Rheumatic Diseases and Osteoporosis

14

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14.1 Introduction

Inflammatory joint diseases, such as seronegative spondyloarthropathies (SnSp), rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), systemic sclerosis, and vasculitides, are characterized by bone complications including osteoporosis (OP) and fragility fractures (FF).

The course of OP is closely connected with the activity of the underlying disease and other risk factors, including low body mass index (BMI) (<18 kg/m^2), early menopause (<45 years), low-energy fractures, renal failure, diabetes, smoking and alcohol use, high bone turnover, vitamin D deficiency, low intake or impaired absorption of calcium, and low calcium concentration. However, active inflammation, glucocorticoids (GC) therapy, long disease duration, immobilization, and reduced physical activity are considered the main risk factors altering both the quality and the amount of bone mineral density (BMD) associated to these diseases [1]. It is well-known 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 regulation of the bone homeostasis, with increasing osteoclast activity through receptor activator of the nuclear factor kappa-B ligand (RANKL) and receptor activator of the nuclear factor kappa-B (RANK) pathway, with the prevalence of bone resorption on bone formation in rheumatic diseases [2]. Therefore, treatment with synthetic and

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biological disease-modifying antirheumatic drugs (DMARDs) is of major importance, not only to control disease activity but also to limit generalized bone loss. GC are frequently used in the treatment of rheumatic diseases because they suppress the systemic inflammation with a subsequent beneficial effect on bone mass, even though one of the principal complications of GC long-term use consists of an important alteration of bone metabolism. FF risk is positively related to their daily dose and increases during the first 6 months of therapy, and the relative risk of fractures is higher for forearm, hip, and vertebral sites and depends on the duration of GC therapy itself [3].

This paper focuses on three inflammatory joint diseases, SnSp, RA and SLE, because OP and FF represent the main extra-articular complications of these diseases.

14.2 Osteoporosis in Seronegative Spondyloarthropathies

SnSp are a heterogeneous group of disorders with clinical features that include axial and peripheral arthritis, psoriasis, inflammatory bowel disease, and uveitis. The group, which affects approximately 0.5–1.5% of the Western population, comprises chronic inflammatory diseases such as ankylosing spondylitis (AS), psoriatic arthritis (PsA), reactive arthritis, inflammatory bowel disease-related spondyloarthropathies, and undifferentiated spondyloarthritis. In the context of SnSp, AS and PsA are the most frequently observed conditions; both are immunoinflammatory disorders characterized by bone involvement and associated with different prevalence of low bone mineral density (BMD), OP, and an increased risk of OP-related FF.

Chronic and persistent inflammation is an important risk factor for bone loss in AS and PsA due to its deleterious effect on bone remodelling. As a consequence, bone balance is negatively affected; indeed, imbalance between osteoblast bone formation and osteoclast bone resorption with net prevalence of osteoclastogenesis occurs [1]. Furthermore, additional and relevant risk factors for OP and FF to take into account are GC treatment, low levels of vitamin D, sarcopenia, intestinal malabsorption, hypo(immo)bilization, and reduced physical activity due to compromised mobility, joint pain, and functional impairment.

Emerging and increasing evidence highlights the harmful role on the bone played by inflammatory cytokines, such as tumor necrosis factor (TNF)-α, interleukin (IL)-1, IL-6, IL-17, and IL-23. In fact, chronic inflammation is characterized by overexpression of inflammatory cytokines involved in the upregulation of the receptor activator of the nuclear factor kappa-B ligand (RANKL); RANKL is responsible for inducing osteoclastogenesis by binding to receptor activator of the nuclear factor kappa-B (RANK) on the surface of cells of the osteoclast lineage [2, 4].

It is not fully defined the role of dickkopf-1 (Dkk-1), the potent inhibitor of the Wnt/β-catenin pathway, whose levels in AS are below those of the healthy control population. It was speculated that the decrease in Dkk-1 results in increased Osteoprotegerin (OPG) and up-regulation of the Wnt pathway leading to activation of β-catenin, which transcriptionally enhances OPG gene expression [5]. Even less known is the role of Dkk-1 in PsA.

Since TNF-α, IL-17, and IL-23 are cytokines involved in the pathogenic mechanism of the typical lesions of AS and PsA, including the skeletal ones, it follows that neutralizing their effects with more innovative drugs can provide favourable results on maintaining bone homeostasis. Available data suggest that the anti-inflammatory treatment with TNF-α inhibitors, while having a positive effect on BMD at the spine and the hip, is less effective in reducing the risk of fracture [6].

Traditional anti-osteoporotic drugs for OP and FF prevention according to local recommendations and in combination with calcium and vitamin D are indicated.

14.3 Osteoporosis in Ankylosing Spondylitis

AS, the prototype disease in the spectrum of SnSp, is a progressive inflammatory rheumatic disorder that primarily affects the axial skeleton, including the sacroiliac joints. AS usually presents during the third decade of life and rarely after the age of 45 years. Its prevalence is generally reported between 0.1 and 1.4%. There is some gender disparity with a 2–3:1 male-to-female ratio rather than the previously thought 5–6:1.

Many studies have shown decreased BMD levels by dual-energy X-ray absorptiometry (DEXA), with an OP prevalence range from 19 to 62% [6]. The frequencies differ widely as a consequence of different duration, activity and extent of disease and of the degree of the impaired back mobility.

One of the main features of bony damage in early AS is the excessive loss of the trabecular bone in the centre of the vertebral body causing osteopenia or OP [7]. In long-standing disease the presence of structural bone lesions, such as syndesmophytes (new bone formation "bridging" two or more adjacent vertebrae), may be responsible for increased BMD. Therefore, in early AS, DEXA measurements should include both the spine and the hip, while in long-standing disease, only the hip BMD level should be considered; however, active or past hip osteoarthritis can represent a confounding factor.

Generally low BMD levels are associated with high disease activity expressed by relevant inflammation indices and abnormal values of Bath Ankylosing Spondylitis Functional Index (BASFI), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Bath Ankylosing Spondylitis Metrology (BASMI) [8]. In early SA, risk factors for low BMD seem to be related to male gender and decreased functional capacity [9].

A systematic review showed a high prevalence of osteopenia versus OP for the lumbar spine (39% and 16%, respectively) and for the femoral neck (38% and 13% respectively), particularly in patients with a short disease duration. This high prevalence was not expected in a relatively young and predominantly male population [10].

A study in a cohort of 204 patients (57% men, mean age 50 ± 13 years) found a prevalence of OP of 21% in participants aged ≥50 [11]. Low BMD was associated with age, disease duration, and inflammatory parameters.

In a study of 103 patients, osteopenia at the hip and spine was found in 56% and 41%, respectively, of patients with disease duration <5 years, with an additional 11

and 15% having OP. In patients with a longer disease duration (>10 years), 29% were osteoporotic at the hip and only 4% at the lumbar spine [12].

Given the low BMD, the alteration of the biomechanical properties of the spine, and the structural bony damage, patients with AS have a fourfold FF risk, during their lifetime, compared with the general population, even from minor injury.

Vertebral FF are a common finding in AS, but their prevalence is highly variable up to more than 40% [13]. The discrepancies in prevalence rate reflect inadequate design or lack of power of the studies, inconsistency in the definition of vertebral FF, differences in recruitment, sex distribution, age, and vertebral FF assessment methods. Vertebral FF may depend on the low BMD and/or the increased spine vulnerability secondary to the bone lesions, with reduced shock absorption, induced by the disease; however, they appear to be related more to the duration and structural severity of the disease rather than to BMD. Vertebral FF should be promptly and carefully considered in any patient with neck or back pain that is changed in intensity or character as they are often associated with neurological signs and symptoms.

A case-control study of 53,108 patients with fractures concluded that the risk of fractures was higher in AS than in rheumatoid arthritis (RA), with the largest increase for vertebral fractures (odds ratios 7.1 and 2.7, respectively) [14].

Recent data suggest both low BMD and high prevalence of vertebral FF even in patients with early-onset disease [15].

Patients with AS are also at increased risk of nonvertebral FF; in a large study, this risk was found to be statistically significant, even after adjustment for potential confounding factors (smoking, alcohol consumption, body mass index, and use of oral steroids) [16]. According to the results of the same study, the regular use of nonsteroidal anti-inflammatory drugs (NSAIDs) seems to eliminate the excess vertebral and nonvertebral FF risk with an unknown mechanism.

Increased levels of RANKL and low levels of OPG have been detected in the sera of patients with AS. Furthermore, cross-sectional studies have highlighted an association between low vitamin D concentrations and both susceptibility and disease activity, suggesting a potential role of vitamin D related to its skeletal and immunological effects [17]. Paradoxically, although subjects with AS generally exhibit localized regions of enhanced bone formation at sites of spinal involvement, some of them may have low BMD at the spine [18]. It is possible to speculate that this happens when and if the local inflammatory process is still active and persistent.

TNF-α inhibitors appear to increase lumbar spine and hip BMD [5]; so far there is no clear evidence of an anti-fracture effect. It is likely that also the novel biotechnological drugs targeting IL-17 and IL-23/17 axis can exert the same effects. More research is needed to assess the effects of these agents on bone quality and fracture risk.

14.4 Osteoporosis in Psoriatic Arthritis

PsA is an inflammatory chronic rheumatic disease affecting both peripheral and axial joints in addition to skin. PsA usually occurs in the age of 40–50 years old; male-to-female ratio is from 0.7:1 to 2.1:1.

Prevalence of low BMD is not well defined; studies addressing the topic have shown conflicting results as far as the prevalence of OP in patients with PsA is concerned. Though most of the studies have found no significant increase in OP concluding that the magnitude of the problem seems to be mild, others suggest a higher prevalence than previously thought [19, 20].

OP, when present, recognizes pathophysiological mechanisms similar to those of AS and appears to be related to the duration, extent, and activity of the disease.

A study of 155 patients found no differences in BMD values between patients and reference population [21]. Prevalence of OP was 16%; it was higher in postmenopausal women (28%) than in men (9%) or premenopausal women (4%). Prevalence of clinical fractures was 13%, mainly found in postmenopausal women; however, spine X-ray was not performed so that morphometric vertebral FF were not considered.

A study including 91 patients found no significant differences in mean lumbar spine and femoral neck BMD between PsA patients and controls; however, the prevalence of FF was significantly higher in patients (14.3%) than in controls (4.4%) [22].

A previous study carried out in 45 postmenopausal women with PsA concluded that patients did not have lower BMD even if they had a higher prevalence of FF [23]. In contrast, a study in 100 postmenopausal women with PsA showed that the prevalence of vertebral and nonvertebral FF on radiographic readings did not differ between cases and controls [24].

The higher prevalence of fractures compared with controls found in some studies indicates that alterations of bone quality are a characteristic of the disease, regardless of BMD values.

According to a recent systematic review, high likelihood of bias and inconsistent results of the available studies suggest a need for well-designed longitudinal studies on bone health in PsA [25].

Limited available data on vitamin D status in PsA suggest that patients have low levels of vitamin D with an inverse correlation between the serum level and the activity of the disease [26].

There are limited data on the effect of traditional therapies for OP in PsA patients. However, treatment with the currently available TNF-α inhibitors can potentially positively interfere on skeletal damage related to the disease; it is likely that a similar favourable effect can be exerted by the novel inhibitors of IL-17, IL-23/17 axis, and phosphodiesterase 4.

14.5 Osteoporosis in Rheumatoid Arthritis

RA is an autoimmune, systemic disease that is characterized by distal and symmetrical synovitis with joint destructions. It affects 0.5–2% of the general population, with a female preponderance and an increased prevalence with age. This disease is associated with subchondral bone erosion, cartilage degradation, and systemic bone loss. Periarticular bone loss, adjacent to the inflamed and swelling joints, is a key feature of RA and the result of local inflammation [27]. Generalized bone loss, leading to OP, is the main extra-articular manifestation of RA and may lead to

the occurrence of FF, exacerbating pain and disability and impairing the quality of life of these patients [28]. In the USA, data from the National Data Bank for Rheumatic Diseases indicated that FF are the third cause of mortality in RA patients, after respiratory problems and myocardial infarctions, and the second cause of invalidity, after depression [29].

Even if the patients with RA are at high risk of OP and FF, having several well-known risk factors, such as menopausal status, low BMI, reduced physical activity and disability, vitamin D deficiency, and GC therapy, the inflammatory disease activity may be the most important factor associated with bone loss in RA [30, 31]. Another risk factor for developing OP is represented by the rheumatoid factor (RF) status: the frequency of OP and reduced bone mass is higher in RF-positive than RF-negative patients [32].

The prevalence of OP in RA patients is reported to be approximately twice that in the general population [32]. The frequency of OP in patients with RA ranges from 12.3 to 38.9% at the lumbar spine and from 6.3 to 36.3% at the hip [33–34]. According to a recent report, the frequency of OP in Korean postmenopausal women with RA was of 46.8% [31]. Above all, there is at least a twofold increase in the risk of vertebral FF in RA patients, and a higher risk, up to sixfold, has been reported in patients with a long-standing disease [34–36]. Recently, RA has been taken into account as an independent risk factor in the assessment of fracture risk [37, 38].

An important part of the accountability for the increased fracture risk is the reduced bone strength, which can be explained by disturbances in bone remodelling. It is known that upregulation of pro-inflammatory cytokines, such as TNF-α, IL-1, Il-6, and IL-17, is responsible for the overexpression of RANKL that promotes osteoclasts differentiation and leads to an increased bone resorption. More recently, it became known that formation of the bone is also hampered in RA patients [39]. This is orchestrated by osteocytes, which send their molecular signals based upon loading and unloading forces, resulting in changes in RANKL/OPG and the Wnt pathway. Inhibitors of the Wnt signalling pathway, such as Dkk-1 and sclerostin, result to be upregulated in active RA [40], leading to apoptosis of osteoblasts and hence to a decreased bone formation. Additionally, OPG is inhibited by increased receptor activation for RANKL expression, which leads to a prolonged lifespan of osteoclastic cells.

GC are frequently used in the treatment of RA. It is well demonstrated that GC have an action both in retarding the progression of erosive joint damage in early RA and a control of disease activity [41–43]. The use of GC is restrained by the occurrence of their side effects, and one of the principal complications of long-term GC use consists of an important alteration of bone metabolism. GC mainly suppress bone formation because they determine a decrease in osteoblastogenesis, interfering with osteoblastic differentiation and maturation and inducing loss of function and apoptosis of osteocytes [44, 45]. Risk of fracture in patients who received long-term GC therapy is about 33–50%, positively relating to daily and cumulative dose [46, 3].

Several studies have shown a lower BMD in RA as compared to controls [47–49], the largest effect being measured at the hip. The observed BMD reduction is approximately of 2–17% 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 3.7–8.5% at the hip and 4.2–5.0% at the femoral neck (according to the age group) [32]. In a study focused on perimenopausal women, a BMD reduction of 5.5% was observed at the lumbar spine [50]. In the largest study conducted on 94 male patients with RA, no reduction was observed at the spine BMD, and a significant decrease at the hip (6.9%) was observed in the oldest patients only [51]; one longitudinal result suggests that BMD loss is lower in males than in pre- and postmenopausal women [52]. A recent study showed that in premenopausal women with RA both spine and hip BMD values were significantly lower than in age-matched controls and that such a difference was maintained at the hip after adjustment of BMD for GC therapy and disease activity indices [53]. This suggests that the disease itself is responsible of the significant bone loss, in particular at predominantly cortical skeletal sites. An association between low-dose GC use (≥6 months) and OP has not been observed [54]. This may be explained by a control of the disease activity and an improvement of function of the co-treatment with low-dose GC and GC-induced OP (GIO) preventive therapy [55, 56].

A common observation in all studies is the large interindividual variations, explaining why there is an apparent discrepancy between a relatively modest mean reduction in BMD and a high prevalence of OP. Among the confounding factors affecting the interpretation of BMD results in RA patients is the long duration of the disease, including the course of the disease itself, and an association has been observed between the severity of RA and the risk of OP [57].

Patients with RA are at increased risk of FF at the hip, vertebrae, and pelvis [35, 58, 59]. Humerus and tibia/fibula fracture risk is also increased in some but not all the [35, 58] studies. The risk of wrist fracture seems not to be increased in RA as compared to controls [35, 58].

In the General Practice Research Database, 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 of 1.5 (1.4–1.6) [35]. Indicators of a substantially elevated risk of hip fracture were the long duration of the disease, low BMI, and the use of oral GC. Two important observations for the potential mechanisms of bone fragility have been made in this study: the risk of fracture is the same in men and women; the fracture risk remains elevated after excluding patients who had taken GC at any time during the follow-up.

RA is characterized by a higher severity of spine involvement with a higher risk of having two or more fractures compared to controls [34, 60]. The incidence of vertebral FF is 6.7 per 100 patient-years according to a study with a mean follow-up of 2–3 years [61]. Patients with incident vertebral FF are those with older age, lower BMD, higher disability, and previous nonvertebral fractures. Being diagnosed as having RA, the risk is related to vertebral deformities independent of BMD and GC use [34]. Presence of vertebral FF is inversely related to the use of DMARDs and GC, enhancing the hypothesis that an appropriate control of the disease may be a protective factor against bone fragility [60]. Low bone quality might be the cause of the frequent prevalence of vertebral FF in patients with RA [62]. Vertebral FF may

not emerge to clinical attention in RA because of analgesics use for painful joints. Thus, vertebral fracture assessment technology on DEXA devices should be used in these patients at the time of BMD measurement.

The incidence rate of nonvertebral FF in IORRA cohort study is 3.5/100 patient-years and does not change in 10 years, despite a striking improvement in RA disease control [63]. This study could indicate that OP treatment and nonvertebral fracture prevention remain important, regardless of RA disease activity.

DMARDs, as methotrexate (MTX), and biotherapies, as anti-TNF therapies, have proved to be successful in retarding joint destruction in RA while being able to control inflammation. The goal of the treatments is the remission of the disease and the prevention of the structural damage; prevention of bone complications is therefore expected.

Infliximab was able to decrease bone resorption; at its introduction as 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 was observed [64]. 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 MTX and infliximab, as compared to those treated by MTX alone, at the femoral neck and the hip: −0.35 vs. −3.43% and −0.23 vs. −2.62% [65]¸ there was no change at the spine level. Other studies showed that infliximab and etanercept were able to arrest BMD loss at the spine [66, 67]. The BeSt study compared prospectively the efficacy of four treatment strategies in RA: (a) sequential monotherapy of several DMARDs, (b) step-up combination therapy, (c) initial combination therapy with tapered high-dose prednisone, and (d) initial combination therapy with infliximab. In the group with better suppression of inflammation, the BMD loss was less than in other groups [68]. In a study of 50 patients with active RA who started adalimumab in addition to stable MTX e prednisone (less than 10 mg/day) at baseline, BMD was associated with disease activity and duration; after 12 months, adalimumab arrested further decrease in BMD, with an inverse association between decrease in serum C reactive protein (CRP) levels and increase in BMD, but a greater increase at femur BMD was observed in patients who received concomitant low doses of prednisone [69]. While most studies were of short duration, up to 1 year, the BMD sparing effect seemed to maintain thereafter in a cohort of 184 established RA patients: only a small decrease of hip BMD and a stable spine BMD was shown after a mean follow-up of 4 years of anti-TNF treatment [70]. In a large sample size study, the use of biologic DMARDs (infliximab, adalimumab, etanercept, golimumab, certolizumab, rituximab, abatacept, tocilizumab, anakinra) did not lead to a reduction in the risk of nonvertebral osteoporotic fractures [71]. In a group of 8419 RA women, it was found that the use of anti-TNF in combination with MTX was not associated with a reduction in the risk of FF [72]. Another recent study also did not report any advantages of TNF inhibitors over traditional nonbiologic therapies for the prevention of bone loss and fracture in RA patients [73].

At this stage, there is increasing evidence on the beneficial effect of anti-TNF agents to prevent bone loss, even if the clinical impact, in terms of fracture risk reduction, has yet to be confirmed. Therefore, the administration of bisphosphonates

(BP), as well as other agents, such as teriparatide and denosumab (a monoclonal antibody against RANKL), might be important for OP treatment and consequent fracture reduction in RA patients.

14.6 Osteoporosis in Systemic Lupus Erythematosus

SLE is an autoimmune disease characterized by chronic inflammation and the production of a wide array of autoantibodies. SLE can virtually involve any organ/system; in its clinical picture, active disease, chronic damage, and comorbidities overlap [74].

SLE typically affects young women in their childbearing age, with a peak of incidence between 15 and 40 years of age and a male to female ratio of 1:9. Disease onset is less common in childhood and in elderly population with female to male ratios of 2–6:1 and 3–8:1, respectively [74]. Because the survival of patients with SLE has improved dramatically over recent decades, attention is now focused on disease complications leading to increased morbidity and mortality.

Of note, the musculoskeletal system is frequently involved, and OP is one of the most common comorbidities, found in 1.4–68% of this population [75–77]. This wide variation in prevalence may be related to the study design, sample size, GC use, disease activity and duration, patient demographics, and under-recognition as more than 75% of patients are thought to have suboptimal screening [78]. A systematic review and meta-analysis, which evaluated the mean difference of the BMD level between SLE patients and controls, has been recently published [79]. Literature showed that SLE patients had significantly lower BMD levels than controls ($p < 0.001$).

In SLE, FF also occur in younger patients as compared with those with primary OP, and 4–30% of patients may develop FF despite normal BMD [76, 77, 80–82]. The most common sites of FF are the hip, vertebra, ankle, rib, foot, and arm [76, 80]. OP and associated FF may result in severe pain, disability, impaired quality of life, and increased mortality [83, 84].

The pathogenesis of OP and the occurrence of FF in SLE are likely to be multifactorial, involving both non-disease-related and disease-related factors.

It has been established that the old age, postmenopausal status, low body mass index, reduced physical activity, and constitutional symptoms are the possible risk factors for OP [75–77, 85, 86].

Pro-inflammatory cytokines including IL-6, IL-1, and TNF-α are overexpressed by activated immune cells in SLE patients and have a direct action on the bone, increasing on one side osteoclastic bone resorption and on the other reducing osteoblastic bone formation [2, 7, 77, 85, 87]. It is well known that upregulated RANKL/RANK/OPG signalling and downregulated Wnt/β-catenin pathway are responsible for bone loss associated with inflammatory rheumatic diseases [2, 7, 85, 87]; in addition, polymorphisms in the RANKL and OPG genes appear to play an important role in bone remodelling process and in FF occurrence in SLE [88].

OP and atherosclerosis are common clinical problems and share bidirectional correlation [89, 90]. Cardiovascular disease is a well-recognized complication of

SLE, and there has been a growing interest in the biology and mechanisms underlying premature and accelerated atherosclerosis in this disease [91, 92]. To date, the role of inflammatory immunological pathways has been recognized for both the increased risk of cardiovascular disease and low BMD [86, 92, 93]. Oxidized low-density lipoprotein (LDL) and LDL cholesterol (LDL-c) play an important role in the generation and progression of atherosclerosis; additionally, it has been shown that high serum LDL-c level may also be a risk factor for low BMD and for nonvertebral FF [80, 86]. Oxidized lipids are able to activate T cells, which in turn can induce increased production of TNF-α and RANKL; moreover, oxidized lipids may negatively influence osteogenesis by reducing osteoblast differentiation and maturation. As a consequence, LDL and LDL-c may be considered the link between OP and atherosclerosis, and in fact in active SLE patients, high serum levels of LDL and LDL-c were inversely correlated with BMD [80, 86, 93].

Although some clinical and cross-sectional studies failed to demonstrate a relationship between disease activity and bone loss in SLE [80, 94, 95], a recent 5-year prospective study in Chinese women with SLE demonstrated an association between high disease flare rate and increased bone loss in spine and hip [96]. In addition, low complement C4 levels were a predictor of low lumbar spine BMD in the Hopkins Lupus Cohort, and low complement C4 was an independent contributor to the association between low BMD and carotid atherosclerosis [93, 97].

The relationship between organ damage and reduced BMD is still debated. While several studies report such a relation [96, 98], the results of other studies [75] failed to identify organ damage as a risk factor for OP and FF [76, 94, 95]. Lupus nephritis occurs in up to 60% of SLE patients during the disease course and can result in renal failure. In chronic renal failure, the development of both secondary hyperparathyroidism and low 1,25[OH]2D levels will adversely affect bone mass. However, an association between impaired renal function and low BMD was reported in only one study, in older female SLE patients [99].

Hypovitaminosis D is highly prevalent in SLE as a result of avoidance of sunshine, photoprotection, renal insufficiency, and the use of GC, anticonvulsants, calcineurin inhibitors, and, probably, antimalarials which alter the metabolism of vitamin D or downregulate the functions of the vitamin D receptor [82, 87, 100]. Studies that included healthy controls reported lower vitamin D levels in SLE patients in 12/14 (86%) [101]. Vitamin D insufficiency (25OH-D serum levels <30 ng/mL) was also recently documented in 60% of non-supplemented female SLE patients in the Mediterranean region [102]. A cross-sectional evaluation of bone metabolism parameters in 186 SLE patients showed vitamin D insufficiency in 79% with a mean level of 21.8 ± 15.7 ng/mL; of note, 25OH-D levels <20 ng/mL were found in 52.2% of patients [82].

With respect to bone mass, hypovitaminosis D, which predisposes to secondary hyperparathyroidism, represents an additional risk factor for OP. A significant association between low 25OH-D levels and low vertebral BMD was found in [103]. A positive correlation was also observed between 25OH-D levels and lumbar spine and total hip BMD in Chinese young male SLE patients [104]. Furthermore, a 6-year prospective study in 126 Dutch SLE patients confirmed that low 25OH-D

levels at baseline were significantly associated with bone loss in the lumbar spine and hip [105].

The active form of vitamin D [1.25(OH)2D] is a steroid hormone that, in addition to its actions on calcium and bone metabolism, exhibits a wide spectrum of immunomodulatory and anti-inflammatory effects, as extensively documented by experimental studies [100, 101, 106–108]. Although these effects have been also reported in clinical studies and reviews specifically evaluating SLE patients, the relationship between vitamin D status and the onset, activity, and complications of the disease is currently theoretical, and further well-designed trials are needed [100, 101, 106, 108–110].

Most patients develop SLE in their premenopausal years, and some of them do so in the years preceding the achievement of peak bone mass. Both the disease and its treatment (e.g., cyclophosphamide) can also induce amenorrhoea and premature menopause, which cause bone loss. Furthermore, it has been suggested that other endocrine dysfunctions may affect negatively bone mass in SLE. The hormonal status of SLE patients has been described as a relatively high oestrogenic and low androgenic state; low plasma androgens in active and inactive SLE and an association between low dehydroepiandrosterone sulphate levels and low BMD have been reported [80, 85, 87].

The antimalarial drugs chloroquine (CQ) and hydroxychloroquine (HCQ) are frequently used in SLE patients as immunosuppressants. The mechanism of action has been linked to an effect on DNA, antigen processing, cytokines, lysosomal membranes, and T-cell proliferation [85]. Additionally, CQ and HCQ were thought to interfere with the synthesis of 1,25(OH)2D, by inhibiting hydroxylase α1 [85, 87].

With regard to the skeletal effects, studies in SLE patients demonstrated conflicting results [77, 80, 85]. Two cross-sectional studies in SLE female patients reported a significant correlation between HCQ and higher BMD in the spine and hip [111, 112]; additionally, treatment duration was significantly associated with higher BMD in the spine [112]. Conversely, a cross-sectional and a 6-year prospective study in Dutch SLE patients showed a negative correlation between BMD and HCQ use [105, 113]. In a 5-year prospective study, no influence of HCQ treatment on BMD was found [96]. Thus, it is still unclear whether the antimalarial drugs ultimately affect bone metabolism, and further studies on this possible adverse effect are needed [77, 80, 85, 87].

In SLE patients, GC, commonly used at high doses for the treatment of disease flares, significantly improved survival and the quality of life [85]. However, there is no doubt that GC and other immunosuppressants could represent an additional risk factor for bone loss and FF [3, 44, 45, 77, 85, 114]. Longer duration of GC therapy and cumulative and high-dose GC use appear to be associated with bone loss and FF in SLE patients [3, 44, 45, 77, 80, 82, 96, 114, 115]. Moreover, cumulative dose [116] and duration of GC therapy independently predicted higher FF risk in SLE patients compared with controls, using the FRAX tool, the most widely used algorithm for assessing the 10-year individual FF risk [37, 117, 118].

For cyclosporine A (CyA), a possible deleterious effect on the skeleton has also been suggested based on the high frequency of FF occurring in transplant recipients

treated with this drug. However, in rheumatic diseases including SLE, CyA is used at lower doses than in transplant recipients, and present data do not allow to confirm the relationship between CyA and bone loss in SLE patients [77, 82, 85].

Cyclophosphamide, commonly used to treat severe SLE comorbidities including renal and neurologic involvement, may contribute to treatment-related OP by inducing amenorrhoea and premature menopause secondary to ovarian failure [77].

Chronic treatment with antiepileptics and anticoagulants may also contribute to bone loss and FF occurrence by negatively affecting bone mass, as documented in some studies [77, 80, 82, 85].

Although estimates for the prevalence of OP and FF in SLE patients indicate that their burden may be dramatically elevated, bone health care in SLE is still suboptimal, and quality-improvement efforts should address OP screening, prevention, and treatment [78]. There is no consensus regarding the optimal method of identifying bone loss and risk of FF in SLE; the FRAX and the DeFRA (the Italian algorithm derived from FRAX) could represent useful tools to establish the need for pharmacological treatments [38].

At present, there are no specific guidelines regarding OP prevention and treatment in SLE patients.

Calcium and vitamin D are recommended in all patients treated with GC [44, 45, 114, 119, 120]; special attention must be paid to obtain the target 25OH-D serum level above 30 ng/mL, as recommended by multiple scientific societies [121, 122].

BP are considered the first choice to prevent bone loss and reduce FF risk in GIO [44, 45, 114, 119, 120].

However, when considering premenopausal women, there is no generally recommended treatment, and BP should only be prescribed in patients with high risk of FF, as these drugs may be long term stored in the bone and are associated with foetal abnormalities in animal models [77, 85, 87, 119].

Teriparatide, which counteracts the most relevant pathophysiological mechanisms of GIO [45, 114, 119, 120], has been shown to be superior to BP in both FF rate and BMD in patients with GIO [114, 119, 120] and SLE [123].

Denosumab could represent an attractive effective agent in the treatment of GIO [114, 120, 123]; additionally, since denosumab is not incorporated in the bone, this drug may be also advantageous in premenopausal patients [77, 114, 119, 120, 124]. A recent study has shown that denosumab is superior to BP in SLE [125].

Conclusion

Several, if not all, inflammatory rheumatic diseases may be complicated by increased bone loss and elevated FF risk. We focus on RA, SLE, AS, and PsA because OP and associated FF are largely documented in these diseases.

The pathogenesis of OP and the occurrence of FF are likely to be multifactorial, involving both non-disease-related and disease-related factors. In addition to disease state, several factors including genetic, metabolic, and hormonal factors may have a deleterious effect on the bone. Increasing evidence highlights the role of complex interactions involving chronic inflammation, RANKL/RANK/OPG signalling, and Wnt/β-catenin pathway. Even if clinical studies

have demonstrated that adequate immunosuppressive therapy prevents both local and generalized bone loss, there is no doubt that the chronic use of GC and other immunosuppressants could represent an additional risk factor for bone health.

There are no specific guidelines regarding OP prevention and treatment in rheumatic diseases.

A healthy lifestyle and calcium and vitamin D supplementations are diffusely recommended in almost all patients; BP are considered the first choice in patients at risk of FF with caution in their use both in premenopausal and younger patients. Denosumab and teriparatide might be an attractive additional option.

Whether TNF-α inhibitors and other biologic agents are ultimately effective in reducing FF risk remains so far inconclusive.

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