Review

Mechanisms of bone loss in inflammatory arthritis: diagnosis and therapeutic implications

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Abstract

Rheumatoid arthritis represents an excellent model in which to gain insights into the local and systemic effects of joint inflammation on skeletal tissues. Three forms of bone disease have been described in rheumatoid arthritis. These include: focal bone loss affecting the immediate subchondral bone and bone at the joint margins; periarticular osteopenia adjacent to inflamed joints; and generalized osteoporosis involving the axial and appendicular skeleton. Although these three forms of bone loss have several features in common, careful histomorphometric and histopathological analysis of bone tissues from different skeletal sites, as well as the use of urinary and serum biochemical markers of bone remodeling, provide compelling evidence that different mechanisms are involved in their pathogenesis. An understanding of these distinct pathological forms of bone loss has relevance not only with respect to gaining insights into the different pathological mechanisms, but also for developing specific and effective strategies for preventing the different forms of bone loss in rheumatoid arthritis.

Keywords: bone loss, cytokines, osteoclast, osteoporosis, rheumatoid arthritis

Introduction

Inflammatory joint diseases such as rheumatoid arthritis (RA), the seronegative spondyloarthropathies, and juvenile arthritis comprise a heterogeneous group of disorders that share a propensity to destroy the extracellular matrices of joint cartilage and bone. To dissect the pathophysiological mechanisms that are responsible for the loss of cartilage and bone, it is necessary to determine whether the destruction of these matrices is mediated by the same cell types that remodel these tissues under physiological conditions. This question can be addressed in part by careful histopathological examination and characterization of the diseased joint structures using techniques that identify the phenotype of cell populations within the bone and cartilage matrices. In addition, it is essential to know whether the loss of bone and cartilage is the result of impaired synthesis of the extracellular matrix components or is related to an enhanced rate of their breakdown. The development of biochemical assays for quantitating bone and cartilage remodeling indices (formation and degradation) and the availability of improved imaging techniques for assessing bone and cartilage loss have provided new insights into these pathological events. This review focuses on the mechanisms of bone loss in RA, and explores the diagnostic and therapeutic implications of these findings.

IL = interleukin; ODF = osteoclast differentiation factor; RA = rheumatoid arthritis; TNF = tumor necrosis factor.

Rheumatoid arthritis as a model of inflammatory arthritis

Among the inflammatory arthritides, RA represents an excellent model for gaining insights into the local and systemic effects of joint inflammation on skeletal tissues. Three forms of bone disease have been described in RA. These include: focal bone loss affecting the immediate subchondral bone and bone at the joint margins; periarticular osteopenia adjacent to inflamed joints; and generalized osteoporosis involving the axial and appendicular skeleton [1–3]. Although these three forms of bone loss have several features in common, careful histomorphometric and histopathological analysis of bone tissues from different skeletal sites provide compelling evidence that different mechanisms are involved in their pathogenesis.

A general understanding of the cellular and biochemical events associated with skeletal remodeling is essential for defining the pathophysiology of bone loss in RA. Throughout life the skeleton is in a dynamic state of remodeling, during which discrete packets of bone (termed bone remodeling units or basic multicellular units by Frost [4] and Parfitt [5]) are resorbed and new bone formed to replace the resorbed matrix. In trabecular bone each remodeling cycle (estimated to be between 3 and 4 months) is initiated at a previously quiescent bone surface by the recruitment of osteoclast precursors, which are cells of monocyte/macrophage lineage. These precursor cells subsequently differentiate into active bone resorbing osteoclasts [6]. After cessation of the resorption cycle the bone surface is lined by osteoblasts that synthesize new bone matrix. This unmineralized bone matrix, or osteoid, subsequently undergoes mineralization. Under physiological conditions the activity of the osteoclasts and osteoblasts is tightly controlled, such that with each remodeling cycle the amount of bone that is removed is exactly replaced. This process provides a mechanism for repair of local microdamage to the skeleton and permits adaptation to changing biomechanical factors.

Although the focal bone erosions and juxta-articular and systemic bone loss in RA involve different regions of the skeleton, implicit in each of these patterns of bone loss is the presence of a disequilibrium in the absolute rate of bone resorption and formation that is independent of the specific cellular and pathological events. An understanding of these distinct pathological forms of bone loss has relevance not only with respect to gaining insights into the different pathological mechanisms, but also for developing specific and effective strategies for preventing these forms of bone loss in RA.

Focal bone loss in rheumatoid arthritis

Insights into the pathogenesis of the progressive focal bone erosions and subchondral osteolysis that characterizes RA have been provided by histopathological analysis of the bone–pannus junction and subchondral bone marrow [7–11]. These studies demonstrated the presence in resorption lacunae of multinucleated cells that express the entire repertoire of mature osteoclasts, including the presence of tartrate-resistant acid phosphatase and cathepsin K activity and the expression of calcitonin receptor mRNA. These observations provide good evidence that the focal bone resorption at these sites is mediated by cells with phenotypic features and functional activities of authentic osteoclasts. These conclusions are further supported by work in animal models of inflammatory arthritis [12,13].

Additional studies indicate that rheumatoid synovial tissues are enriched with cells of the monocyte/macrophage lineage that, with appropriate stimuli, can be induced to differentiate into preosteclasts and ultimately into fully functional osteoclasts [14–16]. In addition, several studies have shown that synovial tissues are a rich source of a number of cytokines and inflammatory mediators that possess the capacity to induce the recruitment, differentiation, and activation of osteoclasts. These include interleukin (IL)-1α and IL-1β, tumor necrosis factor (TNF)-α, macrophage colony-stimulating factor, IL-6, IL-11, parathyroid hormone-related peptide, and the newly described T-cell derived cytokine IL-17 [17–23]. Of interest, many of these cytokines, especially IL-6, IL-11, and macrophage colony-stimulating factor, function under physiological conditions of bone remodeling to induce osteoclast differentiation. The local production of these factors by the inflamed synovium, as well as the production of proinflammatory factors, including IL-1α and IL-1β, TNF-α, IL-17 and parathyroid hormone-related peptide, by the inflamed RA synovium could be responsible for the recruitment of osteoclast precursors to the bone microenvironment where they are induced to differentiate to activated osteoclasts.

Recent studies [24] have identified an additional potent regulator of osteoclast differentiation: osteoclast differentiation factor (ODF). Under conditions of physiological bone remodeling, interaction of ODF with its receptor, receptor activator of nuclear factor-κB, on the surface of osteoclast precursors leads to differentiation of these cells to osteoclasts. Of interest with respect to the T-cell infiltrate within RA synovium, ODF is identical to the TNF-related activation-induced cytokine that is expressed on antigen-stimulated T cells [25]. Our laboratory and others have recently reported the expression of ODF in T cells and fibroblast-like cells in rheumatoid synovium [26–28]. That ODF plays a role in the pathological bone resorption in inflammatory arthritis is supported by the studies of Kong *et al* [28], who demonstrated that treatment with osteoprotegerin, the soluble receptor for ODF, prevents bone erosions in a model of adjuvant arthritis.

The demonstration that the focal bone erosions in RA are generated, at least in part, by cells expressing an osteoclast phenotype suggests that agents that affect osteoclast recruitment, differentiation or activity would be rational targets for preventing this form of bone loss. Only limited data are available regarding this topic and, thus far, although there are data that indicate that agents that block osteoclast-mediated bone resorption can prevent systemic bone loss, there are no definitive findings from trials in humans that demonstrate the efficacy of these therapies in blocking focal bone erosions in RA [29–35]. There are data in animal models of inflammatory arthritis, however, that indicate that inhibition of osteoclast-mediated bone resorption with bisphosphonates may have efficacy in blocking focal bone erosions [36,37]. Clearly, further studies are needed to explore fully the potential beneficial effects of agents that block osteoclast-mediated bone resorption in this form of bone disease.

The absence of more definitive data regarding the utility of therapeutic intervention in the prevention of focal bone disease in RA is due in part to the difficulty of assessing the progression of bone erosions, because standard radiographs lack sufficient sensitivity to detect and quantitate the progression of bone lesions. Recent advances in magnetic resonance imaging techniques that employ gadolium-diethylenetriaminepenta-acetic acid and T2-pulse sequences to suppress fat signals allow for the identification of early focal bone loss. These techniques hold significant promise for the evaluation of treatment interventions to block focal bone erosions [11]. Further studies with these technologies, as well as other refinements in imaging modalities, should enhance the feasibility of these types of investigation.

Periarticular osteopenia

The second form of bone loss observed in patients with RA is the presence of periarticular osteopenia adjacent to inflamed joints. Histological examination of this bone tissue reveals the presence in the marrow space of local aggregates of inflammatory cells, including macrophages and lymphocytes. There is an increase in the surface of bone covered by osteoid, as well as an increase in resorption surfaces, which are often populated by osteoclasts. These findings are consistent with an increase in bone remodeling with a net increase in bone resorption [38,39]. Although decreased joint motion and immobilization in response to the adjacent synovial inflammation probably contribute to the juxta-articular bone loss, these changes could also reflect local responses within the marrow space to proinflammatory products released from the adjacent RA synovial tissues. Although osteoclasts are the likely cell type responsible for the bone resorption in this form of bone loss, the absence of direct synovial interaction with the bone surfaces indicates that different cellular interactions are involved in the recuritment and activation of the bone resorbing cells.

Axial and appendicular osteopenia

The third form of bone loss associated with RA is generalized axial and appendicular osteopenia, which has been detected using multiple different techniques for assessing skeletal mass [40–43]. Importantly, there is compelling evidence that the reduction in bone mass is associated with an increased risk of hip and vertebral fracture [41,44–46]. Although there has been speculation that cytokines such as IL-1α or IL-1β, TNF-α and IL-6 (released into the circulation from inflamed joints) contribute to systemic bone loss by acting in an endocrine manner to affect bone remodeling adversely, there are no direct data to support this hypothesis [2,3]. In part, the difficulty in defining the specific pathogenetic mechanisms responsible for this pattern of bone loss in RA can be attributed to the presence of multiple confounding factors in this patient population. These include the influence of patient sex, age, mobility, disease activity and duration, and the concomitant use of immunosuppressive therapies and/or glucocorticoids, all of which have independent effects on bone metabolism. Among these variables, disease activity and duration appear to be of particular importance with respect to the risk for reduced bone mass [40,47]. Of importance, a significant amount of generalized skeletal bone appear to be lost early in RA and the magnitude of this loss is associated with the level of disease activity [40,45,48,49]. These findings have obvious implications with respect to early interventions to prevent bone loss.

Several different approaches have been used to define the mechanisms responsible for the generalized bone loss associated with RA. Histomorphometric analysis of bone biopsies [50,51] indicate that, in the absence of corticosteroid use, the generalized bone loss in RA is related to a decrease in bone formation rather than to an increase in bone resorption. In contrast, analysis of biochemical markers of bone turnover using the pattern of urinary excretion of collagen pyridinoline and deoxypyridinoline crosslinks to quantitate bone resorption [39,40,52–55] indicates that systemic bone loss in RA is related primarily to an increase in bone resorption rates. Furthermore, excretion of both urinary markers was significantly increased in patients with active disease who lost bone quickly. The discrepancy between the findings from histomorphometric and biochemical markers studies could in part be related to the stage of the disease at the time of the analyses (eg early versus late), as well as to the level of disease activity. The importance of disease activity on bone remodeling indices was illustrated by the studies of Gough *et al* [39] who showed that the levels of the urinary markers of bone resorption were highly correlated with C-reactive protein. Bone formation indices, as assessed by measurement of serum alkaline phosphatase and procollagen I carboxyterminal propeptide levels, were not significantly suppressed, suggesting that suppression of bone formation was marginal and not a dominant factor contributing to the accelerated bone loss in patients with active disease.

Therapeutic approaches to prevent generalized bone loss in rheumatoid arthritis

Increasing awareness of the morbidity associated with generalized bone loss in patients with RA has lead to the initiation of several clinical trials designed to prevent systemic bone loss. Most of the studies have focused on the effects of antiresorptive therapies on generalized bone loss. Results of these investigations indicate that agents including estrogens, calcitonin, or bisphosphonates may have clinical efficacy in preventing systemic bone loss. For example, in prospective studies [32–35], estrogens were shown to improve bone density modestly in postmenopausal women with RA. Similarly, calcitonin in short-term studies [30,31] has been shown to increase trabecular bone volume and bone mineral density as assessed by forearm densitometry. In a prospective controlled 3-year trial, Egglemeiger *et al* [29] showed that treatment with the bisphosphonate pamidronate resulted in a significant increase in bone mineral density in the lumbar spine and hip compared with a placebo group. This was accompanied by a reduction in urinary hydroxyproline excretion in the pamidronate-treated group, which is consistent with suppression of bone resorption. Of interest, those investigators detected no change in the progression of focal bone erosions in their treated patients, suggesting that the bisphosphonate failed to prevent this form of bone loss. Whether this lack of efficacy in preventing focal bone erosions was related to drug dosage or to other factors related to disease activity or concomitant therapies will require further investigation.

Treatment strategies to increase bone mass

To date there have been no studies in patients with RA that have explored treatment modalities specifically designed to increase bone formation rates. In part, this reflects the absence of agents that can directly increase osteoblastic activity. Recently Lane *et al* [56] used a regimen of intermittent low-dose parathyroid hormone to treat corticosteroid-induced osteoporosis. These findings indicate that this strategy, or a related approach using, for example, other cytokines or growth factors with the capacity to increase bone formation, may hold promise for the treatment of generalized bone loss in patients with RA.

Critical to the successful evaluation of the efficacy of agents designed to prevent the various forms of bone loss in patients with RA will be the development of cost-effective, sensitive, and specific noninvasive techniques for monitoring the effects of these treatments on the bone disease. It is also essential that these approaches be able to identify the effects of these treatments on the specific patterns of bone loss. The overall goal of treatment of RA is the suppression or eradication of the primary immune disorder that is responsible for the synovial lesion. It is nevertheless possible to develop treatment strategies that can help protect the skeletal tissues from the ravages of the inflammatory process, even in the absence of a definitive disease cure.

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