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REVIEW

Osteoporosis and Rheumatoid Arthritis: A Review of Current Understanding and Practice

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Abstract

This review presents a current perspective on the association between rheumatoid arthritis (RA) and osteoporosis. Many factors contribute to the increased risk of osteoporosis and fracture in RA patients. These factors include advanced age, duration of disease, long-term glucocorticoid use, and poor inflammation control inflammation in RA. This review discusses current guidelines and their limitations in assessing bone health in RA-related osteoporosis. Available anti-osteoporotic treatments, their mechanisms of action, and their potential benefits in managing the interaction between RA and osteoporosis are discussed. We also consider potential advancements, including areas of future development in RA and osteoporosis diagnosis and management.

Key words: osteoporotic fracture; glucocorticoid-induced osteoporosis; rheumatoid arthritis fracture; rheumatoid arthritis mortality; disease control

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Introduction

Rheumatoid arthritis (RA) is an autoimmune condition causing inflammation of the joints, usually in a symmetrical pattern and typically affecting the hands and feet most severely, with multiple extra-articular manifestations. It affects around 1% of the world's population (Safiri et al, 2019). RA is a heterogeneous condition with approximately 70% of those diagnosed having detectable autoantibodies, which are typically associated with more severe and erosive disease (van Delft and Huizinga, 2020). The pathogenesis is complex and has a substantial genetic component; there is a loss of self-tolerance with the development of autoantibodies in susceptible individuals. Not all individuals will develop RA: as the immune system remodels to a pro-inflammatory state in susceptible individuals, synovitis will develop and in chronic stages there will be severe damage to cartilage and bone (Andreev et al, 2022).

In healthy individuals, the skeleton is constantly remodelled to treat microdamage from daily activity: osteoclasts resorb bone in a delicate balance with osteoblasts laying down the new osteoid matrix, which then becomes mineralised (Ashai and Harvey, 2020). This mineralisation gives bone mineral density (BMD). Osteoporosis is a chronic disease characterised by loss of bone mineral density with

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changes to the microarchitecture, thereby increasing the risk of fractures (Kirkham-Wilson and Dennison, 2021). Bone density is assessed via dual-energy X-ray absorptiometry (DXA) scanning (World Health Organisation, 1994). A diagnosis of osteoporosis is made when BMD is more than 2.5 standard deviations below that of a healthy, young, adult mean (World Health Organisation, 1994). This method does not adequately capture the risk of fracture in all populations, especially those at increased risk, and so the Fracture Risk Assessment Tool (FRAX) score is typically used to calculate a 5- and 10-year fracture risk. This risk is then compared to the treatment threshold and anti-osteoporotic agents are started as appropriate (Ashai and Harvey, 2020).

The association between RA and bone health has been long appreciated, with several studies performed over the years being combined in a systematic review and meta-analysis reporting an estimated point prevalence of osteoporosis among RA patients of 27.6% (95% CI 23.9–31.3%) (Moshayedi et al, 2022). However, recent advances in managing RA have led researchers to consider whether relationships have been affected by advances in therapeutic options for RA patients (Zerbini et al, 2017). The importance of considering bone health in RA was highlighted in a recent population-based longitudinal cohort study using the UK Biobank data that investigated long-term conditions in people with RA and the impacts these had on all-cause mortality and major adverse cardiovascular events (MACE). This study indicated that participants with both RA and osteoporosis had more than double hazard ratio for all-cause mortality compared to matched controls and more than triple the hazard ratio for MACE (McQueenie et al, 2020). The significantly increased risk of mortality, as well as the risk of fractures themselves, make this an important topic.

Rheumatoid Arthritis, Osteoporosis and Fracture

In this section we discuss the relationships between RA and bone health. The delicate balance of osteoblast and osteoclast activity, which is needed in health for bone remodelling in response to daily wear and tear, becomes dysregulated in rheumatoid arthritis and osteoporosis (Ashai and Harvey, 2020) (Fig. 1). The link between these two conditions remains unclear but the association is demonstrated in multiple studies (presented in a recent meta-analysis) which show people with rheumatoid arthritis have a risk ratio of around 2 for the development of osteoporosis compared to the general population (Moshayedi et al, 2022). This increased risk is present in both sexes and is most evident in hip and vertebral fractures—both of which can have devastating consequences for mortality and quality of life. The causes of this excess risk are multifactorial (Xue et al, 2017).

Epidemiological studies have suggested that 30–50% of people with RA have osteoporosis as a comorbidity, dependent on age and sex as described in a recent review (Ashai and Harvey, 2020). A bi-directional Mendelian randomisation study undertaken in 2021 shows no causal genetic relationship between osteoporosis and RA, or vice versa, and instead highlights the secondary effects of RA, for example

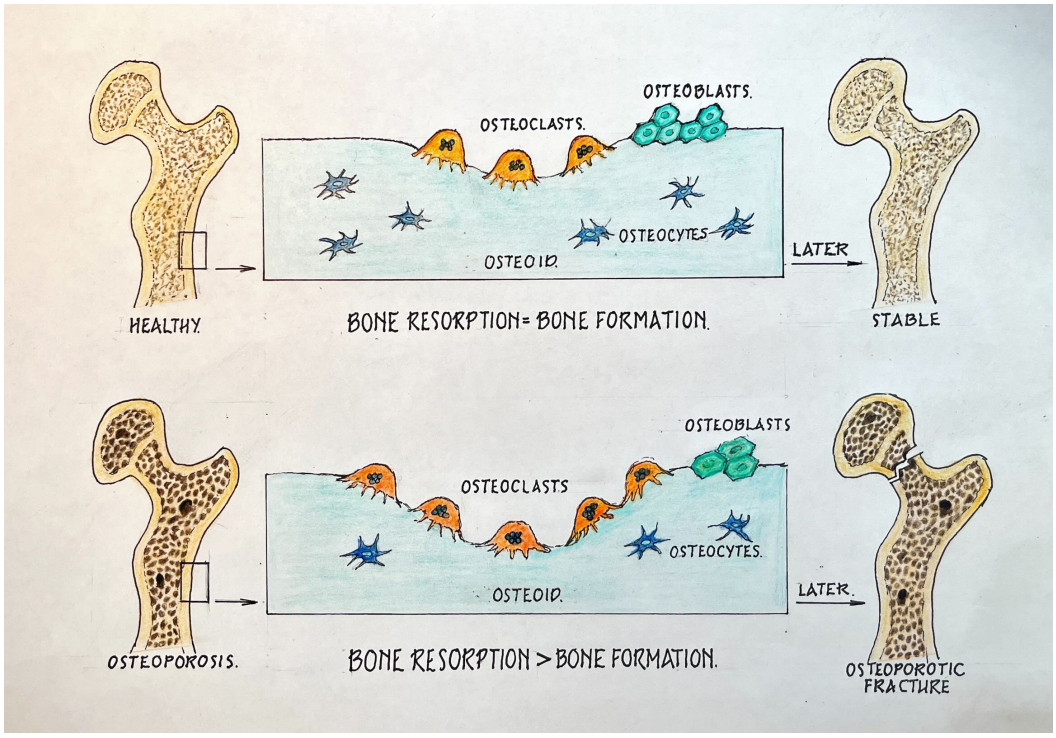

Fig. 1. The balance of osteoclast and osteoblast bone maintenance is lost in osteoporosis.

pain limiting activity levels resulting in weakening of bones, as the likely cause of association (Liu et al, 2021).

RA can present at any age but is most diagnosed during the 50s and 60s; fragility fractures also increase with aging and this pattern is demonstrated in RA, although the rates of fracture in RA are higher than in an age-matched population (Ashai and Harvey, 2020). A case-control study from Spain found rates of major osteoporotic fracture in post-menopausal women with RA (with a median age of 64 years) to be 3.55/100 compared to matched controls with a rate of 0.72/100. More than 60% of these fractures occurred in the spine. Those with a previous fragility fracture have the highest risk of further fracture (Gómez-Vaquero et al, 2023). Despite increasing age being a risk factor for osteoporosis and fracture there is still increased risk in younger people with RA. A retrospective observational cohort study from the UK found that the incidence rate of first and subsequent fractures is higher in those with RA than aged-matched controls at any adult age. The increased incidence rate was significantly higher in women below age 50; the rate was also higher in men below 50 with a diagnosis of RA but not significantly (Erwin et al, 2021). Although the age of the person is crucial to understand the increased risk of osteoporosis, the time since diagnosis also appears to influence the risk of osteoporosis and potential fracture. An early population-based cohort study from the UK indicates that a diagnosis of RA for more than ten years confers a 3-fold risk of fragility fracture at the hip compared to matched controls (van Staa et al, 2006).

Controlling the inflammation of rheumatoid arthritis is protective against the development of osteoporosis and fragility fracture and is the basis for the current 'treat to target' strategy (Ashai and Harvey, 2020). RA leads to local inflammation

of the synovium with the production of multiple pro-inflammatory cytokines, such as interleukin-1, interleukin-6 and tumour necrosis factor, which results in damage to the cartilage and bone local to the joint but also more systemic loss of bone mass. These pro-inflammatory cytokines activate osteoclasts causing bone resorption, and bone loss is then potentiated by immobility due to pain from inflammation. The cytokine production is interrupted by suppressing the disease, and there is a beneficial reduction in pain and the associated ability to undertake more weight-bearing exercise (Fardellone et al, 2020).

The impact of glucocorticoid use in RA on bone health is controversial. There appears to be a strong link between steroid use, especially for a prolonged period, and loss of BMD in people with RA (Fardellone et al, 2020). Despite this, not all studies can demonstrate this effect and in one study a protective effect was demonstrated, likely due to better control of systemic inflammation (Ghazi et al, 2012). A cumulative dose of glucocorticoid may be the risk (Gómez-Vaquero et al, 2023), with shorter courses less damaging based on BMD loss being a continuous process meaning there is no safe low dose for prolonged use (Ashai and Harvey, 2020).

The risk of fracture in RA is potentiated by increased falls in the context of reduced BMD; this is despite the advances in the treatment of RA with the ability to suppress inflammation through a combination of corticosteroids, disease-modifying antirheumatic drugs (DMARDs) and biologic agents. People with RA may have impaired ability to heel-toe walk and an inability to stand without using their arms—both markers of weakness which contribute towards unsteadiness when mobilising. This increased fall risk, in the context of already reduced BMD as associated with RA contributes towards the increased fracture rate seen in BMD despite excellent treatment options to control inflammation (Clynes et al, 2019).

Assessment of Bone Health in Rheumatoid Arthritis

In this section, we discuss the assessment of bone health in RA. There are no specific guidelines for the screening of bone health in RA, within the UK, which is likely to contribute to the underdiagnosis of osteoporosis until the primary incidence of fragility fracture is identified. A 2022 publication from the USA attempted to address this by combining recommendations from multiple sources: they concluded that patients with a pre-disposition to fracture (such as RA) and those on glucocorticoid therapy should be screened for osteoporosis once post-menopausal or over the age of 50 in men. Screening should be undertaken in those ages 40 and 50 who are taking 2.5 mg prednisolone (or an equivalent dose of an alternative glucocorticoid) daily for over three months. BMD testing should be undertaken in those under the age of 40 who have a very significant risk of fractures such as sustained use of high-dose glucocorticoids or previous fracture (Wysham et al, 2022). Although not specific to RA this guidance, when applied to those with RA, clearly indicates who and when to screen based on many of the risk factors outlined above.

The fracture prediction algorithm FRAX uses several established clinical risk factors for fracture to provide 10-year risks of major osteoporotic fracture (MOF) or

Table 1. Current treatments available to people with concomitant osteoporosis and rheumatoid arthritis.

Class of agent	Drugs available	Grade of evidence
Bisphosphonates	Oral therapies, e.g., alendronate, risedronate	Strong (several RCTs)
Bisphosphonates	Intravenous therapies, e.g., zoledronate	Good (some RCTs)
RANKL inhibitors	Densoumab	Strong (several RCTs)
Sclerostin inhibitors	Romosozumab	Emerging (few studies)

RANKL, receptor activator of nuclear factor kappa-B ligand; RCTs, randomized controlled trials.

hip fracture (University of Sheffield, 2008). While these include a diagnosis of RA as a binary yes/no variable, FRAX does not consider any RA-specific characteristics such as disease duration, level of inflammation and autoantibody positivity, all of which may be needed to gain a more accurate estimate of fracture risk (Wysham et al, 2021).

In the UK, the National Osteoporosis Guideline Group (NOGG) produced a clinical guideline 2021 for preventing and treating osteoporosis, recognizing people with RA as a specific risk population (National Osteoporosis Guideline Group and UK, 2021). It highlights that RA is a risk factor recognized in the FRAX tool which can prompt DXA scanning when appropriate. NOGG also highlights that RA is a risk factor for fracture beyond that associated with glucocorticoid use so it should be viewed as an additional risk on top of that potentially caused by medication (Gregson et al, 2022). Therefore, a specific guideline for fracture prevention in people with RA would be beneficial in improving the identification and management of osteoporosis in this population.

Treatment of Osteoporosis in Rheumatoid Arthritis

In this section, we discuss the treatment of osteoporosis in RA. The treatment approach for osteoporosis in the context of rheumatoid arthritis is multi-faceted. Beyond lifestyle advice regarding a healthy diet, ensuring adequate calcium and vitamin D levels, and taking regular exercise (often limited due to the pain associated with RA) there are a variety of targeted drug treatments (Table 1). Achieving disease control of the RA inflammation appears to protect against loss of bone mineral density which may be protective against osteoporosis and the associated morbidity of fracture (Ashai and Harvey, 2020). Management should be the same where fractures occur as any other patient with a fragility fracture.

The use of bisphosphonates in people with RA who develop osteoporosis is recommended, as they have been found them to be protective against bone loss, especially over a short period (Huang et al, 2022). However, in glucocorticoid-induced osteoporosis (GI-OP), additional treatment for osteoporosis may be needed to prevent fracture (Takahata et al, 2022).

For those who have significant loss of bone mineral density in the context of co-morbid RA, escalated treatment may be required. One approach is denosumab,

a receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitor that suppresses bone resorption and inhibits osteoclast maturation; denosumab increases BMD and reduces vertebral fractures (Cummings et al, 2009). Denosumab also effectively increases BMD and prevents fractures in those with GI-OP, unlike bisphosphonates (Yamaguchi et al, 2020). A recent meta-analysis looked to determine if denosumab could be used as a treatment for RA due to its inhibition of joint erosion—it was found to strengthen bones in people with RA but not improve disease activity. The effect of denosumab was influenced by age with older patients, and those who have had RA for longer, benefiting more than those in middle age with a shorter time since diagnosis (Yagita et al, 2021).

A recently approved anti-osteoporosis drug, romosozumab, offers an alternative to denosumab and is under investigation for use in people with RA and osteoporosis. Romosozumab has a dual action against bone loss—as an anti-sclerostin antibody it activates bone lining cells and promotes bone matrix production by osteoblasts, and it also suppresses bone resorption by modulating the expression of osteoclast medications. The benefit of romosuzumab versus denosumab is currently unclear (Mochizuki et al, 2023).

Tumour necrosis factor (TNF) inhibitors are used to treat RA and so have been explored as potential treatments against osteoporosis in those with concomitant RA. A small retrospective cohort study of patients exposed to bisphosphonates and TNF inhibitors showed no higher BMD than bisphosphonates alone (Lee et al, 2020). Similarly, the Janus kinase (JAK)-inhibitor, tofacitinib, which offers people with RA an oral biologic option, showed reduced fracture rates in people with RA and osteoporosis compared to a placebo but had higher fracture rates than the TNF-inhibitors (adalimumab or entercept) included in a post hoc analysis (Hansen et al, 2022).

Areas of Recent Advancement in Fracture Prediction

This section considers initiatives that may improve patient care. The need to improve fracture prediction in RA is clear-people with RA are at consistently higher risk of fracture than the general population and this increased risk is multifactorial with distinct risk factors additional to those of the general population. Although FRAX includes a diagnosis of RA within its calculation it is limited by the heterogeneity of RA and its treatments (Senosi et al, 2022). Considering the duration and severity of RA, and the level of inflammation will improve our prediction of fracture risk in these patients.

BMD assessment via DXA scanning is the current gold standard for the diagnosis of osteoporosis in all patients without previous fragility fractures. Despite this, most fragility fractures happen in people with a T score above the osteoporosis cut-off (Compston et al, 2019). One consideration for improving fracture prediction is the possible use of trabecular bone score (TBS), which can be calculated from lumbar spine DXA scanning. TBS provides a unitless score which indicates a level of bone strength and is based on the texture of bone: a higher score indicates

stronger (or finer) bone texture. It might be suggested that this may be helpful in RA patients. A retrospective study of 143 RA patients found that of the 52 with vertebral fractures a third had normal BMD on DXA but only 4% had normal TBS suggesting higher specificity (Buehring et al, 2020). A recent review highlighted how TBS can be used independently of BMD to predict fracture risk in rheumatic disease and was particularly useful in RA for those who had a FRAX score around the intervention threshold, especially in younger women where there would be a meaningful clinical application (Richards and Leslie, 2022).

Machine learning (a branch of artificial intelligence (AI)) offers another opportunity to improve fracture risk recognition. A longitudinal cohort study in China explored machine learning use in older adults with RA and osteoporosis: a retrospective analysis of 487 patients (aged 60 or older) was undertaken. A Random Forest Classifier model (a commonly used machine-learning algorithm) was then constructed allowing 22 variables to be included. Variables included rheumatoid factor presence in serum and previous osteoporotic fracture. Based on this, a predictive model was developed for a more individualised fracture risk calculation in this subset of patients. Further consideration can now be given to the use of AI as a predictive instrument to determine individual risk in patients with RA and osteoporosis (Chen et al, 2022).

Future Directions

Refinement of fracture prediction tools may improve our capability to predict future risk in RA patients accurately. New technologies, including AI, offer the potential to better understand the relationship between RA and fracture in the future. This increased understanding may lead to predictive modelling and the opportunity for earlier intervention for those most at risk of fracture. While the approval of the sclerostin inhibitor romosozumab may be an additional therapy in the treatment of low bone density in RA patients, ultimately TNF-inhibitors and JAK-inhibitors may represent the future of treatment for RA and osteoporosis to find one treatment capable of controlling both conditions and re-establishing the healthy bone cycle.

Conclusion

The relationship between RA and osteoporosis is complex and the reasons for this association are multifactorial, including age, duration of disease and uncontrolled inflammation. Thirty to fifty percent of those diagnosed with RA have osteoporosis and this represents a major part of the co-morbidity experienced in RA. The fracture risk associated with RA and concurrent osteoporosis can have devastating consequences for quality of life, as well as mortality. People with both RA and osteoporosis have twice the rates of all-cause mortality and three times the risk of MACE. Improving control of RA is beneficial for bone density directly, but it is also beneficial through increased physical activity.

Beyond controlling the systemic inflammation of RA bisphosphonates are the first line treatment in osteoporosis, but in the case of GI-OP they may induce low-turnover osteoporosis, so in prolonged use of glucocorticoids additional treatments

may be needed. Escalation to denosumab is particularly beneficial in older people with longstanding RA and romosuzumab may be of benefit.

Key Points

- 30–50% of people with rheumatoid arthritis have osteoporosis.
- The risk of fracture in rheumatoid arthritis is two times higher than matched controls and this confers a significant mortality and morbidity risk. The risk of developing osteoporosis in rheumatoid arthritis is multi-factorial and rises with increasing age, increasing length of disease duration, prolonged use of glucocorticoids and lack of disease control.
- The lack of UK-specific guidelines for the diagnosis of osteoporosis in rheumatoid arthritis may present missed opportunities to diagnose and prevent it before fracture; however, rheumatoid arthritis is included in the FRAX fracture prediction calculation.
- Anti-osteoporotic treatments are available for people with rheumatoid arthritis.

Availability of Data and Materials

This review has been written following a comprehensive review of literature on this topic with most papers included being published since 2020. The reference list included all material used.

Author Contributions

ED and FKW made significant contributions to the design of this review. FKW wrote the initial draft and designed the figure, with guidance from ED. ED reviewed the initial submission, amended the article following reviewers' comments and provided the table. Both authors contributed to important editorial changes in the manuscript. Both authors read and approved the final manuscript. Both authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

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