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Pathogenesis of Bone Erosions in Rheumatoid Arthritis: Not Only Inflammation

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Abstract

It is a matter of fact that the inflammatory pathogenesis does not explain all the skeletal manifestations of Rheumatoid Arthritis (RA), and the development of bone involvement is sometimes unconnected from the clinical scores of inflammation. On the basis of recent studies, we would like to make a point of the new available evidence about the metabolic pathogenic component of bone erosions. We assume that in this process an additional role could be played by metabolic factors, such as the parathyroid hormone (PTH), DKK1 (the inhibitor of the Wnt/β catenin pathway) and cortical bone mineral density. The result is a new pathogenic hypothesis for bone erosion in RA, which supplements the inflammatory one: the reduction of osteoblasts activity and the increase of the osteoclasts one, involved in the pathogenesis of bone erosions and osteoporosis, are not only the consequence of the action of inflammatory cytokines, but also of increased levels of DKK1 and PTH. On the other hand, osteoporosis, in particular at the cortical sites, facilitates the appearance of erosions.

Failing to assess and correct these metabolic alterations may explain an insufficient response in terms of prevention or healing of bone erosions to the disease modifying antirheumatic drugs.

Introduction

It has been suspected for so long that the three typical manifestations of bone involvement in rheumatoid arthritis (RA) (focal bone erosions, juxta-articular osteoporosis and systemic osteoporosis) could be the consequence of a common pathological mechanism [1] of both inflammatory and metabolic nature.

It is a matter of fact that the inflammatory pathogenesis does not explain all the skeletal manifestations of the rheumatic disease and the development of bone involvement is sometimes unconnected from the clinical scores of inflammation [2]. On the basis of recent studies in this review we would like to make a point of the new available evidence about the metabolic pathogenic component of bone erosions.

The Patogenesis of Bone Erosions: Not Only Inflammation

It is well known that at 5 years from the beginning of RA, 30-50% of patients has evidence of focal bone erosions [3]. This phenomenon is the result of many complex interactions from the cells and the cytokines/chemokines system at the synovial and surrounding tissues level, which culminates with bone destruction. In addition to the articular crumbling, RA is also associated with a generalized bone loss with a higher prevalence of osteoporosis: RA patients have double the normal risk of undergoing a femoral fracture [4] and they are 4 times more likely to have vertebral fractures [5,6]. Both erosions and systemic osteoporosis are related to the unbalance between osteoblasts and osteoclasts activity [7,8]. Some of the cytokines involved in RA physiopathology, as the tumor necrosis factor alpha (TNF-α) and RANKL, are also involved in the pathogenesis of both focal and systemic bone lesions [9,10]. The balance between the osteoblasts and osteoclasts activity in course of RA is conditioned not only from distinctive inflammatory factors (TNF-α, IL1, IL6, IL17, IFN-gamma...), but also from metabolic factors (IGF1, estradiol, parathyroid hormone, 1,25(OH)2D, leptin, ...) related to the disease *per se* or influenced by the use of some drugs as glucocorticoids.

The erosiveness of RA is typically very precocious and it is at the maximum level in the first years of the disease; the rapid establishing of the structural damage in RA is determined by a close interaction between the synovial joint membrane, cartilage and subchondral bone. The fundamental role is played by osteoclasts [8], both from the synovial and the medullary side [11]. The activation and replication of osteoclasts would be primarily linked to inflammation: a significant correlation between the inflammation score and the number of osteoclasts was shown [11].

During intense phlogosis the RANK-RANKL system is activated by inflammatory citokines (TNF-α, IL-1, IL-6, IL-17, PGE2) both at the medullary and at the synovial level and this generates the proliferation of osteoclasts [12,13]. Recently, it has been also described in RA patients an improved differentiation of the mononuclear cells of peripheral blood into osteoclasts, possibly due to an increase of osteoclasts blood precursors and a reduced apoptotic potential of mature osteoclasts [14]. An additional role could be played by the chronic increase of a metabolic factor such as the parathyroid hormone (PTH) which, along with 1,25(OH)2D, is a known stimulator of the production of RANLK and of osteoclasts activity [15,16].

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Lately, it has also been observed that, despite osteoclasts are the main actors in the pathogenesis of bone erosions in RA, osteoblasts and their regulatory cytokines (especially dickkopf Wnt signaling pathway inhibitor 1, DKK1), whether directly or indirectly, participate too. In RA patients it was shown that an increase in serum DKK1 levels correlated positively with inflammation markers and with the Sharp scores [17]: considering the inhibitory effect of DKK1 on the Wnt system, and therefore on osteoblasts, this could represent a favorable condition for the erosive or the bone mineral density reducing the evolution of the disease.

DKK1 concentrations are not only influenced by inflammatory factors but also by mineral metabolic ones: for instance the long term effects of PTH on DKK1 [18] could justify an undesired suppression of osteoblasts activity in conditions of chronic hyperparathyroidism.

The Current Predictive Value of Bone Erosions is Low

Being able to predict a probably irreversible radiological damage or its progression is paramount to operate an early intervention and to evaluate the opportunity of a more or less aggressive treatment. The identification of specific risk factors could also enable the discovery of possible pathogenic components; besides, a modest predictive value of the already known risk factors could outline the opportunity to look for newer ones. A review of the past experiences has led to the proposal of predictive models for persistently erosive arthritis [19-22]. The main factors considered were: durations of symptoms (from 6 weeks and 6 months), morning stiffness ≥ 1 hour, joint count ("swollen" and "tender" joints) with arthritis in ≥ 3 joints, a positive "squeeze sign" of metatarsophalangeal and metacarpophalangeal joints, the positivity of rheumatoid factor, the positivity of anti-citrullinated antibodies, the presence of erosions at the hands and/or feet X-rays. In most of the studies conducted in early RA, a relevant factor for the prognosis is the finding of inflammation at the physical or instrumental examination (the number of swollen joints or typical sonographic or MRI abnormalities). Many studies have also taken into account the use of laboratory inflammation markers (such as ESR and CRP) as prognostic indicators in an early phase of the disease, since there is evidence of a correlation between the intensity and persistence of the inflammation and the progression of bone damage [23,24]. All this support the relevant pathogenic role played by inflammation in respect of bone erosions, focal or systemic. As a further confirmation of this it was recently observed that the repair of bone erosion can almost exclusively happen in non-swollen joints [25]. However, CRP could be a not so good predictive marker since this parameter is not infrequently normal in the early phases of the disease and some studies have also questioned the predictive ability of the determination of ESR and CRP in the early phase towards the development of radiological damage at one or two years.

It is also known that the polymyalgia-like onset RA, typical of the elderly, is characterized by high ESR and CRP values at the onset but a little tendency to develop short term erosions. Finally, there can even be radiological progression of the bone damage in absence of phlogosis signs, at least as detectable at physical examination [2]. Therefore inflammation does not explain everything about the bone damage in RA, or at least not every time.

On the other hand even the inclusion of the best prognostic known risk factors (RF and/or anti-CCP positivity, previous bone erosions), as well as inflammatory markers as CRP, to identify or exclude a significant risk of radiological progression, leads to 38% of false positives and 9% of false negatives [26].

Recently it was reported that even including in addition to the inflammatory markers 10 clinical variables (anti-CCP antibodies, RF, BMI, age, duration of symptoms, involvement of lower extremities, HLA, number of swollen joints, sex and anti-vimentin antibodies), only 32% of the bone erosions risk variance can be explained, thus confirming the modest predictive value in terms of erosive risk estimation through the multivariate model based on the actual known factors [27].

There is evidence that many other factors, besides inflammation, are acting and could interfere both in a pathogenic and in a protective extent concerning the bone involvement in RA and many of these are not well clarified yet. Note actually how, among the predictive factors of bone erosion, it's not considered any variable related to the bone or mineral metabolism.

Metabolic Factors Predictive For Bone Erosion

Markers of bone turnover, bone mineral density (BMD), PTH and DKK1 might represent new predictive biomarkers of bone erosions

Markers of bone turnover: Some parameters of the bone or cartilage metabolism have been investigated as possible markers or prognostic indicators of bone erosions [23,24,28-31]: they are the serum, urinary or synovial concentrations of many proteins connected to the bone or cartilage degradation (i.e. fragments of type I or II collagen, oligomeric proteins of the cartilage matrix) or regulators of osteoclasts (RANKL and osteoprotegerin) or osteoblasts activity (DKK1). For instance, it was observed that the urinary pirinolines and desoxypiridinolines excretion, expression of an increase in osteoclasts activity, relates with the scores of disease activity [29,30], confirming the role of the pro-inflammatory cytokines in the activation of bone reabsorption. In another study it was found that the erosive evolution in RA would occur in patients presenting higher levels of serum C-terminal telopeptide of type I collagen (CTX), a marker of osteoclastic resorption [31]. The clinical relevance of these limited observations is anyhow still uncertain.

Bone mineral density: Another possible candidate among the predictors of erosions could be bone mass or bone mineral density (Bone Mineral Density, BMD. The connection between RA and the reduction of BMD that is osteoporosis has gone defining over the years, although it has always been seen as the effect of RA or its pharmacological treatment on BMD, and not as the role of BMD towards the risk of bone erosions.

Traditionally in RA we speak of juxta-articular osteoporosis, generalized osteoporosis and, among the latter, drug-induced osteoporosis, corticosteroids in particular. The prevalence of osteoporosis in women with RA ranges from 30 to 50%, depending on the sites evaluated through bone densitometry [32]. If we also consider less severe conditions, such as osteopenia, the prevalence rises and touches 80%.

Bone mineral loss in RA appears to depend not only by the use of corticosteroids, although most of the available studies have been strongly conditioned by the use of corticosteroids: there are only few studies conducted in subjects who did not receive similar treatments, and either way always in less active diseases. On the other hand it should be considered that corticosteroid treatment in RA, through reducing the pathogenic component linked to phlogosis and especially if at lower dosages, could have neutral or even benefic effects, at last in the short-term, both regarding osteoporosis (notably the juxta-articular form [33]) and the erosion risk [34]. All this despite the well-known deleterious effects of corticosteroids towards bone (increase of bone resorption and inhibition of neoformation) and mineral metabolism (negativization of the calcium balance by reduction of the intestinal calcium absorption and increase of renal losses with consequent secondary hyperparathyroidism).

As already observed in 1994 at the vertebral level [35], recently as well it was reported that a high disease activity (evaluated through CRP or DAS28) represents an independent risk factor for hand BMD loss after 5 years [36].

In an Italian experience [32], besides confirming the deleterious effect of the corticosteroid treatment used in clinical practice and the classical risk factors for osteoporosis (menopause, age, BMI), an independent one was documented, represented by Health Assessment Questionnaire (HAQ). In premenopausal patients, in which we could exclude concomitant effects of an estrogenic deficiency, significantly

reduced femur BMD values were reported [37], even after the correction for age, BMI and the cumulative dose of corticosteroids, thus confirming the disease *per se* as a risk factor for osteoporosis.

But what is the relationship between BMD and bone erosions? The correlation is clear and predictable if one evaluates the hand BMD, expression of a contingent juxta-articular osteoporosis. In some studies it was actually reported a statistically significant inverse correlation of the hand BMD and the prevalence of erosions [38]. There is available evidence in this sense also in terms of radiogrammetry: the cortical thickness and in particular the internal diameter evaluated at the level of the II metacarpal bone was seen to correlate significantly with the Sharp score for erosions [39]. The wrist BMD was noted to be inversely correlated with the prevalence of erosions too [40]. The latter were also seen to be correlated with axial or systemic osteoporosis. It is known that subjects who have an erosive disease present a higher incidence of osteoporosis, both at lumbar spine and femur [32,41,42]. Also Solomon et al. [43] investigated in a cross-sectional study the relationship between bone erosions and BMD in 163 postmenopausal women affected by RA [43]. It was observed a negative correlation between femur BMD and the erosion risk, but the significance of this correlation was lost at multivariate analysis when age, disease activity evaluated with DAS-CRP, BMI and the use of corticosteroids were included. The results of these studies suggest that the functional damage associated with erosions and therefore the disease severity could be responsible for the generalized osteoporosis. Most of these results derived from cross-sectional studies, with all the consequent limits implied.

In one of these studies, for instance, there was a significant correlation between the cortical hand BMD reduction evaluated through digitalized radiogrammometry and the development of erosions through time [44-46]. In another study this correlation was observed also with the reduction of systemic BMD and in particular at femur level [47]. Recently, a multicentric Italian study involving more than 20 rheumatology centers [48], besides confirming the role of the severity and the duration of the disease and the positivity of anti-CCP and Rheumatoid Factor as risk factors for bone erosions, documented that femur BMD is significantly lower in subjects with bone erosions than in those without them . Femur BMD remains significantly correlated to erosions even when the data were corrected for the main variables which could influence bone mass such as age, inflammatory markers (ESR, CRP), functional status (HAQ, ADL), BMI, blood 25(OH)D levels, corticosteroid or bisphosphonates therapy. These results are in contrast with the ones of Solomon et al. [43] but are justified by the large size of our series, 7 times higher.

The relationship between femoral BMD and erosions is better than the one observed between the latter and lumbar BMD [43,47-49]. This observation is, from a certain point of view, unexpected since the trabecular bone is more metabolically active and therefore a greater influence of proinflammatory cytokines would be expected on this site. On the other hand it is also known that with aging there is a loss of accuracy of the assessment of vertebral BMD due to concomitant osteoarthritis.

From another point of view, however, the greater correlation of erosions with the femur BMD, site of mainly cortical bone, is not surprising since these skeletal complications affect primarily this histological type of bone. The meaning of the direct correlation between femur BMD and the incidence of erosions appears to be scientifically and clinically relevant: if this observation, a result of a cross-sectional study, with all the consequent limits this implies, will be confirmed by longitudinal studies, it could mean that a high BMD, especially at the level of the cortical bone, has a protective role against the risk of bone erosion.

Actually, in a sub-analysis of the BeSt study the progression of the erosive score was faster in patients with lower BMD [47] and in an another recent study the radiographic erosion score after 3 years in patients with osteopenia/osteoporosis at baseline was double the patients with normal BMD [49]. Since there is also a positive regression between BMD and BMI, the correlation we found could justify the protective effect already described in several studies [43,50,51] of a high BMI against the risk of occurrence of bone erosions.

BMD and its variations, in addition to the traditional clinical mean of assessment of bone mass, could be proposed as indicator for severity and prognosis of erosive complications in RA, obviously to be placed side by side to the radiographic evaluation, ultrasound and magnetic resonance imaging.

Generalized osteoporosis and bone erosions are likely to share not only the same pathophysiological mechanisms, but also to influence each other. Therefore they require an even more combined therapeutic approach.

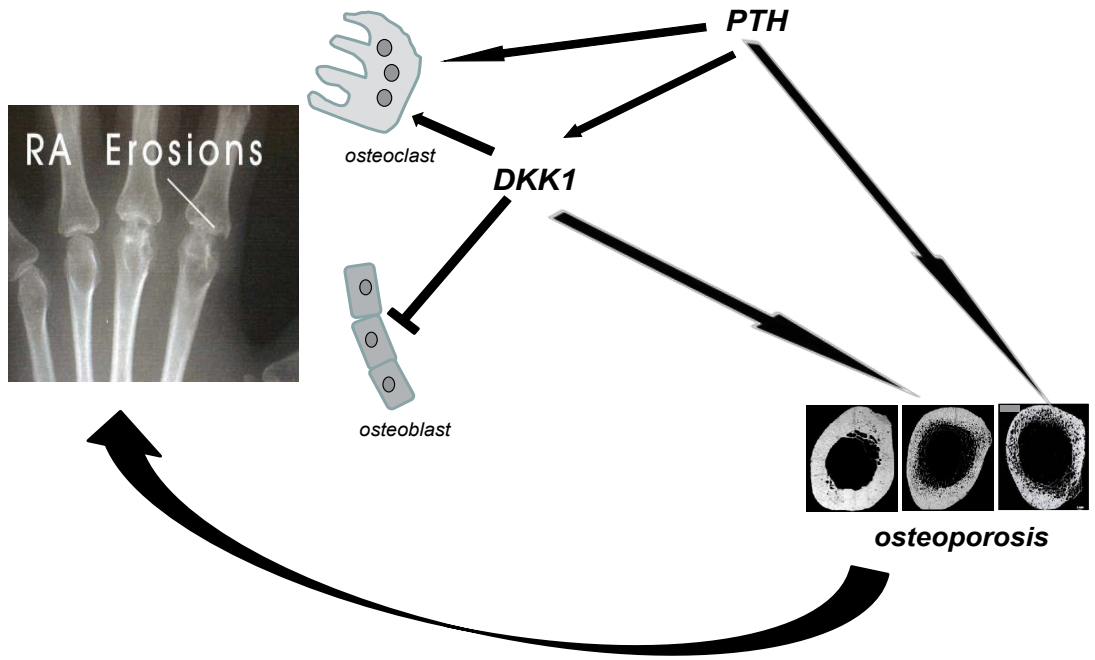

Figure 1: Metabolic pathogenesis of bone erosion. Chronic increase of PTH induces osteoclastogenesis, osteoporosis in cortical bone, and expression of DKK1. DKK1 itself leads to inhibition of osteoblast differentiation, and reduces focal and systemic bone formation. Osteoporosis of cortical bone increases the risk of bone erosions.

PTH: From physiopathology, the risk of osteoporosis associated to a chronic condition of hyperparathyroidism is well known, involving especially the cortical bone. Secondary hyperparathyroidism, probably, but not only, due to a vitamin D deficiency, is particularly common among RA patients [49]. It seems now quite relevant the recent observation that chronic higher levels of PTH may be directly associated, in RA, to a greater risk of erosions [48], perhaps due to a greater impairment of the cortical bone. This generates a new metabolic hypothesis of the pathogenesis of erosions which supplements the inflammatory one. The increased bone resorption and the contemporary reduction of bone formation, predisposing the erosions, could be attributed to the known chronic effects of PTH, stimulator of osteoclast activity and inhibitor of osteoblast activity. Moreover the involvement of PTH in the metabolic pathway of DKK1 could contribute to the pathogenesis of bone erosions [50].

DKK1: Recent studies documented the important role of DKK1, the physiological inhibitor of the Wnt system, in the regulation of periarticular bone remodeling [51,52]. The Wnt system is not only renowned for promoting bone neo-formation by osteoblasts but also for inhibiting bone resorption by osteoclasts [53-55].

Elevated levels of DKK1, under the stimulus of TNF-α, were found into the synovial fibroblasts and in the serum of RA patients [52,56] in whom they correlate with inflammatory markers and with the presence of bone erosions [17,50,57,58]. It has been demonstrated that some polymorphisms of genes regulating DKK1 expression affect the progression of bone erosions [59] and it also has been demonstrated that the DKK1 blockade could prevent bone erosions and the systemic loss of bone [60]. A chronic treatment with PTH induces an increase of serum DKK1 levels [18] and these positively correlate with the PTH levels in different clinical conditions [61-63], including RA [50].

The levels of DKK1 in RA also correlate inversely with BMD, in particular in the sites of mainly cortical bone as the femur [50].

Conclusions

Recent studies revealed an important role of some factors of bone metabolism in the pathogenesis of erosions. The result is a new pathogenic hypothesis for bone erosions in RA (Figure 1), which supplements the inflammatory one: the reduction of osteoblasts activity and the increase of the osteoclasts one, involved in the pathogenesis of bone erosions and osteoporosis, are not only the consequence of the action of inflammatory cytokines such as TNF-α, but also of increased levels of DKK1 resulting from inflammatory and also metabolic factors, including PTH. On the other hand osteoporosis, in particular the cortical involvement, facilitates the appearance of erosions.

Failing to assess and correct these metabolic alterations may explain an insufficient response in terms of prevention or healing of bone erosions to the drug treatment of RA.

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