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REVIEW

Skeletal complications of rheumatoid arthritis

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Abstract Rheumatoid arthritis (RA) is associated with local and systemic inflammation that induces many changes in the skeletal health. Locally, periarticular bone loss and juxta-articular bone erosions may occur while joint ankylosis, generalized bone loss, osteoporosis, and fractures may develop secondary to inflammation. The aim of this narrative review is to summarize the clinical evidence for abnormal skeletal health in RA, the effects of disease modifying anti-rheumatic drugs (DMARDS) on bone health, and the effects of drugs for the prevention or treatment of osteoporosis in the RA population.

Keywords Ankylosis · Bone erosions · Bone fracture · Osteoporosis · Rheumatoid arthritis

Abbreviations

ACPA	Anti-citrullinated protein antibodies
BMD	Bone mineral density
BMI	Body mass index
CI	95% confidence intervals
CT	Computerized tomography
DMARDS	Disease modifying anti-rheumatic drugs
DKK-1	Dickkopf-related protein 1
FRAX	Fracture risk assessment tool
GC	Glucocorticoids
MRI	Magnetic resonance imaging
OR	Odds ratio
RA	Rheumatoid arthritis
RANKL	Receptor activator of NF-kB ligand
RF	Rheumatoid factor
RR	Relative risk
TNFα	Tumor necrosis factor alpha
TKR	Total knee replacement
THR	Total hip replacement

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Introduction

Rheumatoid arthritis (RA) is one of the most common autoimmune diseases affecting nearly 1% of the population and is associated with disability and systemic complications. The pathogenesis of RA is not fully understood but likely results from a combination of factors including environmental (smoking, periodontitis, or gut microbiome), genetic (susceptibility genes), and epigenetic modifications that promote loss of tolerance [1]. RA is characterized by chronic, symmetrically small, and large joint synovitis leading to progressive inflammatory polyarthritis. The majority of RA patients have autoantibodies, including rheumatoid factors (RF) and anti-citrullinated protein antibodies (ACPA) [2]. RA patients may develop periarticular osteopenia, erosions of the subchondral bone of the joint margins, and systemic osteoporosis with increased risk of fractures (Table 1). Prior to effective DMARDS, joint fusion was a significant complication of RA synovitis but is now less common. Skeletal complications of RA are declining with utilization of DMARDS likely secondary to decreasing the pro-inflammatory cytokines driving the chronic inflammation. However, despite significant progress in the treatment of RA, some skeletal manifestations of disease including fractures and osteoporosis still occur at high frequencies.

Table 1 Rheumatoid arthritis is associated with several skeletal manifestations

Complications	Prevalence	Risk factors
Periarticular erosions	63% at diagnosis, 74% in year 1, and 97% by year 3	Seropositivity and smoking
Small joint ankylosis	0.8% by X-ray and 10.6% by MRI	Long-standing disease
Cervical ankylosis	RR 2.56 (1.99–3.30)	Female gender, seropositivity, joint erosions, younger age, long RA duration, long-term corticosteroids and higher markers of disease activity, and wrist fusion
Fractures	Vertebral RR 2.34 (2.05–2.63) Hip RR 3.03 (2.03–4.51)	Duration of disease, severity of disease, ACPA, low BMI, glucocorticoids, and falls
Osteoporosis	15–36%	ACPA, smoking, vitamin D deficiency, and sarcopenia
Osteonecrosis of jaw	0.26–0.94% (similar to non-RA population)	Glucocorticoid use, bisphosphonates, denosumab, and tooth extraction
Secondary osteoarthritis	25% joint replacement at 20 years	Total number and volume of erosions, duration >10 years, age, biologic DMARDS, and glucocorticoid use

Localized periarticular bone erosions occur early in rheumatoid arthritis

Juxta-articular bone erosions, breaks in the cortical bone with loss of underlying trabecular bone, are a hallmark of RA and occur early in disease. Bone erosions, visible by ultrasound, high-resolution computerized tomography (CT), magnetic resonance imaging (MRI), and plain radiography, are typically found on the radial aspects of the finger joints at sites where the synovium contacts the bone. Erosions are predictive of more severe course of rheumatoid disease with increased disability and mortality [3]. Within 3 years, 63% of RA patients will have erosions with 74% of these occurring in the first year and 97% within the second [4]. For some patients, erosions may be present within the first 3 months of clinical disease [4]. ACPA antibodies are the strongest predictor of clinical radiographic progression [5, 6]. A recent study evaluated the contribution of RF to erosions and joint space narrowing and found that RF positivity strongly predicted radiographic progression in early RA patients recruited from 1986 to 2001; however, in a modern early RA cohort recruited from 2002 to 2013, the presence of RF failed to predicted radiographic progression [7]. Other RA-associated autoantibodies including anti-carbamylated protein antibodies are also associated with increased erosions and joint damage [8]. Smoking is another strong risk factor for radiographic progression of RA with an adjusted OR = 2.17, 95% confidence intervals (CI 1.06–4.45) [9]. Smoking also induces ACPA autoantibodies possibly further increasing the risk for erosive RA [10]. Fortunately, treatment with conventional and biologic DMARDS stabilizes and limits joint erosions and damage [11].

Erosions occur secondary to pannus formation at the interconnection of the synovium with the cartilage and bone and are most frequently found on the radial surface sparing the palmar and volar surfaces [12, 13]. Pannus is the result of synovial fibroblast proliferation and infiltration of the synovial lining with inflammatory cells including T and B cells, plasma cells, dendritic cells, monocytes, and macrophages [2]. The synovial fibroblasts within the pannus are inappropriately activated through unknown mechanisms and secrete numerous pro-inflammatory cytokines and metalloproteinases leading to sustained synovial inflammation. These metalloproteinases further promote cartilage catabolism at the synovium cartilage interface leading to the classic juxta-articular bone erosion. A unique feature of RA bone erosions is their relative resistance to fully repair even when disease is well controlled. Failure to repair is largely due to inhibition of bone formation by the upregulation of inhibitors of WNT signaling preventing osteoblast differentiation. Potent WNT inhibitor, Dickkopf-related protein 1 (Dkk-1), is upregulated in the synovial tissue by pro-inflammatory cytokines like TNFα [14]. Elevated serum DKK-1 levels are associated with radiographic progression in the 2-year prospective ESPOIR cohort of 813 patients with early RA [15]. Other WNT inhibitors including frizzled-related protein-1 and sclerostin are also increased by synovial inflammation and participate in suppression of bone formation [16, 17]. While treatment of RA with DMARDS promotes stabilization of bone erosions, total erosion healing is still controversial [18, 19]. Anti-sclerostin antibody treatment of osteoporosis is currently in phase III trials, and it will be of great interest to see if WNT-inhibition will promote RA erosion healing.

Joint ankylosis may occur in long-standing rheumatoid arthritis

Spontaneous fusion of the small joints of the hand, wrists, ankle, and forefoot is frequently seen in long-standing RA, especially prior to widespread use of DMARDS. Detected

by conventional radiography, bone ankylosis occurs infrequently (0.8%) and is found almost exclusively in long-standing disease [20]. In a Swedish cohort of 325 RA patients with long-standing disease (≥9 years) recruited between 1998 and 2001, only six (1.8%) had ankylosis of the small joints of the hands whereas no fusion was found in a second cohort of 310 patients with median disease duration of 4 years (range 1.5–10) [21]. Using MRI, ankylosis was detected in 10.6% of RA patients and was strongly associated with longer duration of disease [20].

Cervical spine ankylosis also occurs in RA in approximately 9–80% of patients depending on the imaging modality leading to instability, stenosis, and cervical myelopathy [22, 23]. The presence of wrist joint ankylosis is strongly associated with cervical ankylosis ($p < 0.01$) [24]. Meta-analysis reveals other risk factors for cervical spine involvement in RA include female gender, seropositivity, joint erosions, younger age, long RA duration, long-term corticosteroids, and higher markers of disease activity [25]. Non-biological and biological DMARDS can decrease the incidence of initial cervical spine involvement; however, in contrast to their success in treating peripheral joint manifestations, DMARDS may not prevent progression of cervical disease once it occurs [23].

Rheumatoid arthritis increases fracture risk

RA patients have approximately doubled the risk of fractures compared to gender and age-matched control patients [26, 27] (Table 2). Meta-analysis of seven observational studies including >600,000 patients found a pooled RR of vertebral fractures in RA to be 2.34 (95% CI 2.05–2.63, $p < 0.0001$) [28]. Fracture risk increases with disease activity and duration, with vertebral fractures approaching a sixfold increase with long-standing RA disease [29]. Having RA for >10 years increased the risk of hip fracture as well (RR 3.4, 95% CI 3.0–3.9). However, young women diagnosed with RA prior to age 50, but not similar young men, have increased non-pathologic fractures (RR 1.63, 95% CI 1.36–1.96) with hip and spine fractures being the most prevalent [30]. Low body mass index (BMI) (RR 3.9, 95% CI 3.1–3.9) and use of oral glucocorticoids (RR 3.4, 95% CI 3.0–4.0) were also associated with substantially elevated risk of hip fracture. Clinical osteoporotic fractures (RR 1.3, 95% CI 1.2–1.4) and hip fractures (RR 1.7, 95% CI 1.5–2.0) remained elevated even in patients that had not received glucocorticoids, consistent with underlying RA itself contributing to fracture risk. Another large study from the Women's Health Initiative found that RA increased the risk of hip fracture compared to women without RA (RR 3.03; 95% CI 2.03–4.51, $p < 0.001$) [31]. Opioid use appears to further increase fracture risk in RA perhaps secondary to increased falls. A large nested control study of Canadian RA patients and controls found a significant increase in the odds ratio for nonvertebral fractures highest in the first 20 days of use OR 11.49 (CI 8.81–14.99) but persisting in chronic use as well >356 days OR 1.73 (CI 1.31–2.30) [32]. Taken together, these data indicate that RA is associated with significant increases in fractures and accordingly is included as a separate risk factor in the fracture risk assessment tool (FRAX) used to determine 10-year probability of fracture [33].

Rheumatoid arthritis is associated with osteoporosis

Factors predisposing RA patients to increased fracture including osteoporosis, chronic inflammation, immobility, increased fall risks, vitamin D deficiency, and glucocorticoid use [26, 34]. Generalized osteoporosis (bone mineral density (BMD) T-score <−2.5) is very common and likely is related to an imbalance in bone remodeling resulting in net bone loss. Most studies evaluating bone loss in RA have focused on lumbar spine BMD measurements and have found osteoporosis in 17 to 32% of RA patients with similar numbers if hip BMD is evaluated (15–36%) [35, 36]. Even in the modern era of early diagnosis and treatment, osteoporosis is still prevalent with 26.5% found in a recent cohort of RA patients recruited in 2009 and 2010 [37]. Although glucocorticoid (GC) use significantly increases the risk of BMD loss in RA patients, studies have shown that low BMD occurs in the absence of GC [38]. Loss of BMD occurs early in RA and increases with disease activity [39–42]. However, even recently diagnosed RA patients with disease for <2 years may have osteoporosis (11%) or osteopenia (24.7%) [43]. A retrospective study evaluating the timing of transition to osteoporosis in 360 female RA patients found that this population of women, with a mean age of 53.7 ± 10.2 years, had osteoporosis at baseline (15%) and another 23.2% of premenopausal and 25.9% of postmenopausal women transitioned to osteoporosis during the follow-up period (mean of 7.4 ± 5.0 years) [44]. The difference between pre-and postmenopausal women transitioning to osteoporosis was not significant and low baseline T-score positively correlated with transition to osteoporosis independent of menopausal status. However, other common risk factors for osteoporosis including low BMI, high RA disease activity, high RF titer, and GC use failed to predict transition to osteoporosis [44].

Mechanistically, generalized osteoporosis and fracture risk may be accelerated due to pro-inflammatory systemic cytokines overexpressed in RA. Pro-inflammatory cytokines including TNFα, IL-1, IL-6, and IL-17 induce the expression of receptor activator of NF-kB ligand (RANKL) leading to increased osteoclast development and activation causing generalized osteopenia and osteoporosis [45]. These same pro-inflammatory cytokines negatively impact osteoblast differentiation and their ability to produce mineralized matrix [46]. Increased disease activity, often associated with increased

Table 2 Rheumatoid arthritis is associated with significant increases in fracture risk

Study	Total pts	Gender W (%) M (%)	Ages	Con no.	RA no.	Fragility fractures RR (95% CI)	Major osteoporotic fracture RR (95% CI)	Vertebral fractures RR (95% CI)	Non-vertebral fractures RR (95% CI)	Risk factors for fractures
Ghazi et al. (2012)	404	W100%	62–68	303	101			OR 6.5 (3.1–13.9)		Non-vertebral fracture and falls
Van Staa et al. (2006)	121,045	W 71% M 29%	>40–90	90,783	30,262		RR 1.5 (1.4–1.6)	RR 2.4 (2.0–2.8)	Hip RR 2.0 (1.8–2.3)	Hip risk: >10-year disease, low BMI, and GC
Huusko et al. (2001)	142,343	W 54% M 46%	18–99	141,292	1051				Hip RR 3.26 (2.26 to 4.70)	
Amin et al. (2013)	2342	W 70% M 30%	W 56 M 58	1171	1171	W RR 1.62 (1.36–1.96) W age < 50 RR 2.34 (1.61–3.42) W age > 50 RR 1.43 (1.16–1.77) M RR 1.40 (1.02–1.93) M age < 50 RR 1.74 (0.91–3.30) M age > 50 RR 1.34 (0.92–1.94)	W RR 1.78 (1.43–2.21) W age < 50 RR 4.05 (2.31–7.10) W age > 50 RR1.46 (1.15–1.86) M RR 1.65 (1.13–2.42) M age < 50 RR 1.49 (0.71–3.12) M age > 50 RR 1.77 (1.13–2.42)			
Brennan et al. (2014)	173,430	W100%	>35	172,422	1008	RR 1.43 (.98–2.09)	Twofold increased	6% RA vs. 16.3% controls		
Vis et al. (2011)	150	W100%	50–70		150			Annual incidence 3.7/100	Annual incidence 3.2/100	
Chen et al. (2016)	Meta-analysis 631,210	Both						RR 2.34 (2.05–2.63)		
Weiss et al. (2010)	373,981	W 66% M 34%	25–79	370,602	3379		RR 2.9 (2.8–3.1)	RR 2.7 (2.1–3.4)	RR 2.9 (2.7–3.1)	
Mohammad et al. (2014)	603	W 71% M 29%	≥40		603			13%		Longer RA duration, ACPA, and severity of RA
Yamamoto et al. (2015)	741,598	W 52% M 48%	≥45		8467				W Standard fracture risk ration (DFR) 1.54 (1.4–1.7) M SFR 1.81 (1.51–2.17)	
Wright et al. (2011)	84,255	W100%	50–79	83,295	960		RR 1.49 (1.26–1.75)	RR 1.93 (1.29–2.0)	RR 3.03 (2.03–4.51)	

W women, *M* men, *OR* odds ratio, *RR* relative risk, *BMI* body mass index, *CI* confidence intervals

pro-inflammatory cytokines, as well as markers of bone turnover, significantly increases the risk of osteoporosis [47]. Duration of disease may be a more important indicator of accelerated bone loss in RA [48]. Vitamin D deficiency has been found to be extremely prevalent in RA patients ranging from 35 to 76% of RA patients [49, 50]. More recently, ACPA antibodies have also been associated with lower BMD in early untreated RA patients [51]. Interestingly, this study found that RA patients with high titer ACPA and rheumatoid factor had the most reduction in BMD. These findings, coupled with ACPA antibodies preceding clinical RA by up to 10 years, implicate ACPA in directly promoting dysregulated bone remodeling and the presence of early erosions in newly diagnosed patients. Interestingly, healthy subjects with ACPA also have dysregulated bone metabolism and develop bone loss prior to clinical disease [52]. Mechanistically, ACPA antibodies appear to directly activate osteoclasts and induce bone resorption and erosions by binding to citrullinated vimentin present on pre-osteoclasts and osteoclasts [53]. Additional risk factors for osteoporosis include sarcopenia, opioid use, and smoking. Female but not male RA patients have a high prevalence of sarcopenia (30–40%) that may further contribute to acceleration of bone loss [54–57].

Secondary osteoarthritis and RA

RA-induced joint destruction is one of the leading causes for total knee replacement (TKR) and total hip replacement (THR). RA severity and length of disease contribute to approximately 80% of patients with RA having TKR [58]. Although TKR and THR significantly improve mobility and quality of life, RA patients have increased risk of complications including infections and need for revisions [58, 59]. Based on a prospective population-based study of >30,000 RA patients recruited beginning in 1978, the risk of revision of TKR was 1.6 times higher for RA than osteoarthritis [60]. Meta-analysis of studies between 1990 and 2011 revealed an increased risk of dislocation following THR, risk of infection, and risk of early revision following TKA in RA versus OA [61]. Late revisions, 90-day mortality, or rates of venous thromboembolic events following THA or TKA in patients with RA versus OA were similar [61]. Tight control of RA appears to decrease or delay the need for TKR and THR [62–64].

Rheumatoid arthritis and osteonecrosis of the jaw

Given the significant burden of osteoporosis and fracture risk, many RA patients receive anti-osteoporosis therapies including oral or intravenous bisphosphonates, teriparatide, or denosumab. Although medication-induced osteonecrosis is most frequently seen in patients with malignancy, RA has been suggested to be a risk factor for osteonecrosis of the jaw (ONJ). There are numerous case reports of ONJ in RA patients but limited data suggests that RA is a risk factor for ONJ. Several retrospective studies have failed to find a difference in ONJ disease spectrum, clinical course, or outcomes between patients with RA or without RA [65–67]. In a large Japanese study with 5696 RA patients, only five confirmed cases were reported leading to a prevalence of 0.94% for all RA patients and 0.26% among females with RA ≥65 years of age [68]. Similar to the general population, risk factors for ONJ in RA include long duration of osteoporosis treatment, age, glucocorticoid use, and recent tooth extraction.

Reduction in RA disease activity with DMARDS may improve skeletal health

DMARDS have significant ability to control the inflammation associated with RA, and many studies suggest that individual drugs or combinations of DMARDS that reduce RA disease activity stabilizes or improves skeletal health (recently reviewed in [47, 69]). The skeletal effects of DMARDS include stopping the progression of periarticular erosions, altering bone remodeling to favor bone formation, and stabilizing or improving BMD (Table 3). Although many clinical trials confirm prevention of erosion progression, controversy still exists in the literature concerning the role of DMARDS in promoting full bone erosion "healing" versus erosive regression [19, 86, 87]. In either case, it is clear that biologic or nonbiologic DMARDS can retard local bone destruction if low disease activity is achieved. However, several studies have shown by power Doppler ultrasound or MRI that even patients in clinical remission (28-joint Disease Activity Score-erythrocyte sedimentation rate DAS ≤2.6) may continue to have bone marrow edema or synovitis associated with progression of erosions [88, 89]. Overall, there are a number of trials indicating that controlling RA disease activity with one or more DMARDS might have a protective effect on localized hand BMD or generalized BMD including the spine and hip (Table 3). However, additional studies are required to determine if stabilization of BMD is sufficient to reduce fracture risk in RA patients.

Glucocorticoids are unique in ability to control the symptoms of RA, reduce the rate of erosion progression, but also increase osteoporosis and fracture risk [90]. Meta-analysis reveals that daily GC as low as 2.5 mg prednisolone daily significantly increases the risk of vertebral fractures and doses of 7.5 mg leading to a RR of hip fracture of 1.77 (CI 1.55–2.02) and a RR of vertebral fracture of 5.18 (4.25–6.31) [91]. However, in the setting of early RA with high disease activity, GC treatment has been shown to stabilize BMD in multiple studies (Table 3). The BeSt study analyzed BMD in recent

Table 3 Effects of nonbiologic and biologic DMARDS on bone health in RA

DMARD	Study type	Patient number (treatment)	Study length	Outcome	Reference
MTX vs. SSZ	Retrospective	30 (MTX) 30 (SSZ)	1 year	Stabilized BMD in both groups	[70]
MTX	Retrospective	246 (MTX) 485 (no MTX)	>6 months	No difference in BMD between groups	[71]
MTX vs. MTX/ADA	Prospective	37 (MTX) 33 (MTX + ADA)	2 years	Significant hand bone loss independent of treatment	[72]
LEF vs. MTX	Prospective	20 (LEF) 20 (MTX)	2.5 years	Less hand bone loss in LEF compared to MTX	[73]
IFX	Prospective	102	1 year	No change in hip/spine BMD, decreased hand BMD	[74]
MTX, SSZ, LEF, HCQ, IFX, GC, Gold, CSA, AZA	Prospective	55 (mono), 46 (step-up), 65 (combo + GC), 52 (combo + IFX)	2 years	All groups with decreased hand BMD but less in combo + IFX and Combo + GC, hip and spine BMD were similar between all groups	[75]
TNF-I and GC	Meta-analysis of 11 RA trials	345 (TNF-I) 302 (MTX) 445 (GC + DMARDS) 347 (DMARDS) (from BeST study)	1–3 years	TNF-I and GC have less hand BMD loss, TNF-I no effect on spine or hip BMD, GC no effect on hip BMD, GC significant decrease in spine BMD	[76]
IFX ± GC	Retrospective	52	3.5 years	Hand BMD declined, increase spine BMD, hip BMD stable	[77]
IFX and MTX	Prospective	99 (TNF-I + MTX) 99 (MTX)	1 year	MTX alone had decreased spine and hip BMD, stable BMD in IFX + MTX	[78]
GC, MTX, ±TNF-I	Prospective	10 (MTX + GC) 11(ETA + GC + MTX) 10(IFX + GC + MTX)	6 months	TNF-I + GC + MTX had increased bone formation and decreased bone resorption markers, increased stable spine, and hip BMD	[79]
TOC + MTX	Prospective	103 (TOC + MTX)	11 months	Stable lumbar and hip BMD, increased bone formation marker	[80]
TOC + MTX	Prospective	78 (MTX + TOC)	1 year	Stable lumbar and hip BMD, significant increase in spine and hip if patient was osteopenic at baseline	[81]
RTX	Prospective	13 (RTX)	15 months	Decrease in bone resorption markers but no change in bone formation markers	[82]
RTX	Prospective	28 (RTX)	4 months	Decreased bone resorption markers	[83]
MTX, TNF-I, MTX + TNF-, other DMARD, MTX + other DMARD	Retrospective	8419 (from CORRONA study)	4 years	MTX + other DMARDS increased hip BMD, TNF-I decreased all fractures but no change in spine or hip fractures	[84]
TNF-I, ABA, RTX, ANA	Nested case- control	1515 (biologic DMARDS) 6023 (controls) ≥50 years of age	Median duration of biologic use >2 years4 years total	Non-vertebral fracture risk unchanged by biologic DMARDS	[85]

MTX methotrexate, *SSZ* sulfasalazine, *ADA* adalimumab, *LEF* leflunomide, *IFX* infliximab, *ETA* etanercept, *TOC* tocilizumab, *RTX* rituximab, *GC* glucocorticoid, *HCQ* hydroxychloroquine, *CSA* cyclosporin, *AZA* azathioprin, *TNF-I* TNF inhibitors, *ABA* abatacept, *ANA* anakinra

onset RA patients over 2 years with goal-directed therapy including GCs or steroid sparing DMARDS. After 2 years, BMD was similar in patients receiving GCs compared to those that did not receive GCs [92]. Another similar trial followed early RA patients on methotrexate-based treatment and randomized them to receive either 10 mg of prednisone daily or placebo in presence of bisphosphonates and calcium and vitamin D and found an increase in BMD in both treatment groups over the 2-year study, with no difference in BMD among the prednisone versus placebo-treated groups [93]. Taken together, these studies indicate that RA disease control is likely a significant factor for preserving bone mass and that GCs in early RA may be beneficial in achieving this goal. Unfortunately, fracture has not been an end point for these studies, so our understanding if the BMD stabilization or improvement translates into fracture reduction is limited. Additionally, GC-induced fractures occur at higher BMD than seen in postmenopausal osteoporosis [34]; thus, given the high risk of fracture in RA patients, efforts should be made to reduce the daily doses of GC as quickly as possible and preventive measures including calcium and vitamin D supplementation and medications, including bisphosphonates, teriparatide, or denosumab, should be used when appropriate according to recent American College of Rheumatology guidelines on the prevention and treatment of GC-induced osteoporosis [94].

Treatment of RA-associated osteoporosis

Because of the increased risk of fractures, RA patients should have routine assessment for osteoporosis at the time of diagnosis and periodically to review disease activity, review other medications that may increase the risk of bone loss [95], and monitor other conditions that promote osteoporosis including increasing age, menopausal status, and functional status. Similar to osteoporosis assessment in the general population, fracture risk may be assessed with a BMD measurement obtained via dual-energy X-ray absorptiometry (DXA), quantitative computerized tomography (QCT) or ultrasound, or with the FRAX instrument with or without a BMD. Vitamin D stores should be evaluated and replaced and calcium supplementation given. Unfortunately, physician compliance with current guidelines remains low with less than 50% of RA patients taking GC being prescribed therapy to prevent or treat osteoporosis [96].

Multiple studies have shown a BMD protective effect of bisphosphonates in RA patients even when receiving GC [97–99]. A recent study compared the spine BMD of 192 RA patients with age and sex-matched volunteers to determine whether bisphosphonate use was still needed to improve BMD if the patients had tight control of RA disease activity [100]. Compared to controls, RA patients had lower BMD at all sites at the time of enrollment. At 3 years, well-controlled RA patients receiving bisphosphonates had significantly higher percent change in spine BMD than well-controlled RA patients not receiving bisphosphonates (6.2 vs. 1.8%, $p = 0.0001$). Bisphosphonate use significantly increased spine BMD with an OR of 2.13 (CI 1.03–4.38); however, use of biologic agents, reducing GC dose, and tight disease control did not significantly increase BMD at 3 years. These data indicate that even with our improving ability to get low RA disease activity, RA patients are still at risk for low BMD and fracture. Risk factors for treatment failure of osteoporosis in RA include noncompliance with bisphosphonates, daily GC dose ≥7.5 mg/day before the first BMD measurement, immobilization >3 months, and high disease activity score [101].

Other osteoporosis treatments appear to be effective in the treatment of osteoporosis in RA. The discovery of RANKL as a key factor driving the formation and function of osteoclasts has led to the therapeutic targeting of this pathway with anti-RANKL antibody, denosumab. RANKL is upregulated by a variety of stimuli that contribute to excessive bone remodeling including several RA-associated cytokines including IL-1, IL-6, Il-17, and TNFα [102]; thus, therapeutic targeting of RANKL should inhibit osteoclastogenesis and prevent RA bone erosions and osteoporosis. Denosumab significantly improves BMD in RA patients especially if coupled with vitamin D and calcium supplementation [103, 104]. A small study of 49 patients treated with bisphosphonates and 49 treated with denosumab found no significant difference in BMD at 1 year, indicating that one drug is not more effective than the other at 1 year [105]. Several studies have shown that the addition of denosumab to methotrexate or biologics improves bone erosions and BMD (reviewed in [47]). When added to methotrexate, denosumab, but not alendronate, induced partial repair of bone erosions at 1 year when evaluated with high-resolution peripheral quantitative computed tomography [106]. There has been concern about increasing infections in patients receiving immunosuppression with DMARDS or biologics concomitantly with denosumab. However, a recent study analyzed the risk of hospitalization for serious infection in RA patients concurrently treated with biologics and denosumab and found that serious infection risk was not increased in those patients receiving biologics with denosumab compared to zoledronate [107]. These studies support the use of RANKL inhibition to prevent and treat generalized bone loss in RA.

Anabolic agent, teriparatide has also been found to be effective in RA-associated postmenopausal osteoporosis [108]. A recent randomized control trial evaluated the effect of teriparatide on joint erosions in RA [109]. Despite improvement in BMD at the femur and spine, established patients controlled on TNF-inhibitors failed to have a significant reduction in erosion volume in the hands and wrists with the addition of teriparatide for 1 year. These data support the hypothesis that the erosion bone matrix or

microenvironment is no longer conducive to anabolic bone remodeling. However, this was a small study and treatment was limited to 1 year instead of the typical 2-year teriparatide course. Additional studies are needed to fully determine the benefits of teriparatide treatment in RA.

Guidelines for the prevention and treatment of glucocorticoid-induced osteoporosis

The new American College of Rheumatology guidelines for the prevention and treatment of GC-induced osteoporosis encourage early assessment of fracture risk including a clinical assessment of dose, duration, and pattern of GC use, evaluation of falls, frailty, fractures, malnutrition, significant weight loss, low body weight, family history of hip fracture, secondary causes of osteoporosis, ≥3 alcohol drinks per day, height, weight, muscle strength testing, and clinical findings of prior silent vertebral fractures [94]. Patients ≥40 should also have FRAX analysis with or without BMD testing; whereas patients <40 years of age, BMD testing is recommended only if the patient has multiple risk factors or prior osteoporotic fracture. Importantly, FRAX risk should be increased by 20% for GC-dosages ≥7.5 mg, as it may underestimate fracture risk at higher GC doses [110]. Additionally, the guidelines recommend calcium (800–1000 mg/day) and vitamin D (600–800 IU/day) supplementation as well as lifestyle modifications for all patients. The new guidelines, developed using GRADE methodology, focused on making recommendations based on the balance of relative benefits and harms of treatment, quality of the evidence, and patient preferences.

In the new guidelines, patients can be categorized as low risk, moderate risk, or high fracture risk based on the clinical fracture risk assessment. Low-risk patients include younger patients <40 with no history of osteoporotic fracture and no additional risk factors receiving <7.5 mg/day of GC. Additional low-risk patients include those ≥40 years of age with a GC-adjusted FRAX risk for major osteoporotic fracture of <10% or hip fracture risk <1%. For these low-risk patients, there is a *conditional* recommendation for oral bisphosphonates, teriparatide, or denosumab. Moderate-risk patients include patients ≥40 years of age with a GC-adjusted FRAX risk of major fracture 10–19% and hip fracture >1% but <3%, as well as younger patients <40 years of age with a Z-score <−3 or rapid bone loss in a year and predicted to take GC ≥7.5 mg for ≥6 months. Treatment with oral bisphosphates is *conditionally* recommended over alternative medications, including intravenous bisphosphonates, teriparatide, denosumab, or raloxifene, based on safety, cost, and lack of superior anti-fracture benefits from these other medications. High-risk patients include any patient with a prior osteoporotic fracture independent of age and those ≥40 years of age who have GC-adjusted FRAX for major osteoporotic fracture of ≥20% or hip fracture risk ≥3% or a BMD T-score ≤−2.5. For high-risk patients, there is a *strong* recommendation for treatment with the preferred oral bisphosphonates followed by alternative agents listed above. Repeated BMD testing is recommended every 2–3 years for moderate and high-risk patients remaining on GC. Based on the high risk of fracture in RA that is exacerbated by use of GC, many RA patients are moderate to high risk and treatment with oral bisphosphonates, calcium, vitamin D, and lifestyle modifications are recommended.

Conclusions

In summary, RA-associated systemic and local inflammation leads to generalized bone loss, fractures, juxta-articular bone erosions, joint fusion, and secondary osteoarthritis. Patients with ACPA are likely to have early generalized bone loss and bone erosions at the time of diagnosis. In many but not all instances, tight control of RA disease activity with conventional, biologic, or synthetic DMARDS can prevent or stabilize bone erosions, joint ankylosis, and secondary osteoarthritis but may have limited ability to significantly improve generalized bone loss. Recognition of high fracture risk and osteoporosis in RA should prompt clinicians to evaluate fracture risk by BMD or FRAX analysis. While GC in high disease states may be beneficial to local and generalized bone loss in RA, the prolonged use of GC especially at doses higher than 7.5 mg daily increases fracture risk. For patients taking GC, early evaluation of fracture risk with BMD or FRAX assessment is recommended within 6 months. In the RA population, GC-associated osteoporosis may be managed by bisphosphonates, denosumab, or teriparatide at the discretion of the physician.

Compliance with ethical standards

Conflict of interest None.

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