Osteoporosis and rheumatic diseases

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SUMMARY

Numerous rheumatic diseases, including rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, systemic lupus erythematosus, systemic sclerosis, dermatomyositis/polymyositis and vasculitis are characterized by osteoporosis and fragility fractures. Inflammatory cytokines, glucocorticoid treatment, immobilization and reduced physical activity due to painful joints and muscle weakness are considered the main risk factors that cause low body mass density values in these diseases. Emerging evidence highlights the role of inflammatory cytokines, such as tumor necrosis factor (TNF)-α, interleukin (IL)-1, IL-6, IL-7 and IL-17, in the regulation of the bone homeostasis. In fact, chronic inflammation is often characterized by an imbalance between bone formation and bone resorption with a net prevalence of osteoclastogenesis, which is an important determinant of bone loss in rheumatic diseases.

Key words: *Bone, Osteoporosis, Rheumatic diseases.*

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INTRODUCTION

Several rheumatic diseases, including rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, systemic lupus erythematosus, systemic sclerosis, dermatomyositis/polymyositis and vasculitides are characterized by osteoporosis and fragility fractures. It has been established that inflammatory cytokines, such as the tumor necrosis factor (TNF)-α, interleukin (IL)-1, IL-6, Il-7 and IL-17, are involved in the up-regulation of the expression of the receptor activator of the nuclear factor-κB ligand (RANKL). RANKL is responsible for inducing osteoclastogenesis by binding to the receptor activator of the nuclear factor-κB (RANK) (1-3). The bone mass is the result of the balance between the osteoblast activity, which is responsible for bone formation, and the osteoclast activity, which is responsible for bone resorption. Consequently the prevalence of the osteoclast absorptive activity on the osteoblast activity is the final pathogenic event in osteoporosis. Moreover, important risk factors associated with osteoporosis in rheumatic diseases are the glucocorticoid treatment, immobilization and reduced physical activity due to tender joints and muscle weakness.

OSTEOPOROSIS IN RHEUMATOID ARTHRITIS

Osteoporosis is more frequent in rheumatoid arthritis patients than in the healthy population (4-6). In patients with longstanding rheumatoid arthritis the occurrence of osteoporosis ranges from 19% to 32% in the spine and from 7% to 26% in the hip (4, 7, 8). A double frequency of osteoporosis, defined as a T-score less than -2.5 measured with dual energy x-ray absorptiometry (DXA), has been identified in a population of female rheumatoid arthritis patients. Also a population of male rheumatoid arthritis patients has shown a double frequency of reduced bone mass (4, 5). Moreover, patients affected by rheumatoid arthritis have a 1.5 fold higher risk of osteoporotic fractures compared to healthy controls (9).

In rheumatoid arthritis patients, inflammatory cytokines, such as TNF-α, IL-1, IL-6, and IL-17 are responsible for the

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over-expression of RANKL, which in turn is involved in the activation of osteoclastogenesis (10). It has been demonstrated that patients affected by rheumatoid arthritis and osteoporosis have increased levels of RANKL and decreased levels of osteoprotegerin (OPG) (6). Moreover, patients affected by active rheumatoid arthritis have shown lower serum osteocalcin, which is a marker of bone formation, and higher crosslinked N-telopeptidases of type 1 collagen (NTX) and deoxypyridinoline (DPD), which are markers of bone resorption, compared to controls and patients with inactive rheumatoid arthritis (11). All these bone markers have shown a positive correlation with the disease activity (11). On the other hand, as demonstrated in murine models of arthritis, osteoblast activity is reduced (12, 13).

Glucocorticoids, reduced physical activity, low calcium intake, and poor nutrition associated with enhanced basal energy expenditure are other risk factors for osteoporosis in rheumatoid arthritis patients (14, 15).

Nevertheless, in patients affected by rheumatoid arthritis who have never been treated with glucocorticoids, osteoporosis seems to be due to a decrease in bone formation rather than to an increase in bone resorption, as demonstrated by a histomorphometric analysis of bone samples (16, 17). These contrasting results may be due to different stages of the disease or to a different disease activity in the enrolled patients.

Osteoporosis is above all an extra-articular complication of long-standing rheumatoid arthritis. Güler-Yüksel et al. (18) have examined the body mass density (BMD) of a large group of patients with recent onset rheumatoid arthritis (symptom duration <2 years) who had never been treated with disease-modifying anti-rheumatic drugs or corticosteroids. In this large cross-sectional study, BMD was mainly correlated to demographic factors, such as age, gender and genetic features. Moreover, in patients with recently diagnosed rheumatoid arthritis, high disease activity, joint damage and functional disability did not correlate to lower BMD. On the contrary, a longer duration of symptoms and the presence of the rheumatoid factor were associated with osteoporosis and reduced BMD (18). Other studies have shown a correlation between high disease activity and osteoporosis in patients affected by established rheumatoid arthritis (4, 7, 8). Moreover, in rheumatoid arthritis patients, positive correlations have been found between bone loss in the lumbar spine and high health assessment questionnaire (HAQ) scores and between bone loss in both the lumbar spine and the hips and high C-reactive protein (CRP) levels (19). A positive correlation has also been found between CRP levels and urinary markers of bone resorption (20).

Furthermore, in patients with established rheumatoid arthritis an inverse correlation has been reported between joint damage, measured by the Larsen score, and the BMD of the hip, evaluated by DXA (8, 21, 22). However, unlike this result for the BMD of the hip, no correlation has been identified between the BMD of the spine and the Larsen score, because of the presence of spinal osteoarthritis, vertebral lesions, and atherosclerosis of the aorta, which are responsible for increased BMD (8).

Besides systemic osteoporosis, rheumatoid arthritis is also marked by periarticular bone resorption and bone erosions. Periarticular osteopenia, characterized by the loss of trabecular size and number in the metaphyseal regions next to inflamed joints, has been found before marginal erosions become evident (23). Rheumatoid arthritis joints are affected by both cortical bone destruction and bone marrow alteration. Schett et al. (24) have detected the presence of bone marrow edema in inflamed joints using magnetic resonance. In these joints, the thin cortical bone, which separates the synovial membrane from the bone marrow, is penetrated by the synovial tissue, as demonstrated by an increased signal in T2 sequences, since the bone marrow fat is replaced by T and B cell aggregates (23, 25, 26). A mechanism responsible for the communi-

cation between the synovium and the bone marrow may be related to the presence of small channels that allow synovial blood vessels to infiltrate the bone to supply the marrow space (23).
Murine models of arthritis have demonstrated that the osteoclast activity is responsible for bone erosions (27). The inflamed synovial membrane is characterized by the expression of pro-inflammatory cytokines, responsible for inducing osteoclastogenesis, such as IL-1, IL-17, TNF-α, macrophage colony-stimulating factor (M-CSF), and RANKL (23). Moreover, the cells at the pannus-bone interface are characterized by the expression of osteoclast markers, such as tartrate-resistant acid phosphatase (TRAP), cathepsin K, B3-integrin, and the calcitonin receptor mRNA (28).

OSTEOPOROSIS IN JUVENILE IDIOPATHIC ARTHRITIS

Reduced BMD values in whole body, total body less head, lumbar spine and distal radius have been found in patients affected by juvenile idiopathic arthritis (29). Using a peripheral quantitative computed tomography (pQCT) scanner in children affected by juvenile idiopathic arthritis, it has been demonstrated that only the trabecular bone was involved, whereas the cortical bone was normal (30, 31). The disease activity may be correlated to an increased risk of osteoporosis, because patients who were younger at the time of onset have lower BMD (32). In these patients, several risk factors may be responsible for an increased occurrence of osteoporosis, such as malnutrition, corticosteroid therapy, reduced physical activity due to tender joints or muscle weakness, growth retardation, hormonal status and inflammatory cytokines (33). Recently, genetic factors have been associated to a higher risk of osteoporosis in this disease, including the G allele and the GG genotype of the glucocorticoid receptor gene BclI polymorphism, and the GG Sp1 and GG of -1997G/T polymorphism of collagen type I α-1 chain (COL1A1) (34, 35).

OSTEOPOROSIS IN PSORIATIC ARTHRITIS

Some studies have showed contrasting results in the frequency of osteoporosis in psoriatic arthritis patients. On one hand, lower BMD levels have been found in patients affected by psoriatic arthritis compared to healthy controls (36). Moreover, in psoriatic arthritis patients, BMD values of lumbar spine and total femur and serum CTX levels showed an inverse correlation with the duration of arthritis (37, 38). Chronic inflammation and inflammatory cytokines, such as IL-1, IL-6, and TNF-α, which induce osteoclastogenesis and therefore bone mass resorption, as well as glucocorticoid and methotrexate therapies, immobilization and reduced physical activity due to joint pain are considered the main factors responsible for osteoporosis in psoriatic arthritis patients (39, 40).
On the other hand, other studies have not found a reduction in the bone mass in patients affected by psoriatic arthritis (41-43). Recently, Pedreira et al. (44) have not found significant differences in BMD in postmenopausal women with psoriatic arthritis and controls. Moreover, no correlation has been seen between duration of the disease and BMD (45).

OSTEOPOROSIS IN ANKYLOSING SPONDYLITIS

Several studies have found low BMD levels in patients with ankylosing spondylitis (3, 46). The occurrence of osteoporosis in this inflammatory disease is reported in 19-62% of patients (47, 48). These frequencies differ widely as a consequence of the difficulties in measuring BMD in patients with ankylosing spondylitis. It is interesting to note that low BMD has been found in the early stages of the disease, whereas in long-standing ankylosing spondylitis the presence of structural bone lesions, such as syndesmophytes and periosteal bone formation, may be responsible for alterations in DXA measurements (49). Therefore, in the early stages of ankylosing spondylitis,

DXA measurement should comprise both the spine and the hip, while in the long-standing disease, only hip BMD measurement with DXA should be considered as a reliable fracture risk predictor. In chronic ankylosing spondylitis more sophisticated techniques, such as pQCT of the vertebrae, when available, should be considered (49). Furthermore, in patients with long-standing ankylosing spondylitis, the prevalence of vertebral fractures ranges between 1% and 19% (50-53). In patients affected both by ankylosing spondylitis and osteoporosis, the prevalence of vertebral fractures ranges between 29.6% and 33.3% (53).

The etiology of osteoporosis in patients with ankylosing spondylitis is multifactorial. Low BMD levels have been associated with older age, long-standing disease, syndesmophyte formation, use of glucocorticoids, relevant inflammation indices (54). Several studies have found a low lumbar spine BMD in patients with ankylosing spondylitis and high disease activity, expressed by high erythrocyte sedimentation rate (ESR), CRP, bath ankylosing spondylitis functional index (BASFI) and bath ankylosing spondylitis disease activity index (BASDAI) (53, 55, 56). Other risk factors for osteoporosis are immobilization and reduced physical activity due to impaired back mobility, joint pain and potential ankylosis, high frequency of inflammatory bowel lesions in ankylosing spondylitis and the subsequent intestinal malabsorption, glucocorticoid treatment, and increased levels of several inflammatory cytokines, such as IL-1, IL-6, IL-17 and TNF-α (54, 57-62). Also decreased levels of OPG have been detected in the sera of patients with ankylosing spondylitis and osteopenia (63). Furthermore, other risk factors for osteoporosis in patients with ankylosing spondylitis are the presence of genetic variations in the vitamin D receptor gene and low steroid hormone serum levels (63, 64). Patients with ankylosing spondylitis have also shown alterations in vitamin D metabolism associated to high disease activity and lower levels of vitamin D compared with healthy individuals (65-67). Consequently vitamin D may play a potential role in the pathogenesis of ankylosing spondylitis, given its influence on both the bone metabolism and the immune system (67).

The increased occurrence of secondary osteoporosis in patients with ankylosing spondylitis has also been demonstrated on the basis of a histological investigation of bone samples which have revealed increased osteoclast activity and inflammatory aggregates in joints and vertebrae (68). In ankylosing spondylitis it has been hypothesized that osteoclast activity is predominant in the initial phase characterized by bone resorption, whereas bone formation becomes evident at a later stage (69).

OSTEOPOROSIS IN SYSTEMIC LUPUS ERYTHEMATOSUS

Several cross-sectional studies have evaluated BMD and the occurrence of osteoporosis in patients affected by systemic lupus erythematosus, who have shown low BMD and a high prevalence of vertebral and peripheral fractures. The prevalence of fractures in these patients is 6-12.5% (70). The occurrence of osteoporosis in systemic lupus erythematosus ranges from 1.4 to 68%. This wide range is most likely due to the differences between the patient groups investigated in terms of levels of disease activity, ethnicity, age, sex, size and treatment (70). The increased risk of osteoporosis in these patients is due to many factors, such as reduced sun exposure due to photosensitivity, glucocorticoid treatment, use of hydroxychloroquine, reduced physical activity due to tender joints and muscle weakness, which together with neuropathy, epilepsy and visual defects, may also be responsible for an higher fall risk and consequently for a higher fracture risk (70). Chronic inflammation is also responsible for increased bone loss, as demonstrated by higher levels of TNF-α and oxidized low-density lipoprotein (LDL) in patients with systemic lupus erythematosus (71, 72). In fact, oxidized LDL can induce T-cell production of RANKL and TNF-α, which in turn are responsible for inducing

osteoclastogenesis and inhibiting osteoblastogenesis (71, 73, 74). Furthermore, metabolic and hormonal disorders, which may occur in systemic lupus erythematosus, are considered additional risk factors for osteoporosis (70). In fact, several studies have found an association between reduced vitamin D levels and low BMD in patients with systemic lupus erythematosus (75-78). Up to 40% of these patients develop a renal involvement that may be responsible for inducing secondary hyperparathyroidism and low $1,25(OH)_2D$ levels (78). Low $1,25(OH)_2D$ levels may also be a consequence of an hydroxychloroquine treatment, which inhibits the conversion of 25(OH)D to $1,25(OH)_2D$ by reducing hydroxylation $\alpha 1$ (70). Also estrogens may play a role in the pathogenesis of systemic lupus erythematosus as demonstrated by a high estrogenic status, a low androgenic status, increased testosterone oxidation, and decreased dehydroepiandrosterone, which can be often found in these patients (79-81).

Several studies have demonstrated an inverse correlation between a long duration of the disease and low BMD levels (78, 82, 83). According to these results, low BMD levels are associated with a higher organ damage index, which is often correlated with a long-standing disease (83, 84-86). However, no association between disease activity and BMD has been demonstrated (78, 83, 86, 87).

OSTEOPOROSIS IN SYSTEMIC SCLEROSIS

Patients with systemic sclerosis are characterized by several risk factors for osteoporosis, including chronic inflammation, reduced physical activity, intestinal malabsorption, corticosteroid treatment, and chronic renal failure (88-90). Furthermore, a potential association has been identified between subcutaneous calcinosis, which occurs in about 40% of patients affected by systemic sclerosis, and reduced total body skeletal stores of calcium (88-90). More recently, low vitamin D levels and secondary hyperparathyroidism have been described in patients with systemic sclerosis (91-93). In the past, some studies that have attempted to demonstrate an association between systemic sclerosis and a higher risk of osteoporosis have shown conflicting results, probably because they had an inadequate statistical power and failed to distinguish actual differences between BMD values of systemic sclerosis patients and BMD values of controls (94). Nevertheless, numerous recent studies have found a high prevalence of osteoporosis in this disease and BMD values were found similar to or even lower than those of patients with rheumatoid arthritis (92, 95-97). A recent case-control study has demonstrated a higher prevalence of osteoporosis and vertebral fractures in postmenopausal women with systemic sclerosis compared to the control group (93). The prevalence of osteoporosis in these patients was 22% with no difference between to the limited scleroderma or the diffuse scleroderma subsets (93).

OSTEOPOROSIS IN DERMATOMYOSITIS/ POLYMYOSITIS

An increased risk of osteoporosis in adult dermatomyositis/polymyositis patients has been demonstrated for the first time in a recent study (98). An association between low weight, which may be related to a chronic disease, such as dermatomyositis/ polymyositis, and osteoporosis has been seen in these patients, in keeping with results for the normal population (98). An association between disease activity, cortisone therapy and osteoporosis has not been found in these patients, probably because of the limited size of the samples (98-100).

OSTEOPOROSIS IN BEHÇET'S DISEASE

Chronic inflammation, corticosteroid and immunosuppressive treatments, and genetic factors may lead to a greater risk of osteoporosis in patients with vasculitis.

However, there are only a few studies that have attempted to assess the relationship between vasculitis and a higher risk of osteoporosis, all of which have focused on Behçet's disease (101-103). Results have been conflicting, probably because of the limited number of enrolled patients. Two of these studies have shown no significant reduction in BMD values measured both in the lumbar spine and in the hip of patients affected by Behçet's disease compared to healthy controls (101, 103). More recently, Kirnap et al. (102) have demonstrated significant differences in BMD values of the lumbar spine, but not of the hip in a study on 60 patients with Behçet's disease compared to 24 sex- and age-matched healthy controls.

CONCLUDING REMARKS

Bone mineral loss is a common finding in numerous rheumatic diseases. Among all the risk factors investigated, inflammatory cytokines, glucocorticoid treatment, immobilization and reduced physical activity due to tender joints and muscle weakness have shown to play a key role in favoring low BMD values in these diseases. More recently, the increasing interest in osteoimmunology has highlighted the role of inflammatory cytokines, such as TNF-α, IL-1, IL-6, IL-7 and IL-17 in the regulation of bone homeostasis (10, 33, 39, 54, 72). During chronic inflammation, the balance between bone formation and bone resorption may be considerably affected, contributing to a net prevalence of osteoclastogenesis, which is an important determinant of bone loss in rheumatic diseases.

Vitamin D supplementation and drug treatment with bisphosphonates, hormone replacement therapy, teriparatide, calcitonin, denosumab, cathepsin K inhibitors, or monoclonal antibodies against sclerostin should be considered in rheumatic patients for both prevention and treatment of osteoporosis (33, 70, 104-112). Furthermore, numerous studies have demonstrated that an adequate treatment based on the use of anti-TNF-α agents or other immunosuppressive drugs can play a role in preventing osteoporosis in rheumatoid arthritis and ankylosing spondylitis (104, 113-115). However, TNF-α inhibition is only one of the main elements in the very complex mechanism of osteoclastogenesis alongside IL-1, IL-6, IL-7, IL-11, IL-17, M-CSF, transforming growth factor-β (TGF-β), macrophage inflammatory protein 1α (MIP-1α), MIP-1β, inducible protein 10 (IP-10), monokine induced by IFN-γ (MIG), osteoclast-associated receptor (OSCAR), RANK/RANKL signaling pathway, and nuclear factor of activated T cells cytoplasmic 1 (NFATc1) (116). Therefore, even if anti-TNF-α drugs represent an important therapeutic strategy in chronic arthritis, they may not be able to ensure a complete reduction of bone damage.

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