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REVIEW

Osteoporosis in rheumatic diseases

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Abstract

Rheumatic diseases, characterized by chronic inflammation and damage to various organs and systems, include systemic lupus erythematosus, rheumatoid arthritis, ankylosing spondylitis and other connective tissue diseases. Bone is a target in many inflammatory rheumatic diseases. In recent years, the survival of patients with rheumatic diseases has increased markedly and the relationship between rheumatic diseases and osteoporosis (OP) has become more prominent. OP and related fragility fractures increase the morbidity and mortality of rheumatic disease. The cause of OP in rheumatic diseases is complex. The pathogenesis of OP in rheumatic diseases is multifactorial, including disease and treatment-related factors. Osteoimmunology, a crosstalk between inflammatory and bone cells, provides some insight into the pathogenesis of bone loss in systematic inflammatory diseases. The aim of this article is to review different risk factors in rheumatic diseases. Several factors play a role, such as chronic inflammation, immunological factors, traditional factors, metabolism and drug factors. Chronic inflammation is the most important risk factor and drug treatment is complex in patients with OP and rheumatic disease. Attention should be paid to bone loss in rheumatic disease. Optimal treatment of the underlying rheumatic disease is the first step towards prevention of OP and fractures. Apart from that, a healthy lifestyle is important as well as calcium and vitamin D supplementation. Bisphosphonates or denosumab might be necessary for patients with a low T score.

Key words: Rheumatic diseases; Osteoporosis; Systemic lupus erythematosus; Rheumatoid arthritis; Spondyloarthritis; Chronic inflammation

Core tip: Osteoporosis (OP) and related fractures are one of important complications for patients with rheumatic diseases. The pathogenesis of OP in rheumatic diseases is multifactorial, including disease and treatment-related factors. Chronic inflammation is the most important risk factor and drug treatment is complex in patients with OP and rheumatic disease. Controlling rheumatic disease effectively is an important way to prevent OP.

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INTRODUCTION

Rheumatic diseases include rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), systemic sclerosis (SSc), ankylosing spondylitis (AS) and other connective tissue diseases. The characteristics of rheumatic disease are chronic inflammation and damage to various organs and systems. Rheumatic diseases can affect bone, muscle, periarticular attachment and soft tissue. Osteoporosis (OP) is a systemic bone disease characterized by low bone mass and disruption of bone microstructure, increasing skeletal fragility and resulting in fractures occurring easily. Bone mineral density (BMD) is commonly detected by dual-energy X-ray absorptiometry (DEXA). OP is defined by a T score of -2.5 or lower, that is, > 2.5 SD below the average density of a young normal adult.

The survival of patients with rheumatic diseases has increased dramatically during the past few decades. Patients with rheumatic diseases have an increased prevalence of long-term complications, such as cardiovascular diseases and OP[1,2]. Bone is always involved in many inflammatory rheumatic diseases. OP and related fractures are one of the most important complications for patients with rheumatic diseases. Osteoporotic fractures and osteonecrosis increase the morbidity and mortality of rheumatic diseases[3]. The pathogenesis of OP in rheumatic diseases is multifactorial and includes disease and treatment-related factors. Rheumatic diseases could result in bone loss through several mechanisms: inflammation, traditional risk factors and drug-induced factors[4]. OP significantly decreases the quality of life of the person with rheumatic disease but the clinical manifestations of OP are not typical. Glucocorticoid-induced osteoporosis (GIOP) accounts for 5.0%-61.9% of adult rheumatic disease[5]. Although OP has a high rate of prevalence among rheumatic disease patients, most patients do not receive adequate diagnostic evaluation and drug therapy. This article focuses on the relationship between rheumatic diseases and OP.

DATA SOURCES AND SEARCHES

A systematic search of the literature (from January 1, 1990 to August 31, 2014) was performed using the PubMed and Cochrane databases. We also searched for previously published systematic literature reviews.

The following keywords were used for the search: "rheumatic disease" and "bone mineral mass" or "osteoporosis"; "rheumatoid arthritis" and "bone mineral mass" or "osteoporosis"; "systemic lupus erythematosus" and "bone mineral mass" or " osteoporosis"; "ankylosing spondylitis" and "bone mineral mass" or "osteoporosis"; "systemic sclerosis" and "bone mineral mass" or "osteoporosis".

Study inclusion/exclusion criteria

The literature search was performed independently by two of the authors and a consensus reached. The inclusion criteria for papers were as follows: (1) studies in English; (2) full text of articles available; (3) human patients with rheumatic disease; (4) randomized controlled clinical trials; and (5) diagnostic criteria of different rheumatic diseases met respective international diagnostic criteria. The exclusion criteria were as follows: (1) case reports; (2) reader comments; (3) duplicate publications; (4) literature without original data; and (5) studies with < 20 patients.

OP IN SLE

Prevalence and sex

SLE is characterized by a variety of clinical manifestations, a spectrum of autoantibodies and a multisystem involvement. There are debates about OP in SLE. The main controversies are about the prevalence of OP and the secondary debate is the dependence of glucocorticoids (GCs). However, all studies have demonstrated that bone loss is more common in patients with SLE than in the healthy human. Several cross-sectional studies have evaluated BMD and the prevalence of OP in SLE patients. There was a difference in the prevalence of OP in these studies but the results suggest a generalized reduction in BMD[6]. The reported prevalence of osteopenia is 25%-74%, while that of OP is 1.4%-68%[7]. SLE influences mainly reproductive females and is affected by the change of sex hormones. For women, osteopenia was found in 40% of patients, while OP was found in only 5%. Low body mass index (BMI), long-term disease damage and corticosteroid treatment were risk factors for low BMD in premenopausal SLE patients. Lumbar and femoral BMD of premenopausal patients with SLE was decreased and related to disease damage and long-term corticosteroid therapy[8-13]. For postmenopausal SLE patients with long-term GC treatment, OP is always a common and terrible problem. The prevalence of lumbar spine OP is as high as 48%[14,15]. Recently, a cross-sectional study investigated BMD in 67 women with SLE in a Mediterranean region and reported that the prevalence of osteopenia was 28%-46% and OP was 3%-9%[16]. For men, although a few studies of OP in SLE have been reported, they have come to different conclusions. Two studies showed that bone mass in men with SLE was not decreased despite corticosteroid therapy[17,18]. Another study reported different results, that low BMD and low body mass were prevalent for males with SLE. When SLE patients were compared with healthy controls, the Z scores of BMD at the femoral neck and spine were significantly lower in SLE[19]. A recent cross-sectional and longitudinal study indicated that juvenile SLE patients had low bone mass and a decreased peak bone mass and juvenile-onset SLE had a high risk of OP in early adulthood[20]. Another longitudinal study of OP in juvenile SLE

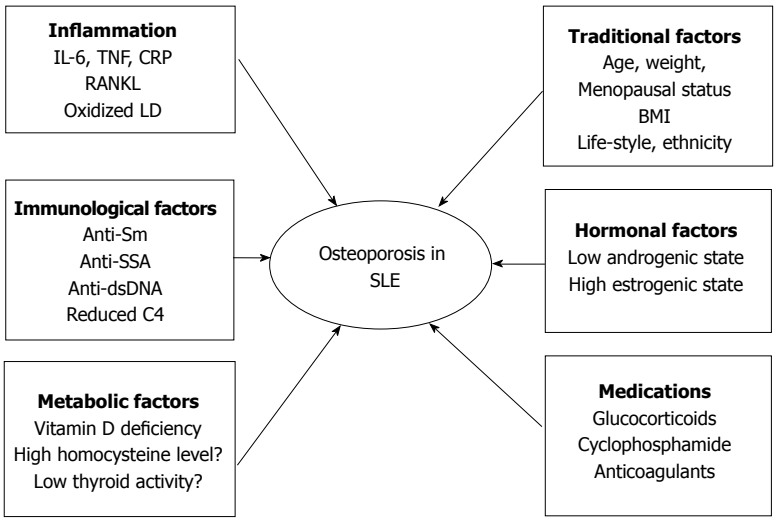

Figure 1 Risk factors of osteoporosis in systemic lupus erythematosus. SLE: Systemic lupus erythematosus; IL-6: Interleukin-6; TNF: Tumor necrosis factor; CRP: C-reactive protein; RANKL: Receptor activator of nuclear factor-κB ligand; LDL: Low-density lipoprotein; BMI: Body mass index; Anti-Sm: Anti-Smith; Anti-dsDNA: Anti-double-stranded DNA.

indicated that BMD had a significant inverse correlation with the cumulative dose of corticosteroids[21].

Risk factors

The reason for OP in SLE is considered to be multi-factorial and includes inflammation, immune-mediated mechanisms, traditional OP risk factors, metabolic factors, serological factors and drug-induced adverse effects (Figure 1)[7].

The inflammation associated with active disease contributes to the development of OP in SLE. Recent literature has affirmed an association between low BMD and the inflammatory feature of SLE. Several inflammation markers, such as tumor necrosis factor (TNF)-α, interleukin (IL)-1 and IL-6, can induce osteoclastogenesis which promotes the proliferation of precursor osteoclastic cells or activation of differentiated osteoclasts[22]. Different studies have provided different views of the pathogenesis of inflammatory bone loss but now it is considered that the key osteoclastogenic cytokine, receptor activator of nuclear factor-κB ligand (RANKL), plays an important role in the balance of osteoclasts and osteoblasts. Osteoprotegerin (OPG) is the physiological decoy receptor that moderates the biological activity of RANKL[23]. SLE is a systemic autoimmune inflammatory disorder with increasing serum TNF-α, IL-1 and IL-6. These cytokines can increase and induce RANKL expression[23,24]. The serum level of oxidized low-density lipoprotein (LDL) is increased in SLE[25]. Oxidized lipids can induce increased production of RANKL and TNF by activating T cells. Both RANKL and TNF increase the activity and maturation of osteoclasts[26]. A 5 year follow up study demonstrated that SLE patients had significant BMD loss in the femoral neck and hip. Disease activity and new organ damage could result in bone loss and new organ involvement was an independent predictor of bone loss at the femoral neck[27].

Immune-mediated mechanisms are associated with OP of SLE and SLE *per se* contributes to the deterioration in bone density, cortical microstructure and bone strength. SLE patients without GC treatment have a significantly lower real BMD at the femoral neck and hip and diminished radial total volumetric BMD and cortical area and thickness when compared with controls[28]. SLE is marked by both humoral and cellular abnormalities, including multiple autoantibodies that may participate in the disease. The absence of anti-SSA and presence of anti-Sm were associated with higher BMD in the lumbar spine. The patients with positive anti-SSA were generally advised to avoid sun exposure, which may explain the relationship between the absence of anti-SSA and lower bone loss[14]. Higher serum anti-double-stranded DNA level was an independent predictor of a higher 10 year probability of hip fracture and this reinforced the concept that the inflammatory state as reflected by high SLE disease activity might be an important driver for bone loss[29]. Although clinical studies could not make a conclusion about an association between disease activity score and low BMD, low C4 levels could predict low spine BMD in SLE[30]. The relationship between organ damage and bone loss was reported by several studies, organ damage resulted in bone loss at both the femoral and the lumbar level, and the relationship between cumulative disease damage and reduced BMD is independent of corticosteroid use[31,32].

Metabolic factors are also risk factors for OP. Vitamin D deficiency, hyperhomocysteinemia and low thyroid activities are metabolic conditions that can induce bone loss in SLE. Vitamin D is a secosteroid hormone that regulates calcium homeostasis, bone mineralization and remodeling, as well as neuromuscular function. Many studies in the past decade have reported increased frequency of vitamin D deficiency among patients with SLE[33-37]. The prevalence of vitamin D insufficiency in SLE patients ranged from 16% to 96% and the prevalence of vitamin D deficiency ranged from 4% to 54%[38]. A number of factors contributed, such as avoidance of sunshine as a result of photosensitivity, dark skin

pigment, sun screen precautions, disease activity, renal failure, use of drugs, such as GCs, antimalarial and antiepileptic agents, and anti-vitamin D antibodies. Homocysteine (Hcy) modulates bone remodeling *via* several mechanisms, such as increased osteoclast activity, decreased osteoblast activity and direct action on the bone matrix[39]. SLE patients have an increased level of plasma Hcy[40,41] but no studies demonstrated an association between hyperhomocysteinemia and OP in SLE[42].

The traditional factors, including age, low body weight and postmenopausal status, are all independent risk factors for OP in SLE. It is unclear if sex and ethnicity have an effect on bone loss in SLE; African-American women have lower hip and lumbar spine BMD compared with white women with SLE[43]. The prevalence of OP in Chinese SLE patients with corticosteroids is 4%-6%, less than that reported in Caucasians (12%-18%)[11]. Two studies have shown that white and non-African Caribbean races were a risk factor for OP in SLE patients[44,45]. Daily dietary calcium intake did not correlate with BMD in premenopausal women with SLE[46]. Smoking and alcohol have not been reported as risk factors for OP in lupus[13,47] but alcohol use was associated with low BMD in Hong Kong men with lupus[19].

Hormonal factors, for example, include the significant positive relationship between serum dehydroepiandrosterone sulfate and low BMD[48].

The last factor is drug-induced adverse effects in SLE therapy. GCs are widely used for the therapy of SLE exacerbations and complications. GCs are a double-edged sword with respect to bone loss, are associated with the development of OP and fracture and can trigger significant bone loss. At the same time, they have good effects by controlling disease activity and systemic inflammation in bone[7]. A dose-dependent relationship has been demonstrated between GC use and spinal bone loss in SLE. Significant bone loss was observed in the lumbar spine for SLE patients with a mean prednisolone dose of > 7.5 mg/d, but this phenomenon was not found in the hip[12]. Hydroxychloroquine (HCQ) may act by inhibiting the change of 25-hydroxyvitamin D into 1,25-dihydroxyvitamin D. An earlier study found that patients with SLE treated with HCQ had lower 1,25-dihydroxyvitamin D levels, although there were no differences in circulating 25-hydroxyvitamin D levels between treated and untreated patients[34]. In contrast, some studies have shown that HCQ is a protecting factor for OP[49]. It has been demonstrated that the treatment of HCQ is related to higher levels of 25-hydroxyvitamin D, which was probably a spurious effect of the drug at the expense of reducing the metabolically active form 1,25-dihydroxyvitamin D[50]. Calcineurin inhibitors, such as cyclosporine A and tacrolimus, have been increasingly used in patients with SLE. The use of the calcineurin inhibitors may potentially lead to a vitamin D resistant state, leading to impairment of the normal physiological effects of vitamin D[51,52]. Other drugs used for SLE that play a role in bone loss are methotrexate (MTX), cyclophosphamide, anticonvulsants, oral anticoagulants and heparin[53].

OP IN RA

Prevalence and sex

RA is a chronic inflammatory disorder in which an erosive, symmetric joint disorder maintains the center stage accompanied by a variable, but at times prominent, degree of extra-articular involvement. The inflammatory synovitis and damage of cartilage and bone is characteristic of RA patients. Bone involvement includes three types: periarticular osteopenia, bone erosion and systemic OP. There are two types of OP in RA: localized, occurring near to the site of inflamed joints, or generalized, involving the systemic bone. Local or periarticular bone loss is the typical radiographic sign in early RA. Systemic OP is prevalent in RA. So far, the use of biological therapy has not decreased the prevalence of OP in RA. RA patients have a lower bone mass in the appendicular and axial skeleton when compared with healthy controls, according to the conclusion of 10 cross-sectional studies[54]. There was a twofold increase in RA in women aged 20-70 years. The prevalence of OP was 16.8% in the lumbar spine and 14.7% in the femur. It reached 31.5% in the lumbar spine and 28.6% in the femur for women aged 60-70 years[55]. A multicenter cross-sectional study of RA and BMD indicated that the frequency of OP as assessed by DEXA was 28.8% at the lumbar spine and 36.2% at the femoral neck[56]. A longitudinal study indicated that BMD loss was lower in men[57]. A large study with 94 male RA patients concluded that a modest reduction in BMD was found only in patients aged 60-70 years. The percentage of BMD reduction in the femoral neck was 5.2% and the reduction in the hip was 6.9%, with no change in the spine. Despite a moderately low BMD, this report showed that the ratio of reduced BMD in men with RA was nearly twofold higher than in the control group[58].

Risk factors

The reason for OP in RA patients is also multifactorial: factors related to the disease itself, antirheumatic drug use and traditional factors, such as low BMI, menopausal status, age and lack of physical exercise (Figure 2).

Local periarticular OP really reflects disease activity in early RA because the acute phase reactants are closely related to this phenomenon, but once periarticular OP appears, it is no longer a sign of disease activity[59]. Generalized OP is a feature of established RA. Some literatures have shown an association between OP and proinflammatory cytokines, such as TNF-α, IL-1 and IL-6[60], and these cytokines were independent risk factors of

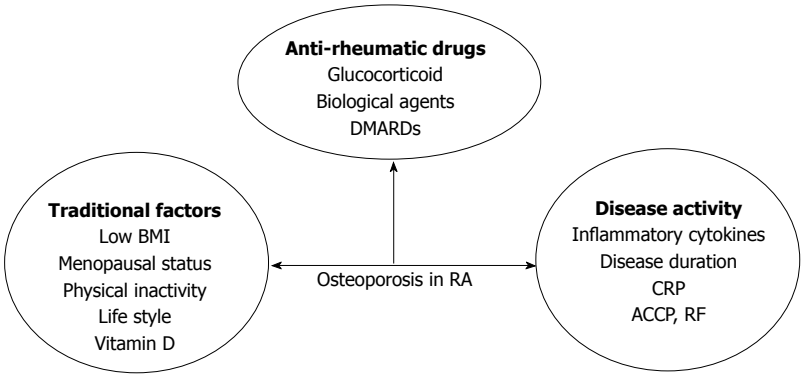

Figure 2 Risk factors for osteoporosis in rheumatoid arthritis. RA: Rheumatoid arthritis; BMI: Body mass index; DMARDs: Disease-modifying antirheumatic drugs; CRP: C-reactive protein; ACCP: Anti-cyclic citrullinated peptide; RF: Rheumatoid factor.

disease activity. IL-1 and IL-6, secreted by activated macrophages, synovial fibroblasts and T cells, result in synovial inflammation, bone damage and systemic manifestations of RA[61,62]. Inflammation has an uncoupling effect on bone resorption and formation. In patients with active compared to inactive RA, bone resorption was increased, whereas bone formation was decreased. These cytokines are closely associated with osteoclast physiology as they extend survival and improve the activity of mature osteoclasts, mainly through RANKL-mediated and Wnt-signaling pathways[63]. Anti-inflammatory treatment, especially with biological agents, in early RA reduces the rate of bone loss[64]. However, there are some debates about the relationship between inflammation and bone loss in RA and recent data show that bone loss starts before inflammation and clinical disease[65].

Osteoimmunology has attracted increased research attention and RA is also an autoimmune disease. There are many autoantibodies in RA, such as those against citrullinated proteins antibody (ACPA) and rheumatoid factor (RF). There are many data supporting the role of autoimmunity in bone destruction in RA. In RA, ACPA is an important prognostic factor. ACPA has a direct and independent stimulating effect on osteoclasts and induces elevated bone resorption[66]. Bone loss occurs in RA patients displaying ACPA without signs of inflammation[67]. ACPA-positive patients generally have not only higher disease activity and disability, but also more radiological damage[67,68]. Healthy individuals with ACPA have low BMD compared with controls without ACPA and the thickness of cortical bone is significantly lower in healthy individuals positive for ACPA[67]. The frequency of OP and lower BMD is higher in RF-positive patients[55,69] and patients with high C-reactive protein (CRP) levels (> 20 mg/dL) are more likely to have a low BMD in the spine and hips[57]. Immobility related to joint pain or damage aggravates bone loss[70]. Disease-related disability, assessed by Health Assessment Questionnaire (HAQ) score, has nothing to do with BMD in the lumbar spine but is inversely related to BMD in the femoral neck and whole body[71,72]. Disease activity and duration are also risk factors in RA and disease activity is the only reason for BMD loss in the lumbar spine. When active RA lasting more than 2 years is compared to inactive RA, mean bone loss in the former is higher.

The use of antirheumatic drugs plays an important role in OP in RA. There are some debates about the role of GCs in RA: on the one hand, low-dose corticosteroid therapy is associated with increased bone loss and fracture risk, but on the other hand, it effectively controls systemic inflammation. GIOP is the most common form of secondary OP. GCs can affect bone by several direct and indirect ways and affect both bone formation and resorption. Although high doses of GCs are related to bone loss, it is well known that GCs have a strong anti-inflammatory effect and low-dose GCs reduce localized bone loss in the hands. In RA patients with low doses of GCs or with rapidly tapered high-to-moderate dose induction therapy, the direct adverse effect of GCs on bone is counteracted by strong suppression of inflammation by GCs[73-75]. The accumulative dose of steroids is more important for OP and there is no threshold dose. Disease-modifying antirheumatic drugs (DMARDs) have anti-inflammatory and structure-modifying properties, leading to better disease control in RA. Traditional DMARDs include MTX, leflunomide (LEF), sulfasalazine (SSZ), HCQ and gold agents. MTX is considered to be the cornerstone of RA treatment and is the most widely used agent. Osteopathy is reported in patients with malignant diseases treated with high-dose MTX; mostly reported in children with long-term maintenance therapy of MTX for acute leukemia[76]. For postmenopausal women, MTX may be associated with OP because bone biopsy samples are consistent with osteoblast inhibition as a consequence of MTX action on the bone cells in RA patients when given at low doses for prolonged periods[77]. Recently, more and more studies have shown no association between low-dose MTX and bone loss and multivariate covariance analysis has shown that reduced BMD is due to disease severity and activity and not to a direct negative effect of MTX on bone[78-80]. The use of low-dose MTX was not associated with any change in BMD in patients without corticosteroid treatment[81]. MTX seems to have some direct effects on bone metabolism and its anti-inflammatory effects reduce the negative effect of RA on bone. LEF is an isoxazole derivative that

inhibits the mitochondrial enzyme dihydroorotate dehydrogenase and prevents bone loss by its active metabolite that can inhibit osteoclastogenesis and osteoclast function[82]. LEF can slow radiographic progression, both in terms of erosion and joint space narrowing. *In vitro*, SSZ inhibited osteoclastogenesis by acting on osteoclast precursor cells and regulating the RANKL-RANK-OPG interaction, primarily by reducing expression of RANKL on synovial fibroblasts and increasing expression of OPG[83]. No studies have investigated whether LEF and SSZ have a sparing effect on BMD or bone strength in RA. Biological DMARDs dramatically improve inflammatory arthritis treatment and prognosis. Biological agents include TNF-α blockers (infliximab, adalimumab, etanercept, certolizumab and golimumab), agents counteracting B cell activity (rituximab) and T cell activation (abatacept), and anti-IL-6 agents (tocilizumab). All TNF-α blockers reduce the progression and formation of joint erosion and joint space narrowing. Infliximab[84,85], adalimumab[86-88], etanercept[89-91] and rituximab[92] can counteract local bone erosion and generalized bone loss. Tocilizumab has a positive, corrective effect on bone balance. It induces a significant decrease in bone resorption, rebalances bone turnover and increases the BMD of RA patients who have osteopenia at baseline[93,94]. Fundamental studies have elucidated that inflammatory cytokines induce osteoclastogenesis through upregulation of RANKL, with subsequent activation of osteoclastogenesis which plays key role in bone loss in RA. Biological agents improve bone formation and reduce bone resorption by controlling active disease and inflammatory cytokine production[95].

Traditional factors result in osteoporosis in RA. Both postmenopausal women and men with RA have a prevalence of OP. The percentage of OP in postmenopausal women is 55.7% and 50.5% in men, with the prevalence of OP higher than in premenopausal women (18%). OP risk factors are strongly dependent on gender and menopausal state[96]. Female sex, increasing age, years since menopause, low weight, familial OP and low BMI are risk factors for osteopenia in patients with RA[57,97-99].

OP IN SPONDYLOARTHRITIS

Spondyloarthritis (SpA) comprises a group of inflammatory diseases, such as psoriatic arthritis (PsA), reactive arthritis (Reiter's syndrome), enteropathic arthritis, undifferentiated spondyloarthropathy and AS. These diseases have some common characteristics, including imaging features, clinical manifestation and laboratory findings. Both sacroiliac joints and spine can be involved and to different degrees, peripheral joints.

Prevalence and sex

AS is the prototype of SpA and the most frequent subtype. AS mainly involves the axial joints, especially the sacroiliac joints. The spine, peripheral joints and enthuses can be affected to various degrees. Extraosseous new bone formation is considered a hallmark of AS. Although bone formation may affect the detection of BMD, OP always occurs in the early period of AS. The reported prevalence of OP varies from 19% to 62% in AS maybe because new bone formation and age distribution of the study cohorts make detecting BMD difficult[100]. It was reported that the prevalence of OP in patients with early AS within 10 years after diagnosis was unexpected; 13% in the femoral neck and 16% in the lumbar spine[101]. AS mainly affects young men and men with AS have had an annual total bone mass loss of 2.2% in longitudinal studies[102]. Male patients with AS have decreased BMD in their lumbar spine and femoral neck, and femoral neck BMD in male AS patients is 10% lower than in age-matched male controls[103,104].

In women, one study found a slight reduction in BMD in premenopausal women with early AS, but the difference was not significant[105]. Another study to assess BMD of the hip and spine by DEXA and calcaneal quantitative ultrasound in women with AS showed that women with AS had reduced hip BMD and significantly fewer markers of bone formation than controls[106]. In summary, OP is a significant complication in AS and significant OP can occur even in early disease. The spine is more likely to be damaged than the femur, with the spine still the most important site to diagnose OP in AS.

Risk factors

There are several reasons for OP in AS, such as proinflammatory cytokines, acute phase reactants, immobility, vitamin D, sex hormones, age and disease duration.

The systemic inflammatory cytokines are the core of OP during AS. Maybe inflammation of the entheses and synovium increase secretion of proinflammatory cytokines. Cytokines are a link between local and systemic inflammation on the one hand and result in bone resorption and BMD reduction on the other hand. IL-6, IL-1 and TNF-α are well-known osteoclast activators and play an important role in inflammation in AS. The RANK-RANKL system and its natural inhibitor OPG may be the key in bone-cytokine interrelationships. There is a strong correlation between bone turnover, proinflammatory cytokines and acute-phase reactants, for example erythrocyte sedimentation rate (ESR)[107]. Low BMD is related to high biochemical markers of bone resorption, inflammatory activity and low OPG serum levels in AS patients[108]. Longer disease duration, Bath AS Functional Index (BASFI) and Bath AS Disease Activity Index are also factors associated with OP[100]. Low hip BMD was related to low BMI and high BASFI and Bath AS Radiology Index-total (BASRI-t) score and low lateral spinal BMD was associated with BASRI-t score[109]. In addition, high disease burden, immobility and syndesmophyte formation increased the risk of

OP[110].

Genetic factors and FokI genotypes of the vitamin D receptor gene were significantly associated with the spine as independent predictors of low BMD, which was also affected by BMI, inflammatory level and degree of pain. CRP and ESR values were also closely related to FokI genotypes in male AS patients[111].

Metabolic factors are also risk factors for OP in AS. Bone loss is correlated with low serum sex steroid hormone levels in AS[107,108,112]. Bone loss in AS is associated with endocrine mechanisms such as parathyroid hormone, impaired calcium and vitamin D absorption[113].

In AS, traditional risk factors including a positive family history, older age, low BMI, Caucasian race, postmenopausal status in women or low androgen levels in men, low dietary calcium intake and vitamin D deficiency are risk factors for OP[107].

Therapy for AS mainly involves nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, biological agents including infliximab, etanercept, adalimumab and anakinra, and conventional DMARDs, including MTX, SSZ and LEF. Some NSAIDs inhibit prostaglandin synthesis which has anabolic effects on bone and is thought to be related to higher BMD in men and women[16,114]. However, 16 patients continued NSAIDs during the 24 mo follow-up period and data were inconclusive on the effect of NSAID use on BMD[115]. Studies have shown that TNF-α blockers prevent systemic inflammation-induced bone loss in AS or SpA[116-119]. In a larger cohort of 106 patients with SpA receiving infliximab or etanercept, patients had great improvement in the spine and hip BMD scores; the mean BMD scores in the lumbar spine reached 5.8% and increased by 2.3% in the total femur after 2 years follow-up[120]. A recent study included seven longitudinal studies and one randomized control trial and studied the effect of TNF inhibitors on BMD in 568 AS patients with a minimum follow-up period of 1 year. They found that lumbar spine BMD increased by 5.1% and total hip BMD increased by 1.8% after 1 year of treatment with TNF inhibitors and lumbar spine BMD increased by 8.6% and total hip BMD increased by 2.5% after 2 years. So, they concluded that TNF inhibitors maintain femoral neck BMD homeostasis and increase BMD in the lumbar spine and hip for up to 2 years[121]. Corticosteroids are used less often in AS so there have been few studies about GCs and OP in AS. We have not searched the literature about change of BMD in AS after using DMARDs treatment until now. Drug-related factors play an important role in OP for AS.

OP in other types of SpA

There are only a few studies about bone loss in other forms of SpA such as PsA in OP. The involvement of bone in PsA affects not only mechanisms of bone loss but also bone formation. Periarticular bone loss and general bone loss are present. PsA patients were found to have periarticular bone loss in early disease but overall BMD values are higher than in RA patients[122]. There are conflicting data about bone loss and bone turnover markers in patients with PsA, with some studies showing evidence of association with low BMD and some not, especially systemic OP[123]. Some clinical studies conclude that BMD in patients with PsA has no significant decrease[124-126], but bone biopsies suggest a latent high osteopathy[127]. Recently, some literatures have indicated that the prevalence of OP increased in PsA patients, especially those with longer disease duration and disability[128,129]. When PsA patients were compared with age-matched controls, BMD in the femoral neck and lumbar spine was found to be reduced[130]. Bone demineralization occurs in 11% of young women, 47% of postmenopausal women and 29% men with non-axial PsA. OP is related to HAQ score, reflecting articular function[131].

OP IN OTHER RHEUMATIC DISEASES

SSc, dermatomyositis (DM)/polymyositis (PM) and Behcet's disease (BD) are also rheumatic diseases associated with OP.

OP in SSc

SSc is characterized by skin thickening and fibrosis. SSc can be classified into two subsets: diffuse and limited cutaneous SSc. Before 2004, a review concluded that it was unknown if patients with scleroderma have an increased prevalence of OP[132]. Recently, another review analyzed 19 studies about BMD in SSc. Fifteen studies found that the prevalence of BMD was 27%-53.3% and that of OP was 3%-51.1% in SSc patients compared to controls. Ten studies reported a lower BMD in SSc patients and two studies suggested no difference. It was concluded that SSc patients had a risk of low BMD and fracture. The cause of OP was complex, involving traditional factors, SSc-specific risk factors and drug-related factors[133]. After 2012, a Chinese study indicated that the whole body BMD of SSc patients was much lower than controls and there was no association between BMD and the severity of involvement of the skin and other systems, while advanced age, sex, menopause and low BMI were independently correlated with bone loss in the spine or hip in SSc patients[134]. An Italian study reported that the BMD of SSc patients was significantly lower than controls in the lumbar spine, femoral neck and total femur and serum 25 hydroxyvitamin D3 was significantly lower. In scleroderma patients, serum levels of 25 hydroxyvitamin D3 were greatly associated with parathyroid hormone levels, BMD, stiffness index and bone turnover markers[135]. A study about Spanish SSc patients showed that the prevalence of OP/osteopenia was high, reaching 77% in SSc patients, but there was no relationship between vitamin D and

low BMD[136]. A cross-sectional study suggested that the prevalence of OP was 30% and fractures was 35% in SSc patients, they were higher than healthy controls (11% and 10%) and the degree was very similar to RA (32% and 33%). Age and vitamin D deficiency were thought to be risk factors for fracture in SSc[137]. So far, SSc patients have a high risk of OP but the risk factors need further study.

OP in DM/PM

DM/PM are uncommon idiopathic and autoimmune myopathies with characteristic clinical symptoms of proximal symmetric muscle weakness, rashes and fatigue. OP/fracture is found in about one quarter of adult DM/PM patients. This bone alteration was correlated with lower BMI[138]. Most studies support decreased bone density in juvenile DM patients[139,140]. Low lean body mass and GC pulse treatment were the important factors for low hip BMD in juvenile DM patients[141] and the RANKL/OPG ratio is elevated in children with juvenile DM[142].

OP in BD

BD is a multisystem vasculitis. BD may be a risk factor for OP because the BMD in the lumbar spine is lower than in healthy controls. The serum levels of cytokines such as IL-1, IL-6, IL-2 and TNF-α are increased in BD and there is a negative correlation between IL-1 levels and femur neck BMD[143]. On the contrary, two studies showed no significant BMD reduction in the lumbar spine and hip of BD patients[144,145].

CONCLUSION

In summary, inflammatory rheumatic diseases are always accompanied by elevated bone loss and increased fracture rates. Attention should be paid to bone loss in rheumatic disease. OP in rheumatic disease is complex. Several factors take part in this process, such as the disease itself and traditional, metabolic and drug-related factors. Osteoimmunology, a crosstalk between inflammatory and skeletal component cells, has given some perceptions to the pathogenic mechanism of OP in systemic inflammatory diseases. Chronic inflammation plays a key role in OP for rheumatic disease and inflammatory cytokines regulate the homeostasis between bone formation and resorption. Fundamental studies have demonstrated that the RANKL-OPG system plays a major role in bone loss and inflammatory cytokines upregulate RANKL, which further activates osteoclastogenesis, resulting in OP. Clinical studies have shown that effective immunosuppressive therapy prevents bone loss. Thus, the first step to prevent OP and fractures is to control primary rheumatic disease activity. Apart from that, a healthy lifestyle is important with calcium and vitamin D supplementation and prevention of falls. Bisphosphonates or denosumab might be necessary for patients with a low T score.

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