	No evaluation of bone density
	Tenosynovitis	Measurement of erosion volume Absence of radiation exposure	
CT	Bone erosion	High resolution	No evaluation of bone density, synovitis, and bone edema Ionizing radiation
US	Bone erosion	Non-invasiveness	No evaluation of bone edema
	Synovitis	Easy accessibility	Sensibility depending on joint accessibility
	Tenosynovitis	Low cost	
	Bone density	Monitoring bone change Investigating cortical and trabecular bone separately Absence of radiation exposure	Operator-dependent
DXA	Bone density	Early detection of bone damage Small effective radiation dose	No evaluation of bone erosion, bone edema, and synovitis
DXR	Bone density	Better reproducibility than DXA Higher sensitivity than DXA Predictive of erosive disease	No evaluation of bone erosion, bone edema, and synovitis Ionizing radiation

CR, computed radiography; CT, computed tomography; DXA, dual-energy x-ray absorptiometry; DXR, digitalized radiogrammetry; MRI, magnetic resonance imaging; US, ultrasound. Reprinted with permission from Elsevier [73].

BMD and other clinical risk factors for fractures, including the use of GCs. RA is included as an independent clinical risk factor for 10-year fracture risk calculation for major and hip fractures in the fracture risk assessment tool (FRAX) case-finding algorithm [118]. Stress fractures have been found in 0.8% of patients with RA, can be difficult to diagnose, and were related to GC use but not to BMD [119].

Fracture risk in RA was related to the duration of RA [120], the severity of disease, and its musculoskeletal consequences, such as disability, HAQ score, lack of physical activity, and impaired grip strength [120-122]. Vertebral fractures were related to disease duration and severity [69]. In the general population, fracture risk was related to serum levels of IL-6, TNF, and CRP [123] and parameters of bone resorption [124], all of which can be increased in RA. Extraskeletal risk factors that influence fracture risk include increased risk of fall rates which were related to number of swollen joints and impaired balance tests [125].

Risk predictors of bone changes in rheumatoid arthritis

Currently, the most widely used case-finding algorithm for calculating the 10-year fracture risk for major and hip fractures is the FRAX tool [118]. FRAX includes RA as a risk for fractures, independently of and superimposed on other risk factors, including BMD and use of GCs [118]. No fracture risk calculator that also includes other risk factors that are related to RA, such as disease duration and disease severity, is available. The Garvan fracture risk calculator (GFRC) can be used to calculate the 5- and 10-year fracture risk which includes the number of recent falls and the number of previous fractures but lacks RA as a risk factor [126]. Fracture risk is higher with GFRC than with FRAX in patients with recent falls [126]. In view of the increased fracture risk in patients with RA, systematic evaluation of fracture risk should be considered using FRAX, disease severity, and duration, and GFRC is helpful when patients report recent falls. Risk of low BMD is difficult to estimate in RA [90], and this suggests that bone densitometry should also be considered in fracture risk calculation in patients with active RA [127]. Many risk factors, including baseline disease severity, RF, anti-CCP, baseline bone destruction, the RANKL/OPG ratio, and CTX-I and CTX-II, have been identified for the prediction of bone erosions in RA. This pallet of predictors can now be extended with measurement of changes in periarticular bone (by DXR) and osteitis (on MRI) early in the disease [73,81,82]. Additional studies will be necessary to study the relation between osteitis and bone loss.

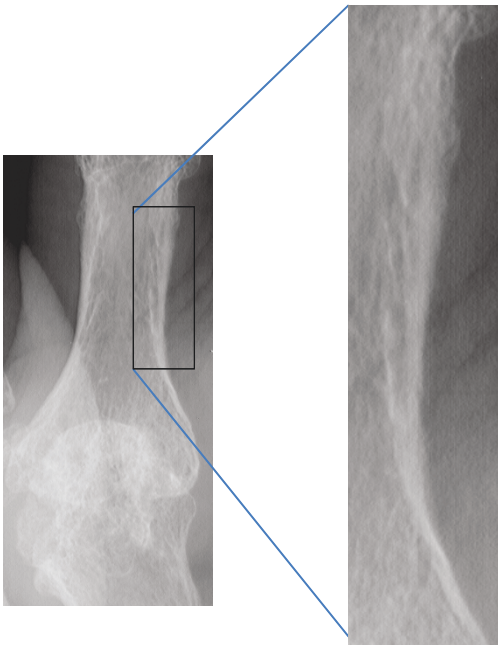

Figure 3. Cortical bone changes in rheumatoid arthritis on classical radiography showing striation and lamellation of cortical bone of the phalanx.

Effect of treatment on bone changes in rheumatoid arthritis

As the pathophysiology of bone loss in RA is taken into account (Figure 4), therapy should be directed at suppressing inflammation and bone resorption and restoring bone formation. No randomized placebo-controlled trials (RCTs) on the effect of treatment on fracture risk in RA are available. However, the available data suggest that control of inflammation (TNF blockade and appropriate dose of GCs), specific inhibition of bone resorption (bisphosphonates and denosumab), strontium ranelate, and restoration of the balance between bone resorption and formation (teriparatide and PTH) are candidates for such studies. Bone loss early in the disease continued despite clinical improvement and sufficient control of inflammation through treatment, indicating a disconnect between clinical inflammation and intramedullary bone loss [128]. However, these studies did not include TNF blockers, and, at that time, remission was not a realistic tool of therapy. Suppression of inflammation with TNF blockers such as infliximab and adalimumab decreased markers of bone resorption and the RANKL/OPG ratio [129], decreased osteitis, and reduced or arrested generalized (in spine and hip) bone loss [75]. Infliximab, however, did not arrest periarticular bone loss [129]. In the Behandelstrategieën voor Reumatoide Artritis (BEST) study, both bone loss at the metacarpals and radiographic joint damage were lower in patients adequately treated with combination therapy of methotrexate plus high-dose prednisone or infliximab than in patients with suboptimal treatment [130].

Several pilot studies on the effect of antiresorptive drugs on bone in RA have been performed. Pamidronate reduced bone turnover in RA [131]. Zoledronate decreased the number of hand and wrist bones with erosions [132]. Denosumab strongly suppressed bone turnover and, in higher dosages than advocated for the treatment of postmenopausal osteporotic women, prevented the occurrence of new erosions and increased BMD in the spine, hip, and hand, without an effect on joint space narrowing and without suppressing inflammation, indicating an effect on bone metabolism but not on cartilage metabolism [133-136].

The effects of GCs on bone loss and fracture risk in RA should be interpreted with caution as GCs have a dual effect on bone in RA. On the one hand, controlling inflammation with GCs strongly reduces bone loss, whereas, on the other hand, GCs enhance bone resorption, suppress bone formation, and induce osteocyte apoptosis.

Studies in glucocorticoid-induced osteoporosis (GIOP) included patients with RA. None of these studies had fracture prevention as a primary endpoint, and no data on the GIOP studies on fracture prevention in RA separately are available (see [137] for a recent review). RCTs in GIOP showed that bisphosphonate treatment (alendronate, risedronate, and zoledronate) and teriparatide prevented bone loss and increased BMD. Alendronate and risedronate decreased the risk of vertebral fractures versus placebo and teriparatide versus alendronate. No convincing evidence on fracture risk in GIOP for calcium and vitamin D supplements (calcitriol or alfacalcidol) is available. However, most RCTs in GIOP provided calcium and vitamin D supplements. Most guidelines, therefore, advocate calcium and vitamin D supplements, bisphosphonates, and eventually teriparatide as a second choice because of its higher cost price in the prevention of GIOP in patients at high risk, such as those with persistent disease activity, high dose of GCs, or high background risk such as menopause, age, low BMD, and the presence of clinical risk factors [138,139].

Taken together, these data indicate that control of inflammation is able to halt bone loss and suppress osteitis in RA. Bisphosphonates are the front-line choice for fracture prevention in GIOP, but in patients with a very high fracture risk, teriparatide might be an attractive alternative. The effect of denosumab indicates that osteoclasts are the final pathway in bone erosions and local and generalized bone loss and that the bone destruction component of RA can be disconnected from inflammation by targeting RANKL.

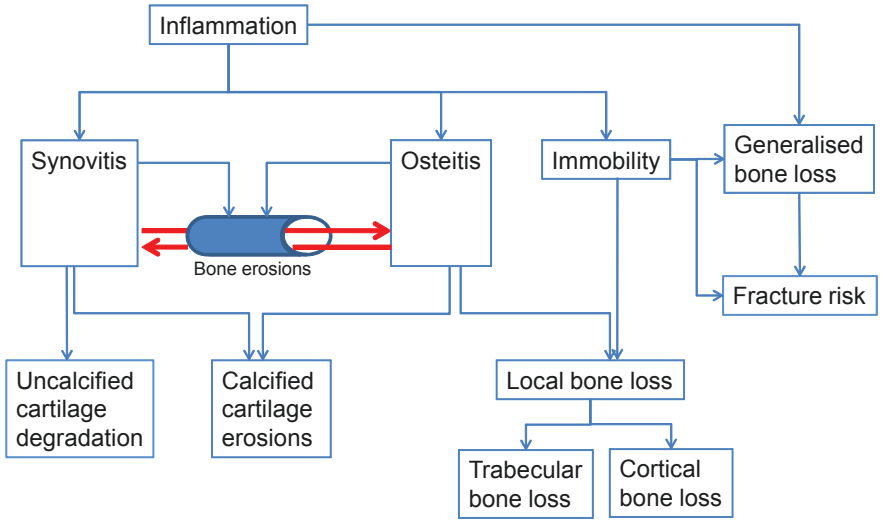

Figure 4. Effect of inflammation on bone and fracture risk in rheumatoid arthritis.

Generalized bone loss in ankylosing spondylitis

Bone loss in the vertebrae occurs early in the disease, as shown by DXA [140] and qCT [141]. In advanced disease, the occurrence of syndesmophytes and periosteal and discal bone apposition does not allow intravertebral bone changes with DXA to be measured accurately. Combined analyses of DXA and QCT in patients with early and long-standing disease indicate that bone loss in the vertebrae occurs early in the disease and can be measured by DXA and QCT but that, in long-standing disease, DXA of the spine can be normal, in spite of further intravertebral bone loss as shown with qCT [142,143]. As a result, in early disease, osteoporosis was found more frequently in the spine than in the hip, whereas in patients with long-standing disease, osteoporosis was more frequent in the hip [75]. Hip BMD was related to the presence of syndesmophytes and vertebral fractures, to disease duration and activity [142,144], and to CRP [145]. Osteitis in the vertebrae precedes the development of erosions and syndesmophytes [41,42].

Fracture risk in ankylosing spondylitis

Morphometric vertebral fractures (with a deformation of 15% or 20%) have been reported to be 10% to 30% in groups of patients with AS [146]. The odds ratios of clinical vertebral fractures were 7.7 in a retrospective population-based study [147] and 3.3 in a primary care-based nested case control study [148]. In both studies, the risk of non-vertebral fractures was not increased.

The risk of vertebral fractures is multifactorial and independent of and superimposed on other clinical risk factors [118].

Vertebral fracture risk in AS was higher in men than in women and was associated with low BMD, disease activity, and the extent of syndesmophytes [144,149]. Vertebral fractures contributed to irreversible hyperkyphosis, which is characteristic in some patients with advanced disease with extensive syndesmophytes (bamboo spine) [150,151].

Apart from presenting with these 'classical' vertebral fractures, patients with AS can present with vertebral fractures that are specifically reported in AS. First, erosions at the anterior corners and at the endplates of vertebrae (Andersson and Romanus lesions) result in vertebral deformities if erosions are extensive and the results of such measurements should not be considered a classical vertebral fracture (Figure 5) [75,152]. Second, in a survey of 15,000 patients with AS, 0.4% reported clinical vertebral fractures with major neurological complications [153]. Third, owing to the stiffening of the spine by syndesmophytes, transvertebral fractures have been described [153]. Fourth, fractures can occur in the ossified connections between the vertebrae [153]. In all of these cases, CT, MRI, and eventually bone scintigraphy are helpful to identify these lesions and the extent of neurological consequences (Figure 6) [154].

Risk predictors of bone changes in ankylosing spondylitis

The diagnosis of vertebral fractures is hampered by the finding that only one out of three morphometric vertebral fractures is accompanied by clinical signs and symptoms of an acute fracture. This is probably even less in patients with AS as fractures of the vertebrae and their annexes can be easily overlooked when a flare of back pain is considered to be of inflammatory origin without taking into account the possibility of a fracture. In case of a flare of back pain, special attention, therefore, is necessary to

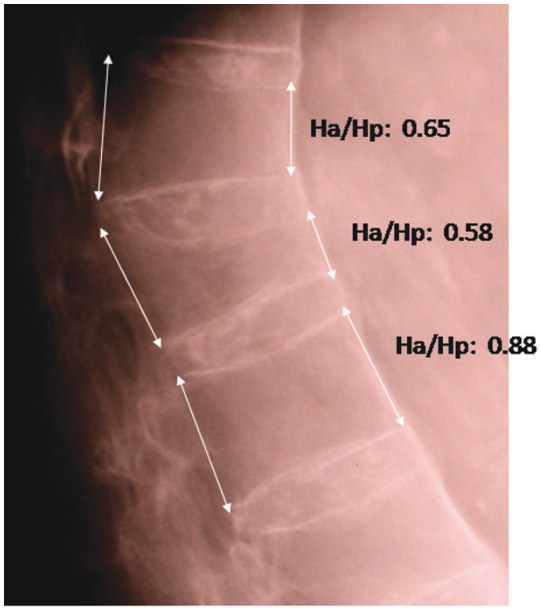

Figure 5. Changes in vertebral shapes in ankylosing spondylitis. (a) Vertebral deformation in ankylosing spondylitis. Ha, anterior height; Hp, posterior height. **(b)** Vertebral deformation due to extensive erosive discitis with osteitis in ankylosing spondylitis (Andersson lesion).

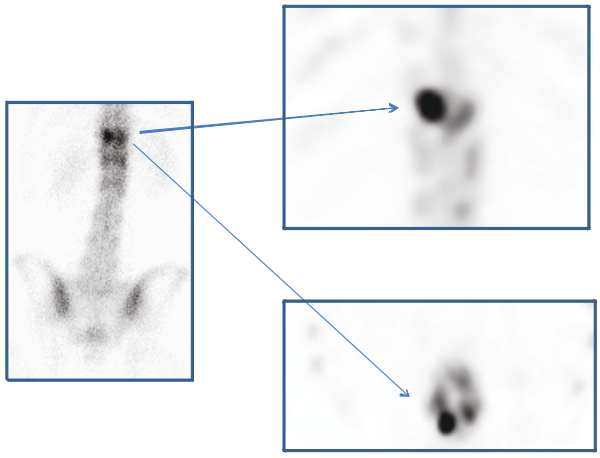

Figure 6. Fracture of dorsal arch and pedicle in a patient with ankylosing spondylitis and bamboo spine and persisting back pain after minimal trauma.

diagnose vertebral fractures in AS, even after minimal trauma. Additional imaging (CT, MRI, and bone scintigraphy) might be necessary in patients in whom a fracture is suspected in the absence of abnormalities on conventional radiographs. On the basis of the limited data on fracture risk in AS, vertebral fractures especially should be considered in patients with a flare of back pain, persistent inflammation, long disease duration, hyperkyphosis with increased occiput-wall distance, bamboo spine, and persistent pain after trauma, even low-energy trauma. The FRAX algorithm can be used to calculate the 10-year fracture risk but cannot be used to separately calculate the risk of clinical vertebral fractures [118].

Risk factors to predict erosive sacroiliitis have been identified. These include male gender, CRP, B27, clinical symptoms, family history [155-157], and the occurrence of syndesmpophytes (such as B27, uveitis, no peripheral arthritis, prevalent syndesmophytes, and disease duration) [72,158,159]. Also, CTX-II has been shown to predict syndesmophytes, which could reflect cartilage destruction during enchondral new bone formation in enthesitis, including syndesmophytes [27]. These risk factors can now be extended with subchondral bone involvement (as defined by osteitis on MRI) that has been shown to predict erosive sacroiliitis [39] and the occurrence of syndesmophytes [160,161]. To predict radiographic erosive sacroiliitis, the Assessment of Spondylo-Arthritis international Society recently developed and validated criteria that included active signs of inflammation on MRI, which are defined as active inflammatory lesions of sacroiliac joints with definite bone marrow edema/osteitis [156,157].

Effect of treatment on bone changes in ankylosing spondylitis

As the pathophysiology of vertebral fractures in AS is taken into account (Figure 7), therapy should be directed at suppressing inflammation, bone resorption, and bone formation. No RCTs on the effect of treatment on the risk

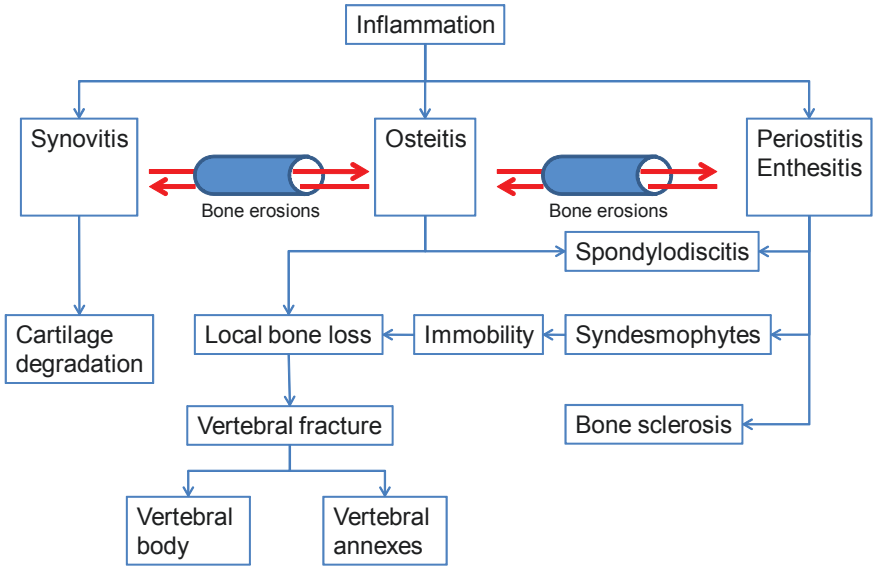

Figure 7. Effect of inflammation on bone and fracture risk in ankylosing spondylitis.

of vertebral fractures in AS are available. In the General Practice Research Database, the use of non-steroidal anti-inflammatory drugs (NSAIDs) is associated with a 30% decrease in the risk of clinical vertebral fractures, but this has not been studied prospectively [75,148]. In general, continuous use of NSAIDs, in comparison with intermittent use, and celecoxib decreased the formation of syndesmophytes [148,162]. The mechanisms of these effects are unclear. NSAIDs inhibit bone formation, as shown in fracture healing, which is also an inflammation-driven model of increased bone formation [163,164]. One other explanation is that pain relief can ameliorate function and decrease immobility [75]. Limited studies with bisphosphonates indicated inhibition of inflammation in AS [165]. Zoledronate did not prevent the occurrence of syndesmophytes in rats [166]. Bisphosphonates, however, can be considered in the treatment of osteoporosis in high-risk patients [167]. TNF blockade decreased osteitis, prevented bone loss, and decreased CRP and IL-6 [145,168] but had no effect on the occurrence of syndesmophytes [169]. Taken together, these data indicate that control of inflammation is able to halt bone loss and suppress osteitis in AS but not the occurrence of syndesmophytes. Further research is needed to understand why NSAIDs could decrease fracture risk and syndesmophyte formation, why TNF blockade prevents bone loss but not syndesmophyte formation, and new ways to prevent syndesmophyte formation.

Discussion and summary

These data indicate that bone is a major target for inflammation and that bone loss and osteoporosis are common features that contribute to the increased fracture risk in RA and AS. However, the problem of bone involvement in RA and AS is more complex than in primary osteoporosis alone. The consistent finding of peri-inflammatory bone loss and osteitis in both RA and AS raises questions, besides fracture risk, about the clinical significance of bone loss.

Periarticular bone loss and osteitis coincide early in RA and AS and not only precede but also predict the occurrence of visible erosions [76]. This raises the question of the mechanism by which these anatomical coincident changes in the joints, entheses, and bone marrow occur. As described above, no direct anatomical or vascular connection between the joint cavity and bone marrow is present, but some healthy subjects can have small erosions in the MCP joints without having RA and have erosions at the entheses and vertebral cortices. In subjects with small erosions before RA or AS becomes apparent clinically, it can be assumed that, when they develop arthritis or enthesitis, the erosions allow immediate contact with bone marrow, resulting in coincident joint, enthesis, and bone marrow inflammation. Healthy subjects without such erosions could develop small erosions, resulting in measurable peri-inflammatory bone loss, before they can be identified on radiographs or MRI because of the spatial resolution of radiology and MRI and the single-plane images of radiographs. Another hypothesis is that RA and AS are primarily bone marrow diseases [170,171], with secondary invasion of the joint via erosions created by intramedullary activated osteoclasts or via pre-existing erosions. Indeed, $CD34^+$ bone marrow stem cells have been shown to be abnormally

sensitive to TNFα to produce fibroblast-like cells [172], suggesting an underlying bone marrow stem cell abnormality in RA.

In AS, the finding of early osteitis is even more intriguing as osteitis is occurring in the vertebrae, where no synovium but periost is present at the anterior sites and discs between vertebrae. Local communication with the periost is possible by the local vascular connections or pre-existing erosions, leaving open the possibility that periost is the primary location of inflammation in AS. The same applies for the intervertebral disc, which has no direct vascular contact but can have pre-existing erosions. Whether RA and AS are initialized in the joints, enthesis, or the bone marrow is a growing field of debate [170], and such hypotheses will need much more study.

Regardless of these anatomical considerations, when the size of bone edema that can be found by MRI and the extent of early periarticular bone loss are taken into account, it seems that inflammation is as intense and extensive inside bone marrow as in the synovial joint in RA and AS and in the enthesis in AS. As bone loss and bone edema occur early in the disease, these findings indicate that bone marrow inflammation – and not just joint or enthesis inflammation – is a classical feature of early RA and AS. To what degree impaired osteoblast function is associated with loss of control of HSC and B-cell differentiation in their subendosteal niches in RA is unknown and needs further study as B-cell proliferation is a feature of RA but not of AS [173-175].

The finding that bone involvement can be disconnected from clinically detectable inflammation is quite intriguing. In RA, bone erosions can progress even when the inflammatory process is adequately controlled (that is, in clinical remission) [176], and progress of bone erosions can be halted by denosumab in spite of persistent inflammation [133-136]. In AS, the occurrence of syndesmophytes can progress in spite of suppression of inflammation by TNF blockade [160]. These findings have been described as a disconnection between inflammation and bone destruction and repair.

The correlation and eventual disconnection between osteitis and bone loss, parameters of disease activity, and erosions suggest a dual time-dependent role for the occurrence of erosions. Early in the disease process, the primary negative effect of pre-existing or newly formed erosions is the connection they create between the bone marrow and the joints, periost, and entheses. In this way, erosions contribute to local amplification of inflammation by allowing bone marrow cells to have direct local connection with extraosseous structures and creating a vicious circle of inflammation between joints, periost, entheses, and bone marrow [177]. Only in a later stage do erosions contribute to loss of function [178]. In this hypothesis, the attack of inflammation on bone by stimulating osteoclasts has far-reaching consequences. First, it would indicate that timely disease suppression and the prevention of the development of a first erosion rather than halting erosion progression should be considered a primary objective, both in RA and AS [179]. Second, periarticular bone loss and osteitis should be considered, at least theoretically, an indication for the presence of erosions, even when erosions cannot be visualized on radiographs or MRI, and periarticular bone loss and osteitis should be considered an indication for early aggressive therapy [180]. Of course, the effectiveness of antirheumatic treatment based on osteitis should be demonstrated. Third, the finding of disconnection between inflammation and bone involvement indicates that, even when inflammation is clinically under control, the degree to which bone-directed therapy is indicated should be studied in order to prevent (further) progression of erosions and syndesmophytes. In conclusion, the involvement of bone as a major target of inflammation in RA and AS raises many questions [10,181-184], opening perspectives for further research in the understanding and treatment of the complex bone disease component of RA and AS.

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Abbreviations

anti-CCP, anti-cyclic citrullinated peptide antibody; AS, ankylosing spondylitis; BMD, bone mineral density; BMP, bone morphogenetic protein; CRP, C-reactive protein; CT, computed tomography; DKK, Dikkoppf; DXA, dual-energy x-ray absorptiometry; DXR, digitalized radiogrammetry; ESR, erythrocyte sedimentation rate; FRAX, fracture risk assessment tool; GC, glucocorticoid; GFRC, Garvan fracture risk calculator; GIOP, glucocorticoid-induced osteoporosis; HAQ, health assessment questionnaire; HRqCT, high-resolution quantitative computer tomography; HSC, hematopoietic stem cell; IFNγ, interferon-gamma; IL, interleukin; MCP, metacarpophalangeal; MRI, magnetic resonance imaging; NSAID, non-steroidal anti-inflammatory drug; OPG, osteoprotegerin; PTH, parathyroid hormone; qCT, quantitative computer tomography; QUS, quantitative ultrasound; RA, rheumatoid arthritis; RANK, receptor activator of the nuclear factor-kappa-B; RANKL, receptor activator of the nuclear factor-kappa-B ligand; RCT, randomized placebo-controlled trial; RF, rheumatoid factor; RR, relative risk; SpA, spondylarthopathy; TNF, tumor necrosis factor.

Competing interests

WFL has received speaking fees form Amgen, Eli Lilly, Merck, and Procter and Gamble.

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