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Osteoporosis Pathophysiology, Epidemiology, and Screening in Rheumatoid Arthritis

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Abstract

Purpose of Review To review the burden of osteoporosis (OP) in rheumatoid arthritis (RA) and to describe the OP screening strategies applied in RA.

Recent Findings RA is an inflammatory condition that predisposes patients to development of OP. OP in RA has a multifactorial pathogenesis with systemic inflammation and glucocorticoid use playing major roles. Newer studies have reported an intriguing association between RA autoantibodies and the development of OP. OP screening strategies in RA patients include clinical and vitamin D assessment, biochemical markers of bone remodeling, and bone imaging evaluations, particularly dual-energy X-ray absorptiometry (DXA).

Summary Fragility fractures are an important comorbidity of RA. OP screening strategies are both feasible and effective in RA patients and recommended by most specialty organizations. Given the considerable exposure to factors related to OP development, such as pro-inflammatory cytokines and glucocorticoid treatment, special attention should be directed to biochemical and DXA results in RA patients.

Keywords Rheumatoid arthritis · Osteoporosis · Screening · Fractures · Glucocorticoids · Autoantibodies against citrullinated proteins

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by local and systemic bone loss [1]. Osteoporosis (OP) is one of the major comorbidities of RA and is caused by a number of complex pathophysiologic processes. Bone fragility in RA results from a mix of systemic inflammation, circulating autoantibodies, and pro-inflammatory cytokine secretion that collectively have deleterious effects on bone. Glucocorticoids, used more for the treatment of RA than for any other inflammatory disease, also play a crucial role in the development of OP in RA. Even with adequate OP primary prevention strategies, through appropriate calcium and vitamin D dietary supplements and acceptable physical exercise, most RA patients will develop OP during the progression of the disease. OP screening strategies are crucial for fracture prevention in RA patients since they have unique risk factors relative to the general population. Dual-energy X-ray absorptiometry (DXA), clinical assessment, biochemical measures of bone remodeling, and, from a research standpoint, high-resolution peripheral quantitative computed tomography (HRpQCT) can help determine fracture risk in RA patients.

This article is part of the Topical Collection on *Rheumatoid Arthritis*

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Pathogenesis of Bone Loss in Rheumatoid Arthritis

Although there is mechanistic overlap, we separately discuss local bone loss (at the joint level) and systemic bone loss.

Local Bone Loss

Periarticular osteopenia results from the reduction of bone trabeculae, both in number and in dimension. Periarticular

osteopenia is the consequence of cortical bone thinning at the insertion of the inflamed synovium, the predominant site of bone erosions in RA [1]. RA patients have increased cortical porosity with lower volumetric bone mineral density (BMD) at both trabecular and cortical site [2, 3]. Local bone loss is an early change in RA patients associated with development of aggressive systemic disease [4]. Bone marrow edema, an early sign of periarticular bone loss [5] and the decline in hand bone mineral density [6], is independently associated with the development of bone erosions. Moreover, peripheral bone mineral density loss is a hallmark of pre-clinical arthritis [7]. The pathogenesis of local bone loss is multifactorial. Not surprisingly, traditional pro-inflammatory cytokines play an important role in the development of periarticular osteopenia. Lower BMD and microstructural deterioration of the bone are related to systemic inflammation and cytokine release (e.g., tumor necrosis factor [TNF] and interleukin 6 [IL-6]) [2, 3]. In addition, T cell–derived receptor activator of nuclear factor kappa-B ligand (RANKL) [8, 9] and autoantibodies against citrullinated proteins (ACPA) are determinants of bone loss [10, 11]. Interestingly, metacarpal bone loss, detected with HRpQCT, was seen in ACPA-positive RA and not in ACPA-negative RA or in other inflammatory diseases such as psoriatic arthritis or inflammatory bowel disease [12]. In addition, ACPA-mediated detrimental activity on periarticular bone loss was also found in sporadic (5.3%) ACPA-positive psoriatic arthritis patients [13]. The latter evidence supports the recent hypothesis of a direct and independent effect produced by ACPA on osteoclasts [14], an effect potentially mediated by IL8-dependant osteoclast activation [15] that, in turn, confers a particular susceptibility of periarticular bone loss in ACPA-positive RA patients.

Systemic Bone Loss

Systemic bone loss leads to OP with an increased risk of fragility fractures. In RA patients, systemic bone loss seems to start early in disease development and in some patients even before the clinical onset of RA [16••]. Both trabecular and cortical bone are affected but cortical sites (i.e., femoral neck and distal radius) appear to be more susceptible to OP [17]. The pathogenesis of systemic and local bone loss in RA is similar. Several studies attest to the critical role inflammation plays in the development of systemic OP in RA. For example, cytokines such as TNF, IL6, IL1, and immune cell-derived RANKL had a detrimental effect on osteoblastogenesis and a positive effect on osteoclastogenesis [18]. Furthermore, RA patients with low BMD displayed high level of circulating senescent CD4+CD28− T cells, cells that expressed RANKL to a greater extent than CD28+ T cells and more efficiently induced osteoclastogenesis [9]. In addition, autoantibodies directed against osteoprotegerin (OPG), a decoy receptor of RANKL, have been discovered in RA patients and are related to higher levels of bone resorption markers [19]. Another important factor in the development of OP in RA is Dickkopf-related protein 1 (Dkk-1), a Wnt signaling inhibitor, that is a key regulator of joint remodeling in RA [20••] that plays a significant role in systemic bone [21]. A 2018 meta-analysis on 1305 patients and 504 controls showed significant elevation of Dkk-1 serum levels in RA patients [22].

Similarly to periarticular bone loss, ACPA are associated with systemic bone loss, with a titer-dependent effect on BMD [23]. The deleterious role of ACPA on bone density may pre-date the onset of clinical arthritis by years, even at systemic level [16]. Glucocorticoids are widely prescribed for the treatment of RA and, at higher doses, have a well-known detrimental effect on bone [24–26, 27•]. Nevertheless, the role of low-dose and short-term treatment with glucocorticoids is controversial [28]. Indeed, reducing systemic inflammation with lower dose glucocorticoids might counteract their unfavorable effects on bone with a resulting null or even positive net bone outcome. In accordance with this hypothesis, many studies and meta-analyses demonstrated that low-dose glucocorticoid users affected by active RA do not experience significant BMD changes compared to controls [29–31]. In contrast, even low-dose glucocorticoid and intra-articular glucocorticoids may not be entirely innocuous to bone [32, 33]. A thoughtful case–control study of hip fractures suggested that both RA and glucocorticoids are likely independent risk factors to bone [34].

The etiopathogenesis of systemic and periarticular bone loss overlaps and shares a common pathway. Moreover, periarticular bone loss is enhanced by the post-menopausal state, present in many RA patients [35], raising the interesting possibility that OP might increase the susceptibility to bone erosions in RA [36]. Indeed, the systemic bone loss that occurred in nearly 60% of early-RA patients is a strong predictor of radiographic joint damage [4]. Another study indicated a possible association between low systemic BMD and the occurrence of atlantoaxial subluxation, a fearsome complication of RA [37]. In this scenario, systemic OP might be a key factor and not a mere spectator of the pathogenesis of RA-associated erosive changes [36].

Epidemiology of Bone Loss in Rheumatoid Arthritis

The epidemiology of bone loss in RA can be divided into epidemiology of OP, epidemiology of fractures, and epidemiology of OP screening and fracture prevention in RA.

Epidemiology of Osteoporosis in Rheumatoid Arthritis

OP is one of the most common comorbidities associated with RA. Data from the UK Clinical Practice Research Datalink (CPRD) showed that the incidence ratio of OP in RA patients who were not taking glucocorticoids was 7.5 per 1000 person-

years, compared to 4.1 per 1000 person-years in healthy controls, with an estimated incidence rate ratio of 1.8 (95% CI, 1.7, 2.0) [38]. BMD decline was related to disease duration (i.e., the longer the duration, the lower the BMD) but not with ongoing RA treatment [39]. Cortical sites (distal radius and femoral neck) appeared more susceptible to OP than trabecular site (lumbar spine) in RA, an effect independent of age or positive antibody status [40]. Other studies have indicated that about one-third of post-menopausal RA patients have OP with a twofold increased frequency of OP at all ages, compared with the general population [40, 41]. A 2014 study showed that the prevalence of OP in RA is approximately 30% [42]. More recently, among a large Korean cohort of post-menopausal women with RA, nearly 50% of patients had OP [43]. Data on the prevalence of OP in pre-menopausal RA women is sporadic. A 2016 study reported that, among women with RA, the proportion of pre-menopausal patients with OP was 13% compared to 0% of healthy and age-matched controls [44]. Compared with healthy women, these pre-menopausal patients with RA had a relative risk of osteopenia of 3.6 (95% CI, 1.6, 8.0) and 14.0 (95% CI, 4.4, 44.6) at lumbar spine and femoral neck, respectively [44]. It was similarly demonstrated that men with RA had an increased risk of having OP, compared with age-matched healthy individuals (22.4% vs 10.5%, $p = 0.049$) [45].

Epidemiology of Fractures in Rheumatoid Arthritis

A systematic review of 25 studies published in 2018 reported that patients with RA have a greater risk of fragility fracture (1.6, 95% CI 1.4–1.8) [46]. The pooled incidence of fragility fractures was 33.0 per 1000 person-years, ranging from 7.0 to 86.3 per 1000 person-years across the selected studies, with greater risk among women. Clinical vertebral fracture incidence was 4.3 per 1000 person-years, but as high as 42.4 per 1000 person-years when defining fractures using radiographic screening. Despite this, the latter systematic review did not show an increasing temporal trend in the incidence of fractures. A more recent Spanish longitudinal analysis, not included in the latter review, of almost 7000 hip fractures in RA patients, showed that incidence of hip fractures increased from 1999 to 2015 [47]. In this analysis, the osteoporotic hip fracture rate increased every year during follow-up, but to a lesser extent in women (3.1%) compared to men (3.5%).

Epidemiology of Osteoporosis Screening and Fracture Prevention in Rheumatoid Arthritis

Dual-Energy X-Ray Absorptiometry Epidemiology in Rheumatoid Arthritis

In 2013, the American College of Rheumatology (ACR) published a list of five medical procedures at risk of overuse in daily practice; DXA scans were one of the five listed [48]. Nevertheless, epidemiological data on DXA usage in RA varies. An international cross-sectional study showed that DXA had been performed in about 60% of RA patients [49], and the rate ratio of DXA utilization was 1.8 (95% CI, 1.6–62.0) in RA patients, compared to the general population [50]. The National Data Bank for Rheumatic Diseases (NDB) longitudinal prospective observational study found that OP screening measures (defined as undergoing BMD measurement) were reported in close to an identical proportion of RA patients [51]. In contrast, a retrospective cohort study revealed that only 30% of women with RA received an incident DXA during a 4-year period (2006–2010) [52]. During an overlaying time frame (2008–2014), there was also a declining trend of BMD measurement and OP treatment from in RA with no improvement observed after release of the 2010 ACR glucocorticoid-induced OP treatment guidelines [51]. In addition, among just over 8000 RA patients followed over a 2-year period (2008–2009), the rate of DXA scans per beneficiary was 0.7 per year while peripheral joint X-rays per beneficiary was 2.6 per year [53]. Notably, 49% of the population under this analysis (81.3% women aged ≥ 65 years) never received a DXA scan during the period; yet 47% received ≥ 2 peripheral joint radiograph and 16% underwent 5 or more radiographs [53]. It is possible that some of these downward temporal trends are associated with a decrease in the reimbursement levels for DXA tests in the USA, making the test financially infeasible for some clinicians to perform in their offices [54]. In summary, DXA does appear to be overused, at least in RA, and its utilization is declining.

Epidemiology of Osteoporosis Treatment in Rheumatoid Arthritis

Studies that directly address the epidemiology of OP therapies in RA are sparse. In an observational study of RA patients, 44.4% were receiving vitamin D supplementation at the time of the study visit [49]; the mean daily calcium intake in RA was estimated around 800 mg [42]. Bisphosphonates are widely used for post-menopausal OP and are probably the most prescribed anti-osteoporotic drug in RA. In an analysis from the Veterans Affairs Rheumatoid Arthritis (VARA) registry, 41.5% of RA patients overall took bisphosphonates, with an average length of treatment around 40 months. Not surprisingly, the number prescribed bisphosphonates was over 25% greater (68.4%) for RA patients who were glucocorticoid users [55]. A large observational study on subjects followed from 2003 to 2014 revealed that two-thirds of RA patients never received any OP treatment, and among those who were treated with an OP medication, 16.9% received bisphosphonates [51], a proportion largely lower than the one seen in the VARA study and in other post-menopausal

OP studies [55–57]. In summary, OP treatment in RA seems to be underused and largely driven by glucocorticoid use.

Laboratory Evaluation and Imaging Assessment of Osteoporosis in Rheumatoid Arthritis

Who Should Be Screened for Osteoporosis in Rheumatoid Arthritis?

In 2016, a task force of the European League Against Rheumatism (EULAR) published a set of recommendations for the daily practice screening of comorbidities in inflammatory rheumatic diseases [58]. The guideline group encouraged screening for risk factors of OP (including body mass index < 19, physical inactivity, glucocorticoid exposure, alcohol intake, family history of femoral neck fracture, and secondary OP and BMD). They advocated that the FRAX global risk score be calculated where applicable (a statement based on individual cohort study and low-quality randomized controlled trials). The EULAR task force, however, did not produce recommendations for specific RA sub-populations, such as ACPA-positive patients or post-menopausal women, groups that might deserve more aggressive screening strategies. However, the frequency of BMD evaluation or the threshold for intervention with anti-osteoporotic medications was not included in these EULAR recommendations. In 2017, the ACR released an updated guideline for the prevention and treatment of glucocorticoid-induced osteoporosis [59]. This guideline, albeit specific to chronic glucocorticoid use, advocates anti-osteoporotic treatment in all individuals ≥ 40 years of age with a moderate-to-high risk of fracture (assessed with glucocorticoid adjusted FRAX) and in those < 40 years of age at high risk factor for osteoporosis (history of fragility fracture and/or high dose glucocorticoid treatment). Moreover, ACR recommended to reassess clinical fracture risk every 12 months and do BMD testing every 1–3 years, depending on ongoing anti-osteoporotic medication, risk factors, glucocorticoid dose, and age. Similar recommendations can be applied to RA patients who are taking glucocorticoids and might be even considered for RA patients who are not on glucocorticoids. Figure 1 summarizes the ACR recommendation on glucocorticoid-induced osteoporosis reassessment in adults, with proposed considerations for RA patients.

Efforts to improve the outcomes of comorbidities in RA including osteoporosis are badly needed. In a 6 month trial, patients were randomized to receive a nurse-led screening (consisting of a guided questionnaire) or a self-administered questionnaire focused on several comorbidities related to RA [60]. The number of OP testing and treatment strategies implemented differed significantly between the nurse-led arm and the self-assessment arm (1.08 vs 0.31, $p < 0.001$). Interestingly, the incidence rate ratio for anti-osteoporotic measures was 3.34 compared with 1.40, 1.77, and 1.60 for measures against other RA comorbidities including cardiovascular events, infectious diseases, and cancer, respectively (all corrected for glucocorticoid treatment). Another study indicated that a 1-day clinic screening for multimorbidities, including OP, is relevant and feasible in RA patients [61]. Therefore, screening strategies may be somewhat efficacious in modifying physician and patient behaviors towards OP prevention and treatment.

Dual-Energy X-Ray Absorptiometry in Rheumatoid Arthritis

Lumbar Spine and Hip Bone Assessment

Lumbar spine and total hip are sites typically evaluated for the assessment of OP. BMD measured at these sites have been used as clinical trial outcome for over three decades, and its reliability for fracture risk assessment is widely recognized [62]. Nevertheless, RA is an independent risk factor for fractures, and patients with RA experience fractures at a lower BMD threshold compared with controls [63]. Another important difference between general OP and RA patients is that the latter seem to be particularly prone to cortical bone OP, namely total hip and femoral neck.

Trabecular Bone Score

Trabecular bone score is an index derived from a computer analysis of lumbar spine DXA that helps to predict fracture risk [64]. The Manitoba BMD Registry analysis reported trabecular bone scores significantly lower in RA patients compared to non-RA patients. Trabecular bone score can be used to improve the sensibility of FRAX algorithm. Using the trabecular bone score adjustment to FRAX, the proportion of RA patients who were reclassified over the intervention cutoffs (major osteoporotic fractures ≥ 20% and hip fractures ≥ 3%) was 4.9, with an odds ratio for being reclassified of 1.7 (95% CI, 1.2, 2.2) and 1.5 (95% CI, 1.1, 1.9) for major osteoporotic fractures and hip fractures respectively [65]. In RA patients with at least a prevalent vertebral fracture, a negative correlation between trabecular bone score and FRAX was found, while lumbar spine BMD was not found to correlate with FRAX [66]. In addition, another study showed that trabecular bone score differed significantly between RA patients with or without a vertebral fracture, while lumbar spine BMD was not dissimilar [67]. In summary, trabecular bone score can be a helpful resource for the assessment of fracture risk in borderline patients. However, trabecular bone score requires specialized software that is not always available on all DXA machines.

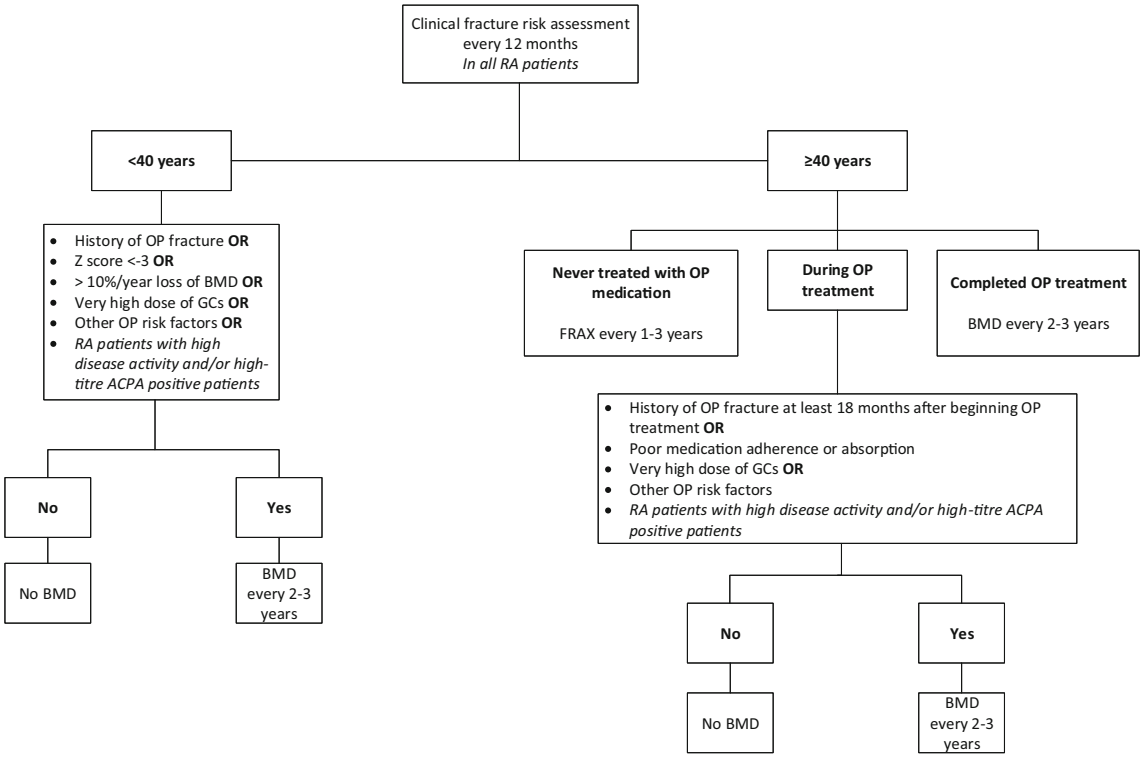

Fig. 1 American College of Rheumatology glucocorticoid-induced osteoporosis reassessment algorithm modified for rheumatoid arthritis patients. Reprinted with permission from 2017 American College of Rheumatology Guideline for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis in Arthritis and Rheumatology published by John Wiley and Sons on June 6, 2017

Metacarpal Bone Assessment

Metacarpal bones are sites of great interest in the evaluation of BMD in RA. However, in destructive forms of RA, the value of these regions is more complicated. In 1994, a method for measuring mineral content an RA patients' hand was developed with the use of DXA [68]. The hand position and form (i.e., ulnar deviation) did not alter bone mineral content measurements but did alter BMD, which strictly depends on the area of the region explored. In this explorative study on 56 RA patients, the hand bone mineral content was inversely correlated with disease duration ($r = -0.62$, $p = 0.0003$), Larsen score ($r = -0.62$, $p = 0.0002$), and Sharp's score ($r = -0.69$, $p < 0.0001$). Other studies explored the significance of hand BMD in RA and the coefficient of variation at the hand ranged between 0.9 and 1.1%, while at the spine and femoral neck, it was about 2.3% and 2.7%, respectively [69, 70]. A more recent study showed that metacarpal BMD loss could predict the progression of joint erosions [71]. In RA patients without erosive disease at baseline, an early BMD loss at the metacarpal site was the only independent predictor of subsequent articular radiographic progression [71]. In another study, in RA patients who experienced BMD loss at the hand site, the odds ratios of erosive disease were 3.5 (95% CI, 1.4, 8.8) and 3.5 (95% CI, 1.4, 8.4) at 5 and 10 years respectively compared to those who did not experience such loss [72]. Moreover, total hand BMD loss was found as a strong predictor of RA development in patients with suspicious arthralgia [73]. While some data for metacarpal bone assessment has yielded positive results, the clinical utility remains unclear due to a paucity of evidence allowing fracture prediction based on this test alone.

FRAX

FRAX is a patented computer-based algorithm developed in 2008 in the UK that is used to calculate fracture risk at 10 years [63]. One of the dichotomous factors included for the estimation of fracture risk is the presence or absence of RA diagnosis, as well as the use of glucocorticoids. FRAX evaluates RA as a dichotomous variable and, as a FRAX limitation, does not includes RA disease activity and RA duration or the effects of ongoing treatment. In an example of a FRAX application [63], the 10-year probability of hip fracture for a woman with a BMI of 25 kg/m^2 aged 70 years in the absence of BMD measurement and any other risk factor is 2.3% without RA and 4.1% with RA (rising above the National Osteoporosis Foundation intervention threshold). From the analysis of combined clinical risk factors, a 65-year-old woman with RA would have a probability of major osteoporotic fracture of 12% with a 26.3% relative increase in fracture risk attributable to RA. In a cohort of RA patients

(66.3% taking glucocorticoids) followed for a median of 5.5 years, OP screening, with the use of FRAX, was performed in 67.4% the patients, with an incidence rate of utilization of 35.6 per 100 person-years. The median 10-year risk factor calculated by FRAX was 10.5% [51]. However, the UK Clinical Practice Research Datalink indicated that FRAX used without BMD might overestimate fracture risk in patients with RA; in proof of point, the mean predicted risk of major osteoporotic fracture at 10 years using FRAX was 13.3%, compared with the observed 8.4% [74]. Possible reasons for this overestimation might be the following: higher competing mortality and insufficient correction for disease severity or duration. In addition, ACPA-positive patients had a greater 10-year risk of major and hip fractures calculated by FRAX compared to ACPA-negative patients, a difference partly explained by higher smoking prevalence, lower femoral neck BMD, and higher rates of other comorbidities among ACPA-positive patients [75]. Nevertheless, FRAX does not currently incorporate the ACPA status of patients despite the growing body of evidence supporting an essential pathogenetic role these antibodies exert [14, 23, 76]. Despite these limitations, FRAX remains a valuable instrument to rapidly calculate the risk of fracture with or without BMD measurement.

Vitamin D Measurement

25-Hydroxyvitamin D deficiency (a level < 20 ng/mL) has been widely reported in RA patients, with an estimated deficiency prevalence in about half of such patients [77]. The relationship between very low levels of 25-hydroxyvitamin D and low mineral density is well established in middle-aged and older adults [78], and, despite smaller populations under analysis, it seems to be true also for RA patients [79, 80]. Besides its effects on bone and calcium metabolism, vitamin D helps regulate immune response. Indeed, two meta-analyses, both published in 2016, reported that 25-hydroxyvitamin D was significantly associated with higher disease activity and greater predisposition to RA [77, 81]. Supporting the latter association, large doses of cholecalciferol ameliorated pain and functional disability in vitamin D-deficient RA patients [82, 83]. However, even if there is a strong biological rationale for the association between vitamin D deficiency and autoimmune diseases, the causal relationship between vitamin D deficiency and RA is yet to be determined. Nevertheless, for a variety of reasons, 25-hydroxyvitamin D measurement should be considered in most RA patients, especially in those who are at risk of having a very low level (e.g., older women and/or those with long standing RA).

Biochemical Markers of Bone Remodeling

Bone turnover markers (BTMs) in RA depend on both peripheral (i.e., bone erosions) and systemic (i.e., whole skeleton OP) osteoclast and osteoblast activity. Indeed, the utility of measuring BTMs can be twofold: monitoring RA activity itself and/or monitoring OP in RA. However, the interpretation of BTM values in RA can be challenging and vary considerably depending on disease activity, duration, and ongoing treatments (including glucocorticoids; with variable effects based on duration of therapy). Amino-terminal propeptide of type I procollagen (PINP), osteocalcin (OC), and bone alkaline phosphatase (BALP) are the most extensively studied markers of bone formation in RA while carboxy-terminal telopeptide of type I collagen (CTX), *N*-telopeptide (NTX), and carboxy-terminal telopeptide of type I collagen (ICTP) are the markers most studied for bone resorption. These markers not only have been investigated for predicting radiological damage, with convincing evidence [21, 84–86] but also were considered for the evaluation of bone loss in RA [84, 87–93]. BTMs are prone to change quickly in response to menopausal status, erosive changes, disease activity, and in response to modifications of RA-specific (i.e., biologics, glucocorticoids) and OP-specific (i.e., anti-resorptives) treatments. Variations in BTM levels might represent observed fluctuations of other confounding variables and not truly the effect of RA on bone. For this reason, BTMs should be evaluated only in select cases and be interpreted on a case-by-case basis.

High-Resolution Peripheral Quantitative Computed Tomography

High-resolution peripheral quantitative computed tomography (HR-pQCT) is a relatively novel technique used to explore the microarchitectural structure of the bone for research purposes. HR-pQCT of the radius and femoral neck predicted the fracture risk better than DXA in post-menopausal women in one study [94]. HR-pQCT was first used in RA patients in 2010 [3, 95] and showed an extremely high capacity of discriminate articular damage with good inter-reader agreement for bone erosions [96]. A 2017 cadaveric study demonstrated that HR-pQCT is highly reliable for the assessment of metacarpal intra-articular bone structure and showed that RA patients had significant deterioration of both cortical and trabecular bone compared to healthy controls [35]. In addition, microfinite analysis at the distal radius of RA patients found that ACPA-positive patients had a significantly decreased bone strength that is associated with greater probability of low-impact fragility fractures [97]. HR-pQCT might be useful to investigate both articular bone damage and systemic bone loss, but it involves higher radiation exposure, higher costs, and in the absence of normative data, it is largely relegated to a research tool.

Conclusions

OP represents the most common comorbidity of RA and might have important consequences, related to not only

fragility fractures but also local bone loss. Systemic and local bone losses in RA start in early stages of the disease and, at least in part, even before the clinical onset of the disease. Initial and periodic OP screening using DXA is feasible and effective in RA, and scientific societies have endorsed initial systematic screening for OP risk in RA patients. Screening strategies should also include an OP risk factor assessment and FRAX calculation. In most RA patients, 25-hydroxyvitamin D should be measured and trabecular bone score as well as BTM measurement should be considered in selected patients. Furthermore, special considerations should be given to selected populations with RA, such as ACPA-positive patients, who are particularly susceptibility to systemic and local bone loss.

Compliance with Ethical Standards

Conflict of Interest Giovanni Adami declares that he has no conflict of interest. Kenneth G Saag declares research grant from Amgen and Merck and consultant fee from Amgen, Lilly, Merck, Radius, and Roche.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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