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Review Article

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Bone Mineral Density Changes and Metabolic Risk Factors in Patients with Rheumatoid Arthritis on Long-Term Therapy: A Narrative Review

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Abstract | Rheumatoid Arthritis (RA) is a chronic systemic inflammatory disease associated with progressive joint damage and important extra-articular complications, including osteoporosis, reduced Bone Mineral Density (BMD), fragility fractures, metabolic syndrome, insulin resistance, dyslipidemia, sarcopenia and cardiovascular disease. Chronic inflammation, reduced physical activity, altered body composition, nutritional deficiencies and long-term pharmacological therapy contribute to these complications. Glucocorticoids are particularly important because prolonged exposure may reduce bone formation and adversely affect glucose and lipid metabolism, although suppression of inflammation may partially counterbalance their skeletal effects. Disease-Modifying Antirheumatic Drugs (DMARDs), particularly biologic and targeted synthetic therapies, generally improve inflammatory control and may help preserve BMD but recent evidence suggests that bone loss can persist despite effective disease control. Metabolic syndrome is also common in RA and contributes substantially to cardiovascular risk. The relationship between RA and lipid abnormalities is complex because active inflammation may suppress circulating lipid concentrations despite increased cardiovascular risk. This narrative review summarizes current evidence regarding BMD changes, osteoporosis, glucocorticoid exposure, DMARD therapy, vitamin D status, metabolic abnormalities, sarcopenia and cardiovascular risk in patients receiving long-term treatment for RA. An integrated approach combining disease control, fracture-risk assessment, BMD monitoring, glucocorticoid minimization, metabolic screening, lifestyle modification and cardiovascular risk management is essential for comprehensive long-term care.

Key Words Rheumatoid Arthritis, Bone Mineral Density, Osteoporosis, Glucocorticoids, DMARDs, Metabolic Syndrome, Vitamin D, Sarcopenia, Cardiovascular Risk

INTRODUCTION

Rheumatoid Arthritis (RA) is a systemic autoimmune disease characterized by persistent synovial inflammation, progressive joint destruction, functional disability and extra-articular manifestations. Advances in treat-to-target strategies and disease-modifying antirheumatic drugs (DMARDs) have significantly improved disease outcomes; however, patients remain at increased risk of osteoporosis, fractures, metabolic abnormalities and cardiovascular disease [1,2].

Bone loss in RA is multifactorial. Chronic inflammation stimulates osteoclast activity, while pain, joint stiffness, disability and reduced physical activity decrease mechanical loading of bone. Age, menopause,

low body mass index, smoking, nutritional deficiencies, vitamin D insufficiency and glucocorticoid exposure further increase skeletal risk [3,4].

A systematic review and meta-analysis estimated the prevalence of osteoporosis among patients with RA at approximately 28%, although prevalence varies according to age, sex, disease duration, treatment and diagnostic criteria [5]. Fracture risk is also increased, with meta-analyses demonstrating approximately a twofold increase in overall fracture risk compared with individuals without RA [6,7].

Long-term therapy adds complexity. Glucocorticoids can suppress inflammation but may reduce osteoblast activity, increase bone resorption, impair calcium metabolism and contribute to muscle weakness. Recent individual-participant-data evidence indicates that even low-dose glucocorticoid therapy may be associated with lumbar-spine BMD loss over two years [8]. In contrast, effective DMARD therapy may reduce inflammation-associated bone loss, although recent evidence suggests that BMD decline can persist despite modern biologic and targeted synthetic DMARD treatment [9,10].

RA is also associated with metabolic syndrome, insulin resistance, dyslipidemia, obesity, sarcopenia and increased cardiovascular risk [11-14]. These abnormalities may share common mechanisms with skeletal disease, including systemic inflammation, inactivity, altered body composition and medication exposure.

This review summarizes the current evidence concerning skeletal and metabolic complications of RA during long-term therapy and discusses implications for integrated clinical management.

REVIEW APPROACH

A narrative literature review was undertaken using PubMed/MEDLINE, Scopus, Web of Science and Google Scholar. Search terms included rheumatoid arthritis, bone mineral density, osteoporosis, fracture, glucocorticoids, DMARDs, biologic therapy, JAK inhibitors, vitamin D, metabolic syndrome, insulin resistance, dyslipidemia, sarcopenia and cardiovascular risk. Priority was given to systematic reviews, meta-analyses, randomized controlled trials, prospective cohort studies, clinical guidelines and recent studies published between 2020 and 2026.

Bone Mineral Density and Osteoporosis in Rheumatoid Arthritis

Reduced BMD is one of the most important skeletal complications of RA. Bone loss may occur systemically and periarticularly, particularly near chronically inflamed joints. The prevalence of osteoporosis is substantially higher in RA than in the general population [5].

The mechanisms are complex. Inflammatory cytokines, particularly tumor necrosis factor-alpha (TNF-α), interleukin-1 and interleukin-6, stimulate osteoclast differentiation and bone resorption through pathways involving receptor activator of nuclear factor kappa-B ligand (RANKL) [15]. Persistent disease activity therefore promotes skeletal deterioration independently of conventional osteoporosis risk factors.

Physical inactivity provides an additional mechanism. Pain, fatigue, joint deformity and functional impairment reduce weight-bearing exercise and muscle loading, thereby decreasing osteogenic stimulation. Reduced muscle strength may also increase falls and fracture risk.

Importantly, BMD does not fully explain fracture risk in RA. Falls, muscle weakness, glucocorticoid exposure, inflammation and altered bone quality may contribute to fractures even when BMD is not severely reduced [6,7]. Therefore, clinical fracture assessment should complement DXA-based BMD measurement.

Inflammation and Bone Remodeling

The interaction between inflammation and bone remodeling is central to RA-associated osteoporosis. Pro-inflammatory cytokines increase RANKL expression and stimulate osteoclast differentiation, producing increased bone resorption [15].

Longitudinal studies support an association between sustained disease activity and progressive BMD loss. Patients achieving remission or sustained low disease activity generally demonstrate more favorable skeletal outcomes than those with persistent inflammation [16,17].

Effective inflammatory control is therefore an important component of bone preservation. Nevertheless, suppression of inflammation does not completely eliminate osteoporosis risk. Age-related bone loss, menopause, glucocorticoid exposure, low physical activity and established osteoporosis may continue to drive skeletal deterioration after inflammatory control has been achieved [9].

Glucocorticoids and Skeletal Health

Glucocorticoids remain useful for controlling acute or severe inflammatory disease but represent an important modifiable risk factor for osteoporosis.

Their adverse skeletal effects include suppression of osteoblast differentiation, increased osteoblast and osteocyte apoptosis, impaired calcium absorption, increased renal calcium loss and reduced sex-hormone activity [8,18].

Evidence concerning low-dose therapy has historically been inconsistent. Earlier randomized trials suggested that low-dose glucocorticoids did not necessarily produce major short-term BMD reductions in early RA, possibly because their anti-inflammatory effects offset some direct skeletal toxicity [18].

More recent evidence provides a clearer signal. An individual-participant-data meta-analysis published in 2026 demonstrated greater lumbar-spine BMD loss after two years of low-dose glucocorticoid therapy, although a significant femoral BMD difference was not observed [8].

These findings support current recommendations for early fracture-risk assessment in patients expected to receive glucocorticoids for more than three months [19].

The clinical objective should therefore be to use the lowest effective glucocorticoid dose for the shortest feasible duration while ensuring adequate osteoporosis prevention in patients at elevated fracture risk.

DMARD Therapy and Bone Mineral Density

Conventional synthetic DMARDs: Methotrexate, leflunomide, sulfasalazine and hydroxychloroquine form the foundation of conventional RA therapy. Their major skeletal benefit is likely indirect, resulting from suppression of systemic inflammation and improvement in physical function.

A recent systematic review found generally favorable or neutral effects of conventional DMARDs on BMD, although evidence remains heterogeneous [10].

Biologic DMARDs

Biologic therapies provide substantial suppression of inflammatory pathways implicated in bone resorption. TNF inhibitors are particularly relevant because TNF-α contributes directly to osteoclast activation.

Studies have reported stabilization or improvement of BMD following anti-TNF treatment, suggesting that effective cytokine inhibition may attenuate inflammation-associated bone loss [20,21].

However, skeletal protection is not universal. Long-term observational evidence indicates that BMD may continue to decline despite biologic treatment and improved disease activity [9]. This may reflect persistent non-inflammatory osteoporosis risk factors, age-related bone loss, glucocorticoid exposure or insufficient treatment duration.

Targeted synthetic DMARDs

JAK inhibitors and other targeted therapies provide potent suppression of inflammatory signaling. Emerging evidence suggests potentially favorable skeletal effects, although long-term comparative evidence remains limited.

A 2026 systematic review of antirheumatic therapies concluded that biologic and targeted synthetic DMARDs may have favorable effects on BMD but evidence is insufficient to establish clear superiority of specific agents [10].

Vitamin D and Skeletal Health

Vitamin D deficiency or insufficiency is frequently reported among patients with RA and may contribute to impaired bone health.

A meta-analysis demonstrated lower vitamin D levels among patients with RA and suggested an inverse relationship between vitamin D concentration and disease activity [22]. Limited sunlight exposure, reduced outdoor activity, aging, obesity and nutritional factors may contribute to deficiency.

Evidence regarding supplementation remains mixed. Recent meta-analysis suggests that vitamin D supplementation may improve some inflammatory and clinical measures in RA, although significant heterogeneity exists between studies [23].

Vitamin D assessment and correction of deficiency are therefore reasonable components of comprehensive skeletal management. However, supplementation should not replace established osteoporosis therapy in patients at high fracture risk.

Metabolic Risk Factors in Rheumatoid Arthritis

RA is increasingly recognized as a condition associated with substantial metabolic dysfunction. Chronic inflammation, inactivity, altered adipokine signaling, glucocorticoid exposure, obesity and changes in body composition contribute to insulin resistance, dyslipidemia, hypertension, metabolic syndrome and sarcopenia [11,12].

A systematic review and meta-analysis estimated the prevalence of metabolic syndrome in RA at approximately 30%, demonstrating that cardiometabolic abnormalities are common rather than exceptional [13].

The coexistence of metabolic and skeletal abnormalities is clinically important. Reduced physical activity may simultaneously worsen insulin sensitivity and decrease mechanical loading of bone. Similarly, sarcopenia may increase falls and fracture risk while contributing to insulin resistance.

Insulin Resistance and Diabetes

Systemic inflammation may impair insulin signaling through cytokine-mediated effects on glucose metabolism. TNF-α and interleukin-6 can interfere with insulin pathways, while physical inactivity and visceral adiposity further increase insulin resistance [11].

Glucocorticoids may compound this problem by increasing hepatic glucose production and reducing peripheral glucose uptake.

Patients receiving prolonged glucocorticoid therapy should therefore undergo appropriate monitoring for hyperglycemia, particularly when obesity, family history or pre-existing metabolic risk factors are present.

Dyslipidemia and the Lipid Paradox

Dyslipidemia in RA is complex because active inflammation may produce unexpectedly low concentrations of circulating lipids despite increased cardiovascular risk.

This phenomenon, known as the lipid paradox, reflects inflammatory alterations in lipid metabolism and lipoprotein function [24]. HDL cholesterol may also lose some of its normal anti-inflammatory and atheroprotective properties during active inflammation.

Successful anti-inflammatory treatment can increase measured lipid concentrations while reducing cardiovascular risk. Consequently, lipid values should be

interpreted in conjunction with inflammatory activity and overall cardiovascular risk rather than considered in isolation.

Obesity, Sarcopenia and Body Composition

Body composition abnormalities are increasingly recognized in RA. Some patients develop increased fat mass while losing skeletal muscle, producing a phenotype that may resemble sarcopenic obesity [11].

Pain, fatigue, chronic inflammation, physical inactivity, aging, inadequate nutrition and glucocorticoid exposure can all contribute to muscle loss.

Sarcopenia is particularly important because reduced muscle strength increases falls, disability and fracture risk. Loss of muscle also reduces physical activity and mechanical stimulation of bone, creating a reinforcing cycle of skeletal and functional decline.

Cardiovascular Risk

Cardiovascular disease is a major contributor to excess morbidity and mortality in RA. A meta-analysis of observational studies demonstrated approximately a 48% increased risk of incident cardiovascular events among patients with RA [25].

This increased risk is partly explained by conventional factors such as hypertension, diabetes, smoking, obesity and dyslipidemia. However, systemic inflammation independently contributes to endothelial dysfunction, oxidative stress, vascular inflammation and accelerated atherosclerosis [12,24].

Effective inflammatory control may therefore have cardiovascular benefits beyond joint protection. Current EULAR recommendations emphasize routine cardiovascular risk assessment and management of modifiable risk factors in patients with rheumatic diseases [14].

Relationship Between Bone and Metabolic Risk

Skeletal and metabolic complications of RA should be considered interconnected rather than independent conditions.

A useful conceptual model is:

- Chronic inflammation → osteoclast activation → BMD loss
- Chronic inflammation → insulin resistance → metabolic dysfunction → cardiovascular risk
- Pain and inactivity → muscle loss → falls → fracture risk

Glucocorticoid therapy may amplify both pathways by contributing to bone loss, hyperglycemia, weight gain and muscle weakness [8,18].

This interaction emphasizes the importance of an integrated approach to long-term RA management.

Clinical Assessment and Management

Long-term management should combine effective RA control with proactive assessment of skeletal and metabolic risk.

DXA remains the principal method for evaluating BMD. However, BMD should be interpreted alongside fracture history, age, glucocorticoid exposure, menopausal status, BMI, smoking, falls and other risk factors [6,19].

Patients receiving prolonged glucocorticoids require individualized fracture-risk assessment. The American College of Rheumatology recommends fracture-risk evaluation in adults receiving glucocorticoids for more than three months at doses of ≥2.5 mg/day [19].

Metabolic assessment should include blood pressure, BMI and waist circumference, fasting glucose or HbA1c, lipid profile, smoking status, physical activity and cardiovascular risk assessment.

Lifestyle interventions should include weight-bearing and resistance exercise, smoking cessation, appropriate nutritional intake, adequate calcium and vitamin D, weight management and fall prevention.

Research Gaps

Several important questions remain unresolved. The long-term comparative skeletal effects of individual biologic and targeted synthetic DMARDs require further investigation. It is also unclear whether improved inflammatory control consistently translates into lower fracture risk independent of BMD.

Future studies should examine the combined effects of inflammation, glucocorticoid exposure, metabolic syndrome, vitamin D status, sarcopenia and body composition on BMD trajectories and fracture outcomes.

Longitudinal studies incorporating DXA, trabecular bone score, bone turnover markers, muscle mass, muscle strength, metabolic biomarkers and cardiovascular outcomes may provide a more comprehensive understanding of long-term RA complications.

CONCLUSIONS

RA is associated with an increased burden of osteoporosis, fracture, metabolic syndrome, insulin resistance, sarcopenia and cardiovascular disease. Chronic inflammation, reduced physical activity, altered body composition, vitamin D insufficiency and long-term glucocorticoid exposure contribute to these complications.

Modern DMARDs improve inflammatory control and may help preserve BMD but skeletal deterioration can persist despite successful treatment of joint inflammation. Glucocorticoids require particular attention because prolonged exposure may adversely affect both bone and metabolic health.

The management of RA should therefore extend beyond control of synovitis. A comprehensive strategy should incorporate disease activity control, fracture-risk assessment, BMD monitoring, glucocorticoid minimization, vitamin D and nutritional optimization, metabolic screening, exercise, fall prevention and cardiovascular risk management.

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