

Osteoporosis in inflammatory joint diseases

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Abstract Rheumatoid arthritis (RA) and ankylosing spondylitis (AS) are two inflammatory joint diseases characterized by bone complications including osteoporosis. In RA, periarticular bone loss, bone erosions, and systemic osteoporosis are observed, with an increased risk of fractures. Determinants of fractures are underlying conditions (as RA has a female preponderance and an increased prevalence with age), severity of the disease, and use of glucocorticoids. However, bone loss can occur even in glucocorticoid-naïve patients. Prospective data show that the optimal control of inflammation in RA is associated with decrease in structural damage and bone loss. RA illustrates the role of inflammation on bone resorption. In AS, osteoporosis is an early event and vertebral fracture risk is increased. Bone loss is related mainly to inflammation, as the disease can occur in young male adult populations, and glucocorticoids are not used in this disease. However, AS is characterized by progressive stiffness and ankylosis of the spine and illustrates also the potential role of inflammation on local bone formation.

Keywords Ankylosing spondylitis · Bone formation · Bone resorption · Osteoporosis · Rheumatoid arthritis · Vertebral fracture

Introduction

Inflammatory joint diseases share in common the presence of an inflammatory process that targets the joints with adverse effects on structure and function. This process can also affect extra-articular tissues and organs. This paper focuses on two inflammatory joint diseases, rheumatoid arthritis (RA) and ankylosing spondylitis (AS), because bone complications are the main extra-articular complications of these diseases. These complications are completely different: bone erosions in RA and bone formation in AS; however, osteoporosis is common in these two inflammatory joint diseases, illustrating the key role of inflammation in bone remodeling. Systemic lupus erythematosus (SLE) is another condition with synovial inflammation; corticosteroid-induced osteoporosis can occur during SLE even in young adult patients. In contrast to RA, bone is not the main extra-articular target in SLE, and joint deformities, if any, are the consequences of destruction of periarticular connective tissues, without bone erosions.

Rheumatoid arthritis

RA is a systemic inflammatory disease characterized by distal and symmetrical synovitis. It affects 0.5% of the general population, with a female preponderance and an increased prevalence with age. This disease is responsible for joints destructions with a high risk of functional impairment and disability in advanced disease. Bone complications are the main extra-articular complications of the disease and can be described as three different forms:

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periarticular bone loss, adjacent to the inflamed and swelling joints (Fig. 1), bone erosions, which share common mechanisms with the periarticular osteopenia (Fig. 2), and systemic osteoporosis.

Fracture risk in RA

Patients with RA are at increased risk of fractures at the hip, vertebrae, and pelvis [1–3]. Humerus and tibia/fibula fractures risk is also increased in some [1] but not all [2] studies. The risk of wrist fracture is not increased in RA [1, 2] as compared to controls.

Using the General Practice Research Database [1], 30,262 patients with RA (ages ≥ 40 years) were compared to controls, with a mean duration of follow-up of 4.3 years; the increased risk of clinical fracture was 1.5 (1.4–1.6), as shown in other population-based studies [4]. Indicators of a substantially elevated risk of hip fracture were long duration of the disease, low body mass index (BMI), and use of oral glucocorticoids. Two important observations for the potential mechanisms of bone fragility have been made in the study: the risk of fracture is the same in men and women; the fracture risk remains elevated after excluding patients who had taken glucocorticoids at any time during the follow-up: RR, 1.7 (1.5–2.0) and 1.3 (1.2–1.4) for hip and clinical osteoporotic fractures, respectively, in patients without glucocorticoids [1].

A special attention has been paid to vertebral fractures (VFs) in RA, as the well-known consequences of recurrent vertebral fractures as chronic back pain, thoracic kyphosis,



Fig. 1 Periarticular osteopenia in rheumatoid arthritis



Fig. 2 Bone erosions in rheumatoid arthritis

functional impairment, and back-related disability have a large impact added to the underlying disability of the disease itself. Population-based control studies have shown that the risk of having at least one vertebral fracture is 1.7 [5] to 2.3 (1.4–3.9) [6, 7] and up to 6.2 (3.2–12.3) in a population of RA patients with a long-standing disease [8]. Distribution of the fractures along the spine is comparable to the distribution observed in controls, with highest frequency at the mid-thoracic spine and the thoracolumbar junction [5]. However, RA is characterized by a higher severity of spine involvement with a higher risk of having two or more fractures [5]. The incidence of vertebral fractures (defined as 20% reduction of vertebral body height) is 6.7 per 100 patient-years according to a study with a mean follow-up of 2 to 3 years [9]. Patients with incident fractures are those with older age, lower bone mineral density (BMD), higher disability, and previous non-vertebral fractures. Being diagnosed as having RA is related to vertebral deformities independently of BMD and corticosteroid use [5]. Whether the presence of vertebral fracture indicates a more severe RA is suggested by the result of a cross-sectional study showing a relationship between the Larsen score, which is a radiological score of joints damage assessing the accumulated disease activity, and presence of vertebral fractures [10]. Vertebral fractures may not come to clinical attention in RA because of analgesics use for painful joints. Thus, vertebral fracture assessment (VFA technology on dual X-ray absorptiometry (DXA) devices) should be used in these patients at the time of BMD measurement. Symptomatic vertebral fractures may be more frequent in patients with RA who are receiving corticoids, as compared to those who are not receiving this treatment [6]. This observation may be

related to a higher degree of surveillance bias in patients with steroids.

The question of risk factors for fractures has clinical implications. Glucocorticoid is one of the important markers of established osteoporosis. Indeed there is a higher prevalence of vertebral deformities and symptomatic vertebral fractures in RA patients receiving glucocorticoids as compared to those without glucocorticoids, with 1.5 times greater risk [6]. However, there is no relationship between cumulative prednisone dose and presence of vertebral deformities [6, 11]. Moreover, studies on early RA have shown that vertebral fractures can be observed in the first year of the disease: 30% of patients with a mean age of 68 years [12]. Glucocorticoid treatment can be considered as a marker for high- or long-standing disease activity, rather than being an independent risk factor.

Main risk factors associated with the risk of vertebral fracture in patients with RA are age, disability, low BMI, previous non-vertebral fracture, long-standing disease, and long-term glucocorticoid use [1, 13]. A long-term risk score of fracture in RA patients has been proposed [1], based on age, sex, duration of this disease, indicators of RA severity, and general risk factors. The score allows the estimation of the 5-year risk of hip fracture: a woman aged 65 years, with long-standing RA necessitating the frequent use of oral glucocorticoids, having a low BMI, and a history of fracture has a 5-year risk of hip fracture of 5.7% (5.3–6.1%) [1]. RA is one of the items of the FRAX[®] to estimate the 10-year risk of fracture in the general population, and the item is stated separately to corticosteroid and other secondary osteoporosis.

Several studies have shown that disability is a risk factor for fractures in RA. In a prospective study, increased disability score was a risk factor for incident vertebral fracture [9]. The link between orthopedic surgery and the incidence of fractures in RA has been reported: total knee or hip replacements are related to joints destruction and are performed in patients who had suffered of the most aggressive and active disease, i.e., those who have an increase in fall. Fall rates in RA patients are higher than in the general population [14, 15]. The increased risk of falling is related to stiff and painful joints, muscle weakness, low postural stability, and reduced physical performance. According to a prospective observational study, 42% of RA patients aged 59±12 years report falls over 1 year [14]. Fear of falling is a common feature in patients with RA [16] and affects activities. Abnormal body composition phenotypes are overrepresented in patients with RA. Accumulated disease activity and inflammation negatively affect lean mass, and sarcopenia is a component of the muscle weakness. Rheumatoid cachexia driven by chronic inflammation has been described in 1994 [17]. Nowadays, with appropriate use of effective disease-

modifying anti-rheumatic drugs (DMARDs), such a finding is not expected; however, women with RA may have sarcopenia and increased fat mass, participating to disability and increased risk of falls and fractures [18]. Changes in muscle function and quality may occur [19]. A change of body composition, with an increase in lean mass, has been observed during an anti-TNF therapy in patients with early RA [20]. Moreover, progressive resistance training programs can be used to prevent part of muscle weakness in RA [21].

Bone density in RA

A generalized osteoporosis is common in RA, at both the axial and the appendicular skeleton, in both female and male patients, and is obviously one of the determinants of the risk of fractures [22]. However, the relationship between decreased BMD and fracture is less clear in RA (and other inflammatory diseases) than in post-menopausal osteoporosis. Moreover, results are different when data are collected in general population or in patients referred in a rheumatology department.

Cross-sectional data

Based on register-based prevalence data, there is a twofold increase in osteoporosis in female patients aged 20–70 years having RA [23]. Several studies have shown a lower BMD in RA as compared to controls [24–26], the largest effect being measured at the hip. The BMD reduction is in the order of 2% to 17% at the hip and from no reduction to 10% at the spine; in a population of 394 female RA patients, no significant reduction in spine BMD was found, in contrast with a significant reduction of 3.7% to 8.5% at the hip and 4.2% to 5.0% at the femoral neck (according to age group) [23]. Some discrepancies may occur among studies, related to the age of the studied population, menopause status, and use of corticosteroids. In a study focused on peri-menopausal women, a BMD reduction of 5.5% was observed at the lumbar spine [27]. In the largest study conducted in male patients with RA, including 94 patients, no reduction was observed at the spine BMD, and a significant decrease at the hip (6.9%) was observed in the oldest patients only [28]; one longitudinal result suggests that BMD loss is lower in males than in pre- and post-menopausal women [29]. Actually, the number of studies conducted in males and their sample size do not allow a definite conclusion. A common observation in all studies is the large inter-individual variations, explaining why there is an apparent discrepancy between a relatively modest mean reduction in BMD and a high prevalence of osteoporosis. This prevalence is in the order of 20–30% at the spine and 7–26% at the hip [10, 13, 23, 29, 30]. Risk factors for having osteoporosis include not only the use of glucocorticoids,

high disability scores, low body weight and age but also rheumatoid factor (RF) status: the frequency of osteoporosis and reduced bone mass is higher in RF+ patients [23]. Seropositive RA is indeed considered as more commonly complicated by extra-articular manifestations than seronegative RA.

Among the confounding factors affecting the interpretation of BMD in RA patients is the long duration of the disease, including the course of the disease itself; an association is observed between the severity of RA and the risk of osteoporosis [30]. There is an association between high radiological RA damage and low hip BMD, and this is confirmed in subgroups of corticosteroid-naive patients. At time of diagnosis, there is no evidence of a prevalent decrease in BMD except the one related to demographic factors. In 381 patients with disease duration of 23 weeks (median), aged 55 ± 13 years, the prevalence of osteoporosis was 9% in the spine, 4% in the total hip, and 11% in either the spine or the hip. These patients had never been treated for RA nor by corticosteroids: the determinants of osteoporosis and reduced BMD were longer symptoms duration and the presence of rheumatoid factor [31]. These data are similar to those obtained in a population of patients with RA and a mean disease duration of 6 months, whose BMD did not differ significantly with controls [32]. These data suggest that spine and hip BMD is expected to be similar to population of same age and gender in RA patients at the time of diagnosis. That means that the assessment of other well-known risk factors such as low BMI, menopausal status, and familial history of fracture is still relevant in patients with early RA.

Prospective data and effects of control of inflammation

In cohorts of patients followed prospectively in the 1990s, including patients without corticosteroids, a decrease in spine and hip BMD is reported. Over 12 months, a BMD decrease of 2.4% and 4.3% at the spine and trochanter was observed in a population of 148 patients with early RA, before treatment with corticosteroids and disease-modifying drugs [29]. In this study, only disease activity was significantly associated with BMD decrease, and suppression of disease activity stabilized the bone loss. Another study of the disease has been conducted over the first decade in 76 RA patients: BMD was measured twice, at an average of 2.3 to 8.9 years after disease onset: the decrease of BMD was not higher than expected [33]. This might be explained by the characteristics of the treatment of these patients, as 90 % of them had already been treated with a disease-modifying drug during the first year of follow-up, and 95% of them had been treated at some time during follow-up. Management of RA has changed over the last

years and the efficacy of treatments is dramatically improved. Thus, the analysis of data concerning bone complications must take into account the period of observation. The large study conducted in GPRD by Van Staa et al., for example, resulted from data collected from 1987 to 2002, and the use of DMARDs was low in this population [1]. Disease-modifying anti-rheumatic drugs, as methotrexate and biotherapies (as anti-TNF therapies), have proved to be successful in retarding joint destruction in RA, while being able to control inflammation. The objective of the treatments is now the remission of the disease and the prevention of structural damage; prevention of bone complications is therefore expected. Infliximab (an anti-TNF therapy) is able to decrease bone resorption as assessed by CTX-1 and ICTP serum levels; at the introduction of this therapy in a population of patients with RA for 11 ± 7 years and failure of other DMARDs, an increase in the ratio between markers of bone formation and bone resorption is observed [34]. There was no BMD change over 1 year. In a small group of 20 patients with early and active disease, BMD loss was significantly reduced in patients receiving methotrexate and infliximab, as compared to those treated by methotrexate alone, at the femoral neck and the hip: -0.35 vs -3.43 and -0.23 vs -2.62% [35]; there was no change, and no difference among groups, at the spine. In this study, determinants of bone loss by multivariate linear regression were increase in C-reactive protein (CRP), a marker of inflammation, and bone erosions. Other studies conducted in largest sample sizes show that infliximab is able to arrest BMD loss at the spine [36]. The BeSt study compared prospectively the efficacy of four treatment strategies in RA: sequential monotherapy of several DMARDs, step-up combination therapy, initial combination therapy with tapered high-dose prednisone, and initial combination therapy with infliximab. In the group with better suppression of inflammation, the BMD loss was less than in other groups. Hand and generalized BMD loss was associated with progression of radiographic destruction [31].

These data support a parallel between inflammation control and bone loss arrest in RA. Actually, this may even lead to a provocative conclusion: any effective anti-inflammatory treatment including low-dose corticosteroids may have beneficial effects on bone loss. This was suggested in a study of 50 patients with active RA who started adalimumab (an anti-TNF therapy); all patients used stable methotrexate and were allowed to use prednisone, at less than 10 mg/day. At baseline, BMD was associated with disease activity and disease duration; adalimumab arrested further decrease in BMD, with an inverse association between decrease in serum CRP levels and increase in BMD, but a greater increase in

femur BMD was observed in patients who received concomitant low doses prednisone, as compared with those who did not use corticosteroids in combination with infliximab [37]. In a double-blind study comparing oral prednisone 7.5 mg/day for 2 years with placebo in early RA, prednisone group had less BMD loss (at the hand) over 1 and 2 years [38]. This does not challenge the evidence that chronic use of high doses of steroids is deleterious for bone but supports the concept that complete control of inflammation (and clinical improvement and increased mobility) is the objective for bone complications prevention, including systemic osteoporosis, in an inflammatory rheumatic disorder.

Hand bone density in RA

Periarticular bone loss is an early characteristic feature of RA (Fig. 1), and thus several studies focused on hand BMD measured by DXA as a mean to assess bone involvement in RA [39, 40]. Hand bone loss in patients presenting with an undifferentiated arthritis occurs rapidly in those patients diagnosed as having RA during follow-up, but not in patients with other inflammatory joint disorders or with non-inflammatory hand joint disorders; in patients with RA, a mean loss in hand BMD of 4.3% occurred over 12 months [41]. The predictors for this bone loss were the presence of RF and elevated CRP. In contrast, no change was measured at the spine and femoral neck in this small group of 13 patients. Hand BMD has been proposed as outcome measure in early RA [41–47]. In theory, the best sites to measure this bone loss would be around the metacarpophalangeal and proximal interphalangeal joints; however, most of the studies report the whole hand BMD because of a better precision and because of a better assessment of the whole inflammatory process of all the joints [46]. In patients who have RA of less than 12 months' duration, individual hand bone loss exceeding the smallest detectable change is observed in half of them over 6 and 12 months [44]. Hand DXA is thus considered by some authors as a sensitive tool to detect bone damage at the early stage of the disease. Over 5 years, hand bone loss is correlated with functional outcome measures [40]. In patients with established RA, with a mean disease duration of 9 years, hand bone loss is observed only in patients with disease duration ≤ 3 years and not in patients with longer disease duration [45], suggesting that hand bone loss is an early event in the course of the disease, stabilized thereafter [40]. Interestingly, this phenomenon is similar to the radiographic progression: 75% of bone lesions occur during the first 5 years of the disease. Digital X-ray radiogrammetry is a mean to measure cortical bone only. This compartment is also affected by RA as shown prospectively with a

decrease of 1% to 5% over 2 years [42, 48]. The cortical barrier of bone is more exposed to inflammation-induced osteoclasts activation than the trabeculae [49]. In a population of 163 patients with early RA, the decrease in hand BMD measured by radiogrammetry at the central part of the metacarpals was 1.7%, 2.8%, and 5.6% after 1, 2, and 5 years, respectively; the largest amount of bone loss was found in patients with severe inflammation [50]. High-resolution computed tomography shows that several damages can occur at the cortical compartment of juxta articular bones in RA [51], including small breaks and corrosion of the surface. While receiving appropriate treatments, with strategies driven by the careful assessment of inflammation, a majority of patients have no BMD loss at the spine and the hip, although a decrease in cortical hand BMD can occur [48]; whether or not this is related to persistent synovitis of hand joints in patients in apparent clinical remission is a relevant hypothesis: indeed even minor inflammatory changes in the joint can induce bone loss [52]. In a 10-year follow-up study of 136 patients with RA (disease duration less than 4 years), early cortical hand bone loss, measured by digital X-ray radiogrammetry, is an independent predictor of subsequent radiographic damage. Moreover, the predictive power is similar to the one of well-known predictors as CRP and anti-cyclic citrullinated peptides [48]. Thus, attention must be paid on peri-articular bone involvement at the hands as a potential predictor of outcome in RA.

Physiopathology of osteoporosis in RA

Patients with RA are at high risk of osteoporosis and fractures because they have several well-known risk factors: menopausal status, low BMI, reduced physical activity, and corticosteroids, but inflammatory disease activity may be the most important factor associated with bone loss in RA. The association between joint damage progression and both hand, spine, and hip BMD loss suggests common pathways between these processes.

Clinical observations support the key role of inflammation in osteoporosis: RA doubles the risk of hip and vertebral fractures, regardless of the use of corticosteroids [1], BMD loss is observed even in non-treated RA patients [29], disease activity is consistently associated with low BMD [29], and optimal control of inflammation stops bone loss, even if the use of low-dose corticosteroids is required [38]. This is in line with data obtained in the general population: even small elevations of C-reactive protein within the normal range increase non-traumatic fracture risk [53]. In a population-based study, variations within the low levels of inflammatory markers, especially interleukin-6, predicts bone loss and resorption [54], and the Health Aging and Body Composition Study confirms

that elevated inflammatory markers are prognostic for fractures [55]. Moreover, blockade of TNF α or interleukin-1 reduces bone resorption markers in healthy post-menopausal women [56].

Markers of bone remodeling and serum cytokines assessments have been used to gain insights into the mechanism of osteoporosis in RA, although their interpretation is complicated by the concomitant use of corticosteroids [57]. Urinary markers of bone resorption are found to be elevated, indicating a role of osteoclastic activation in RA-related osteoporosis [58]. CTX-1, a specific marker of bone resorption, predicts the risk of radiographic progression over 4 years independent of rheumatoid factor or erythrocyte sedimentation rate [59], suggesting that generalized bone loss and local periarticular disease are two sides of a similar phenomenon. The ratio of circulating OPG/RANKL in early untreated RA is a predictor of subsequent bone component of joint destruction [60]. In patients receiving an anti-TNF therapy, infliximab, serum CTX, and RANK L decrease dramatically, in parallel with a decrease in disease activity score, and a benefit on BMD change [36].

Bone loss and erosions are two complications of the same inflammatory process. Osteoclasts are found at the interface between synovitis and subchondral bone, and osteoclast precursors are abundant in the synovium of RA patients. In an osteoclast-deficient animal model, overexpression of TNF leads to chronic inflammatory arthritis, but no bone erosions [61]. The generation of osteoclasts in the synovial tissue allows the penetration in bone through the thin cortical barrier [62]. T lymphocytes stimulate osteoclast formation [63], and Treg cells suppress this phenomenon [64]. The T lymphocyte surface protein CTLA-4, which suppresses the costimulation and activation of these lymphocytes, inhibits RANK-L- and TNF-mediated osteoclastogenesis [65]. Among the T cell subsets, Th17 is the most important osteoclastogenic helper and the IL23–IL17 axis is critical for the arthritis-related bone loss and destruction [66].

RANK ligand is expressed at the pannus–bone interface at sites of bone erosion [67]. Expression of RANKL is upregulated by inflammatory cytokines IL1, IL6, IL17, TNF... which are abundant in the synovial tissue and the synovial fluid and thus are indirectly responsible for activation and survival of osteoclasts [68]. Moreover, these cytokines can induce the expression of receptors on the surface of monocytes, as osteoclast-associated receptor, which are important for osteoclast differentiation [69]. TNF is a key molecule in the pathogenesis of RA; overexpression of TNF can trigger systemic bone loss. RANK L has a permissive effect on the osteoclastogenesis effect of TNF, and osteoprotegerin protects against TNF-induced bone loss [70]. TNF is able to increase bone

resorption only in the presence of permissive amounts of RANK L [71]. In mice overexpressing TNF but lacking IL1, no deleterious bone effect is observed and no bone loss can be measured [72]. These experimental results may be used to explain clinical observations of heterogeneity of the joint destruction severity and bone involvement among patients.

There is no repair phenomenon of bone erosions in RA, suggesting an uncoupling phenomenon between bone resorption and bone formation. Dickkopf-1 (DKK-1) is expressed in synovitis of RA patients and can inhibit the wingless (Wnt) signaling pathway and thus bone formation. TNF is a potent inducer of DKK-1 and thus limits the expression of osteoprotegerin promoted by Wnt [73], suggesting that this cytokine can induce a bone resorption–formation unbalance. Active mineralizing surfaces are reduced at bone surfaces adjacent to inflammation in a murine model of arthritis, with a paucity of cells expressing alkaline phosphatase [74]; however, this compromised osteoblast function has been shown locally and it is unknown if this phenomenon is relevant for systemic osteoporosis.

Treatment of osteoporosis in RA

As most of the patients with RA are receiving glucocorticoids, guidelines on the prevention and treatment of glucocorticoid-induced osteoporosis must be applied, including by using bisphosphonates or teriparatide. Underlying conditions such as menopausal status, level of physical activity, and risk of falls [21] must be assessed for an appropriate prevention of fractures in RA.

The following step should be the dedicated treatment of inflammation-induced bone loss, i.e., of the effects of pro-inflammatory cytokines released into the circulation from the inflamed joints. Their pivotal role is demonstrated by studies of cytokine blockers: bone resorption and osteoclast formation can be inhibited by anti-IL6 [75], anti-TNF [76], and osteoprotegerin [77]. Successful DMARD treatment can result in an increase in osteoprotegerin expression and a decrease in RANK L expression at the synovial tissue level, which correlate with a reduction in erosion scores [78]. Denosumab, a human monoclonal IgG2 antibody that inhibits RANK, has been used in patients with RA in a 12-month double-blind placebo-controlled study. The results were as expected, based on previous experimental data: there was no clinical benefit on arthritis, but a reduction of bone damage. Moreover, denosumab treatment resulted in a sustained decrease in markers of bone turnover and a 2–4% increase in BMD at spine and hip over 1 year [79].

Clinical remission is now a realistic target of therapies in RA, with the objective of complete absence of synovitis.

Anti-cytokines therapies are able to prevent structural damage and have beneficial effects on bone loss. Complete suppression of inflammation is also the objective for optimal prevention of osteoporosis.

Ankylosing spondylitis

Ankylosing spondylitis is one of the spondylarthropathies (SpA), a group of inflammatory joint disorders, including also psoriatic arthritis, inflammatory bowel disease-associated SpA, and reactive arthritis. AS is the typical form of SpA with symptoms related to enthesitis, sacroiliitis, and spinal inflammation. The primary disease localization is thought to be the enthesis, i.e., the zone in which tendons and ligaments insert into the bone. The hallmark of the advanced AS is ankylosing enthesopathies and spine ankylosis (syndesmophytes), related to new bone formation (Fig. 3). This ankylosis is the cause of permanent disability of these patients. Although bone formation seems to be the cornerstone of the disease, AS is also associated with a systemic osteoporosis. This osteoporosis cannot be related to the underlying characteristics of the patients like in RA, as AS is typically a disease of young men, and glucocorticoids are not used in this disease. Osteoporosis has been reported as an early



Fig. 3 Lumbar syndesmophytes in ankylosing spondylitis

event [80] and thus cannot be related only to spine ankylosis and immobilization. AS is an inflammatory disease where both excess in bone resorption and excess in bone formation coexist.

Fracture risk in AS

Patients with AS have an increased risk of vertebral fracture, but not of non-vertebral fractures. VFs are less frequent than in RA but may lead to major neurological complications, a specific observation in AS.

The prevalence of vertebral fractures in AS is very different among studies, and this illustrates the large heterogeneity of the studied populations and the difficulty of diagnosis of these fractures in AS [81]. Spine fractures in AS can be transdiscal, i.e., between two vertebral bodies, in ankylosed spine; although they can occur after a low trauma and reflect bone fragility related to spine stiffness and decreased BMD, they should not be counted among vertebral bodies fractures. Erosions can occur in AS, at the anterior corners of the vertebral bodies, related to the adjacent enthesitis, leading to vertebral deformities, wedging of vertebrae, and hyperkyphosis in some patients. In this population with hyperkyphosis, the prevalence of vertebral deformities reaches 58% [82]. However, these deformities, leading to wedging of the vertebral bodies, should not be taken into account for the estimation of osteoporotic VF prevalence.

Using visual or morphometric definitions (vertebral heights or heights ratios decrease by 15% or 20%), prevalence of VFs is 10–30% [83–88]. In a retrospective population-based study on clinical fractures, the odds ratio (OR) for clinical vertebral fractures was reported to be 7.7 (4.3–12.6) and even higher in men [84]. In a primary care-based nested case–control study (231,778 patients including 758 AS patients), an increased risk of clinical vertebral fracture (OR=3.26 (1.51–7.02)) was reported for patients with AS [89]. Determinants of vertebral fractures and deformities in AS are gender (men more than women), low BMD, disease activity, more extensive syndesmophyte formation and hyperkyphosis. The risk of any clinical fracture (including non-vertebral fractures) increased in patients having AS associated with inflammatory bowel disease; this may be associated with corticosteroid use in these gut diseases, subclinical malabsorption, and a more intense systemic inflammation [89]. In contrast, the risk of fracture has been reported in one study as decreased in patients with AS taking non-steroidal anti-inflammatory drugs (OR=0.65 (0.50–0.84)); whether this effect occurs through a direct bone metabolic effect or an indirect one through a better physical activity allowed by pain relief is unclear [89].

Bone density in AS

Osteoporosis has been reported as an early event in AS [80]. Studies use either DXA or quantitative computed tomography (QCT) for spine evaluation, as syndesmophytes are a cause of artifactual increase of lumbar spine BMD (Fig. 3) [90]; prevalence of low BMD at the spine increases with the use of QCT, but DXA remains the standard method in AS and is reliable at the hip (except in patients with severe AS and coxitis, a condition which, in theory, can limit the rotation of the joint and preclude optimal positioning of the hip). Femoral BMD is associated with vertebral fractures [91] in AS, and in the same study the authors failed to identify a correlation between VFs and lumbar BMD. Prevalence of osteoporosis is 14–27% and 4–14% at the spine and hip, respectively, [85, 92–94] which is unexpected in these patients aged 30–40 years. In a cross-sectional study of 103 patients with AS, the proportion of patients with osteoporosis was 14% at the lumbar spine and 24% at the femoral neck [95]. The proportion of osteoporotic patients varies according to the disease duration: in patients with disease duration <5 years, 11% and 15% were osteoporotic at the hip and spine, respectively; in patients with disease duration >10 years, 29% were osteoporotic at the hip, but only 4% at the lumbar spine, as assessed by DXA. Using QCT, this proportion with long-standing disease was 18%, illustrating the artifactual increase in lumbar spine BMD related to syndesmophytes occurring during the course of the disease. In this study, hip bone loss was detected more frequently in patients with syndesmophytes, suggesting a parallel between local bone growth and systemic bone loss [95]. In another cross-sectional study of 80 patients, parameters related to osteoporosis were disease duration, body mass index, and a disease activity index. The presence of VFs (with a prevalence of 18%) was independently associated with disease duration and modified Stoke AS spine score (assessing the structural damages), but not with BMD, supporting the concept that in AS, as in RA, BMD alone cannot explain the whole spectrum of bone fragility [94].

Physiopathology of osteoporosis in AS

AS raises a paradox: patients have both a systemic bone loss and osteoporosis, and new bone formation, as syndesmophytes. Although AS is an inflammatory disorder, as RA, there is a sharp contrast between the two diseases: very few erosions are observed in AS, with the exception of the anterior corners of the vertebral bodies and the sacroiliitis. Thus, different mechanisms underline the systemic bone loss and the local changes in AS.

Osteoporosis can occur because of reduced physical activity, decreased spine mobility related to pain, stiffness

and ankylosis, and/or subclinical gut involvement. Genetic factors have been suspected, and vitamin D receptor gene may contribute to BMD differences in patients with AS; these polymorphisms are also linked to inflammatory activity [96]. Prospective studies in patients with AS suggest that a decrease in BMD is observed mainly in patients with permanently increased CRP [81, 97]. In patients receiving anti-TNF therapy, there is a dramatic improvement of symptoms, a profound decrease in inflammation, and an increase in BMD [98, 99]. In a 2-year follow-up of 106 patients, we observed 5.8% and 2.3% increase of the lumbar spine and hip BMD, respectively [100], and this increase is prolonged with long-term anti-TNF therapy at both sites (including at the spine in patients without prevalent and incident syndesmophytes) (personal communication). In parallel with these observations, biochemical data suggest the involvement of increased resorption in bone loss in AS [101]. In 63 patients with AS, we found an increase in urinary excretion of pyridinoline, deoxypyridinoline, and crosslinks [92]; bone loss has been found to be related to inflammation, as evaluated by usual parameters and IL6 levels [102]. In patients with AS, serum concentration of RANK L and expression of intracellular RANK L in CD4+ and CD8+ T cells are increased [103]. As expected, the introduction of anti-TNF therapy induces a drop in serum CTX, demonstrating an anti-osteoclastic effect [100]. In this disease with systemic bone loss and local bone formation, the interpretation of bone markers of formation is a puzzle: serum levels of OPG and osteocalcin have been described as increased, decreased, or unchanged.

The HLA B27 transgenic rat is a relevant model of SA, as these animals develop spondylitis, peripheral arthritis, and gastrointestinal and skin lesions. These animals exhibit decreased bone strength, related to a significant decrease in bone volume, trabecular number, and trabecular thickness. Serum levels of CTX, RANKL, and OPG are not changed in these rats having a disease for several months; whether these parameters could be elevated in the early phase of the disease in this model is unknown. However, these HLA B27 rats have an increased RANK L-to-osteoprotegerin mRNA ratio, suggesting the implication of this system in the systemic bone loss; serum levels of PINP and osteocalcin are not changed, but mRNA level of osteocalcin in bone is increased [104].

The question is the temporal and spatial sequence of the three events: systemic inflammation, bone resorption, bone formation. Syndesmophytes are considered to develop from a prior inflammatory lesion, as shown by prospective clinical studies using magnetic resonance imaging at the spine [105]. Bone marrow inflammation is a common feature in AS, and vertebral bodies osteitis is frequent in MRI performed in patients with AS and back pain. This

contrasts with RA, where bone marrow changes are more limited as assessed by imaging techniques (although this does not preclude hypothesis on functional changes of bone marrow in RA).

Local bone formation results from an endochondral process: mesenchymal cells undergo chondrogenic differentiation to being hypertrophic chondrocytes, and the cartilage becomes progressively bone through the osteoblasts activity. The pathways underlying this phenomenon include bone morphogenetic proteins (BMPs, which are members of the transforming growth factor- β superfamily) and wingless-type like (Wnt) signaling. In the spontaneous arthritis model DBA/1 mice (which develop arthritis and joint ankylosis, but not spine ankylosis), different BMPs are expressed during the process of ankylosis; this process is inhibited by systemic overexpression of noggin, a BMP antagonist [106]. Actually, because the elevated levels of BMPs in synovial tissue is similar in AS and RA, the differential result in bone formation is explained also by the predominant site of the inflammatory process: enthesitis is not affected in RA, where bone formation is not observed [107]. Sclerostin expression is impaired in patients with AS, suggesting a specific alteration of osteocyte function [108]. Sclerostin inhibits BMP-stimulated bone formation but shares also characteristics with DKK1, which is an antagonist of the Wnt pathway; Diarra and colleagues changed the feature of arthritis by using anti-DKK: anti-DKK-treated mice exhibited bone formation, which was absent in controls [73]. Serum levels of DKK1 have been found to be very low in patients with AS, supporting the concept of an activity of Wnt signaling in AS [109]. Blockade of DKK1 promotes ankylosing of sacroiliac joints in an animal model of spondylarthropathy [110]. In contrast to these findings, serum DKK1 levels were found to be elevated in another study [111], and these levels increased after anti-TNF administration. Beyond these differences in serum levels, a key point is that the receptor binding of DKK1 is reduced in patients with AS [73].

There is a relationship between this phenomenon of bone formation and inflammation: BMP can be induced by TNF and other pro-inflammatory cytokines [107], but DKK production (and thus decrease in Wnt pathway) is also stimulated by TNF [73]. BMPs and Wnt pathways may act at different stages of the endochondral bone formation and thus may have a different role in the formation of syndesmophytes, but this does not explain all the features of patients with AS: syndesmophytes can occur at sites without evidence of previous inflammation, and the two processes bone resorption/formation can be temporally and topographically distinct, as shown at the Achilles tendon enthesitis [112]. There is evidence for an uncoupling of inflammation and joint remodeling in a

mouse model of SA and, in this model, complete inhibition of TNF does not affect the severity and incidence of joint ankylosis [113]. In two rat arthritis models, bony spurs formation occur shortly after the onset of inflammation and are not affected by inhibition of either TNF α and RANK L [109]. In clinical studies, anti-TNF α therapies are dramatically effective on symptoms and improve BMD [100], but there is no evidence that they affect the structural changes in AS. Other hypothesis raised from the observation of ossifications of human spinal ligaments which mimic syndesmophytes but are not related to an underlying inflammation; endothelin may play a role [114] and, interestingly, DKK1 participates to this mechanism [115].

Thus, for physicians, systemic osteoporosis and structural damages (i.e., bone formation) must be considered uncoupled in AS, suggesting different targets for therapies.

Treatment of osteoporosis in AS

No clinical study has been conducted in this population. In patients without indication for anti-TNF therapy, current guidelines for treatment of male osteoporosis and premenopausal women must be applied. In patients with anti TNF therapy and low BMD, it seems logical to assess the benefit given by this treatment before introducing an antiosteoporotic drug [100].

Conclusion

Systemic osteoporosis is a complication of long-standing inflammation. Patients with inflammatory joint disorders must have BMD measurement and appropriate assessment of fracture risk, including vertebral fracture assessment, underlying conditions, and persistent inflammation. Prevention of osteoporosis can also be a benefit of complete control of inflammation, which is the target of treatment and is now achievable.

Conflicts of interest None.

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