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Osteoporosis evaluation and treatment recommendations in rheumatoid arthritis☆

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A B S T R A C T

In this chapter, we emphasize among rheumatoid arthritis (RA) patients, whom and how to screen for osteoporosis. We highlight certain modalities, advancements in technology, secondary osteoporosis workup, and laboratory testing as well as their caveats. Finally, we discuss current guidance on how to direct the laboratory and radiology testing in the context of the individual patient with RA to guide and select from the osteoporosis treatment options currently available.

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Introduction

Rheumatoid arthritis (RA) is associated with double the risk of fracture when compared to the general population [1]. Unfortunately, osteoporosis screening and treatment rates are low in RA and may be due to the lack of clear guidelines for this high-risk population [2]. In this review, we collate the existing evidence to provide an evidence-based guide to osteoporosis screening and treatment for people with RA.

☆ "The views expressed in this article are those of the authors and do not necessarily reflect the position or policy of the Department of Veterans Affairs or the United States government."

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Diagnosis of osteoporosis in rheumatoid arthritis

Who should be screened?

There are no RA-specific guidelines for osteoporosis screening which likely contributes to the low rates of osteoporosis screening and detection in this high-risk population [2]. To provide evidence-based screening recommendations for people with RA, we combine recommendations from the 2014 National Osteoporosis Foundation (NOF) [3] and the 2017 American College of Rheumatology (ACR) glucocorticoid-induced osteoporosis (GIOP) guidelines [4]. The 2014 NOF guideline states that adults with a diagnosis (such as RA) or taking a medication (such as glucocorticoids (GCs)) should be screened. This recommendation does not apply to healthy young males or premenopausal females without fracture history. There is an additional statement to screen post-menopausal females and males over 50 with clinical risk factors for fracture. We use this statement to base our recommendation to screen all people with RA aged 50 and above [3]. The 2017 ACR GIOP guideline recommends bone mineral density (BMD) screening for anyone 40 years and older who are taking $\geq$2.5 mg prednisone equivalents per day for 3 months or longer [4]. It also provides guidance for BMD testing for people under 40 years of age with significant risk factors such as prior fracture or exposure to very high doses of GCs [4].

For people with RA who do not fit to the NOF or ACR guideline-driven recommendations [3,4] due to age or not being on GCs, we recommend evaluating both RA disease-specific and general population osteoporosis risk factors. RA-specific risk factors associated with low BMD, thereby supporting early BMD screening, are high ACPA positivity, long disease duration, high cumulative disease activity, and cumulative steroid exposure [5,6]. Additionally, screening should also be considered in those with frailty, imbalance, falls, and prior fragility fracture [3,7–9]. In concurrence with the 2017 ACR GIOP guideline, we recommend screening those under 40 years old if they have had a prior fracture, are on high doses of GCs, as well as those with poor functional status and high fall risk [4] (Fig. 1).

Dual-energy X-ray absorptiometry (DXA) assessments

DXA is the gold standard for BMD assessment. We recommend obtaining BMD at the lumbar spine, total hip, and femoral neck for all patients. For those with significant degenerative disk disease in the lumbar spine that may lead to false elevation in BMD or risk factors that contribute to significant cortical bone loss, such as hyperparathyroidism or androgen deprivation therapy, a forearm DXA is recommended [10]. The lumbar spine is the best measure of trabecular bone loss which is influenced by inflammation and GC exposure [11]. Sites of the hip represent cortical BMD which is influenced by mechanical loading through physical activity and body mass, most notably muscle mass [12]. Screening frequency should be based on ongoing risk factors. We recommend BMD screening in 3 to 5-year

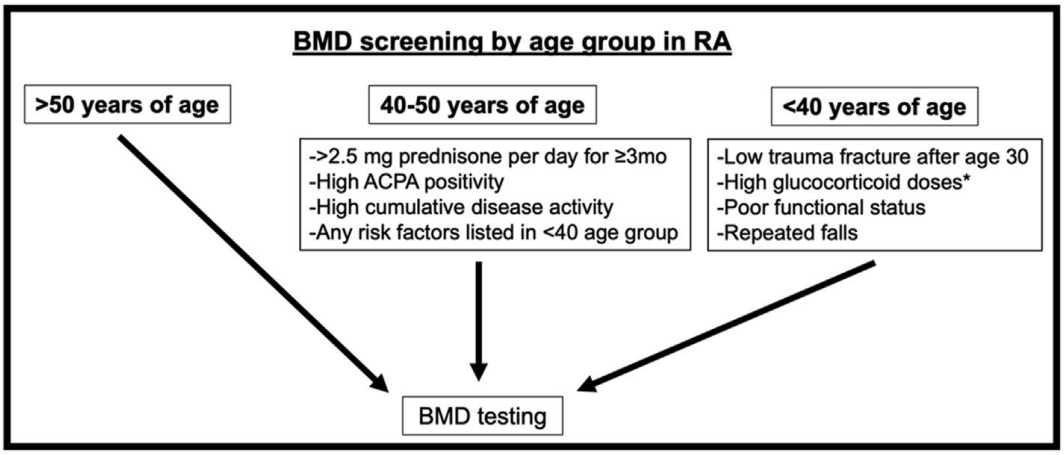

Fig. 1. Recommended bone mineral density screening by age and underlying risk factors for individuals with rheumatoid arthritis.

intervals for people with RA who have normal BMD, well-controlled disease, and are not taking GCs. For those who are being actively treated for osteoporosis or those with ongoing risk factors, we recommend BMD screening every 2 years. Only those patients with significant risk factors, such as very high doses of GCs, should be considered for annual BMD screening [3,4,6,10,13]. Trabecular bone score (TBS) and vertebral fracture assessments (VFA) may offer additional information to improve fracture prediction in people with RA and those on GCs. Currently, indications for VFA consideration do include GC therapy of more than 5 mg daily prednisone or equivalent steroid for longer than 3 months [10,14,15].

Other BMD screening methods

While other imaging methods have been used to assess bone deficits and independently predict fracture such as quantitative ultrasound or peripheral quantitative computed tomography (pQCT) [16], these approaches are not currently recommended as routine screening tests. High-resolution pQCT (HR-pQCT) offers compelling images of the underlying bone microarchitecture with low effective radiation dose. However, the use of HR-pQCT appears to only marginally improve fracture prediction above DXA alone [17]. Quantitative ultrasound has also been shown to predict fractures in several studies [18], though few studies have shown a substantial added benefit above BMD assessment to provide evidence for widespread incorporation in clinical practice [19]. Ultrasound has the potential to improve access to screening in certain practice settings and thus may have other advantages over DXA. While these newer imaging techniques may not be poised to replace DXA as a primary screening tool in the near future, they may have a role in screening within particular sub-populations where DXA may be less accurate, or in following response to pharmacologic treatment.

Fracture risk assessment

We recommend fracture risk assessment through the use of an established risk calculator such as the FRAX or the Garvan [20–22]. Both the FRAX and the Garvan risk calculators can be performed with or without BMD assessments. Although the FRAX utilizes RA as a risk factor in their algorithm, it does so as a dichotomous input variable without weighting important RA-specific risk factors and, therefore, may not provide an accurate fracture estimate [23]. The Garvan fracture risk calculator does not take RA into account but does use fall frequency to inform its fracture risk estimate, which is overlooked by the FRAX [24,25]. We believe these risk calculators offer important insight into fracture risk, and when applying them to the RA population, they will need to be interpreted in the context of RA disease features and severity.

Lab workup

Initial basic laboratory testing should consist of complete blood count (CBC), serum calcium, phosphorus, creatinine with estimated glomerular filtration rate (eGFR), 24 h urinary calcium and creatinine excretion panel, liver function tests (including alkaline phosphatase), parathyroid hormone, and serum 25-OH-D [26,27]. As above, further investigations into secondary causes may be warranted based on the history and physical exam of a patient. Chronic GC use, which is common in RA, may lead to secondary hypogonadism. Assessing if patients have symptoms of androgen deficiency and then deciding to pursue further workup, including obtaining morning testosterone levels and gonadotropin levels, can be considered [24,27].

There is insufficient evidence to support the routine use of bone turnover markers in the screening or management of osteoporosis in RA. While some of these markers have been associated with bone loss and radiographic damage in RA [6], their potential role in patient management remains unclear, and future studies are necessary. While not recommended routinely, in some clinical circumstances, such as in the setting of chronic kidney disease, bone turnover markers may be helpful [28]. For example, bone-specific alkaline phosphatase levels in combination with parathyroid hormone levels

may help to distinguish patients who have adynamic bone disease and inform treatment decisions that could favor anabolic agent choice for osteoporosis management [29].

Pharmacologic osteoporosis treatment strategies in rheumatoid arthritis

Treatment of RA disease activity

Treatment of underlying RA disease is important to minimize osteoporotic fracture risk. It is believed that RA treatments decrease fracture risk through minimizing systemic inflammation, improving physical activity and body composition, together resulting in improved BMD and decreased fall risk.

Cohort studies have shown that those with RA disease in remission have better bone outcomes than those with high disease activity [30,31]. There are no specific RA treatments, beyond GC minimization, that are recommended specifically to preserve BMD and reduce fractures. Multiple randomized controlled trials have evaluated bone turnover markers between groups of RA patients exposed to biologics or placebo and have consistently shown a pattern of increased bone formation and decreased bone resorption markers [32]. The majority of studies evaluating the associations of biologic medications and BMD have been observational and have generally shown stabilization to the improvement of hip and spine BMD [32,33]. Notably, the majority of these studies have evaluated interleukin (IL-6), tumor necrosis factor alpha (TNFα), and abatacept [34–36]. Fewer studies have evaluated fracture outcomes, but those that exist have found no difference in fracture rates between biologic medication groups, although the number of fractures might limit the ability to detect differences between groups [37,38]. One large study using the Danish Biologics Register found no difference in fracture risk between conventional synthetic and biologic disease-modifying agents [39]. There are limited data regarding BMD outcomes in RA populations using conventional disease-modifying anti-rheumatic drugs or Janus kinase inhibitors.

Calcium and vitamin D

An important step in osteoporosis management is to confirm adequate intake of calcium and vitamin D. However, calcium recommended doses are debatable by major societies [40], with most societies suggesting 1000–1200 mg of calcium daily (total of diet and/or supplement) [3,4,13]. It is important to review a patient's dietary intake to avoid excess calcium intake, which has previously been lead to constipation, kidney stones, and increased risk for MI and stroke, although this remains uncertain [40,41].

Vitamin D enhances intestinal absorption of calcium and is essential for calcium homeostasis. Low vitamin D levels may lead to bone resorption and demineralization of bone [42]. Higher levels of vitamin D have also been considered risk factors for hypercalcemia and hypercalciuria; therefore, larger doses used in long term may be harmful [40,41,43]. Most guidelines suggest daily cholecalciferol dose for adults at least 600–800 IU/d ([3,4,40,41,43], and the use of higher doses may be necessary to achieve the target vitamin D if vitamin D deficient [42]. One should check 25-hydro-oxyvitamin D (25-OH) levels as an indicator of vitamin D stores [44].

25-OH vitamin D goals and thresholds vary by national organizations [40,41]. The 2017 ACR GIOP guidelines recommend a goal of $\geq$20 ng/ml, whereas the Endocrine Society Guideline sets a target of $\geq$30 ng/ml (range 30–50 ng/ml). These two thresholds continue to be debated due to differences in many of the prior study designs, analysis, and randomized controlled trials [44]. We would recommend achieving a 25-OH vitamin D level greater than 25 ng/ml to prevent hypocalcemia, especially in patients with chronic kidney disease receiving IV Zoledronic acid or denosumab [40,41].

Who should be treated with anti-osteoporosis therapies?

Similar to BMD screening, there are no guidelines that specifically address osteoporosis treatment for people with RA. We use the 2017 ACR GIOP [4], the Endocrine Society [45,46], and American Association of Clinical Endocrinologists and American College of Endocrinology (AACE/ACE) Guidelines for the treatment of postmenopausal osteoporosis [13] to inform our treatment recommendations.

These guidelines depend heavily on the use of the FRAX risk calculator to inform treatment thresholds [20]. As previously mentioned, RA disease severity, functional status, and fall frequency are not accounted for in the FRAX; therefore, FRAX risk estimates may need modification for those with these risk factors.

Osteoporosis therapies should be initiated for postmenopausal females or males older than 50 with T-scores of −2.5 or less or at T-scores between −1 and −2.5 with a FRAX 10-year risk ≥20% for MOF or ≥3% for hip fracture [4,13,45,46]. The 2017 ACR GIOP guideline recommends multiplying the MOF risk score by 1.15 and the hip fracture risk score by 1.2 for those taking ≥7.5 mg prednisone equivalent per day. Importantly, the 2017 ACR GIOP guideline recommends osteoporosis treatment for the prevention of osteoporosis at lower FRAX thresholds for those on chronic GCs (MOF ≥10% or hip fracture >1%). Lastly, the 2017 ACR GIOP guideline includes treatment recommendations for those under 50 years of age [4].

The ACR GIOP guideline recommends bisphosphonate as first-line therapy, especially for both prevention and treatment of those with low fracture risk. While bisphosphonates do remain the primary therapy choice, anabolic agents can be considered based on risk stratification for GIOP patients at imminent or highest risk of fractures, especially if they are deemed to have declining BMD on antiresorptives or fracture despite being on antiresorptive therapy [4]. This is in line with other society guidelines advocating model of assessing the individual patient as low, intermediate, high, or very high risk for fractures [46,47]. Ultimately, a shared decision-making process with the patient engaged in the treatment plan is encouraged as other factors will play a role in the final choice of agents, such as patient preference, ease of daily injections, and ability to adhere to the medication regimen.

Osteoporosis-specific pharmacologic therapies

Few trials have evaluated osteoporosis treatments specifically in people with RA. Here, we provide general guidance for treatments based on evidence from the general population as well as GIOP trials as they often enroll substantial proportions of participants with RA.

Bisphosphonates

There is evidence to show that bisphosphonates reduce fracture risk, especially in GIOP, and that starting oral bisphosphonates within 6 months of GC initiation was associated with a decrease in incident hip and vertebral fracture [48,49]. It is imperative to educate patients on correct administration of oral bisphosphonates which includes taking it on an empty stomach without any medications or food, drinking a full glass of water, as well as staying upright for at least 30 min to avoid symptoms of reflux. If there is already a history of upper gastrointestinal disorders, such as reflux disease, esophagitis, difficulty swallowing, or concern for adherence, IV Zoledronic acid is a reasonable alternative as long patients are assessed for renal function and vitamin D status. For both oral and IV bisphosphonate formulations, it is important to counsel patients on the risks of osteonecrosis of the jaw which is a rare side effect [45]. Currently, a longer duration of bisphosphonates beyond 5 years has been associated with the risk of atypical femoral fracture (AFF). There are likely compounding factors influencing GCs role in AFF risk, but the current studies do support GCs as a risk factor for AFF [50,51]. Duration of therapy and drug holidays remains currently debated and necessitates an individualized review of patient's characteristics and balance of risks versus benefits [4,45,46].

Denosumab

Denosumab is an inhibitor of receptor activator of nuclear factor-kB ligand (RANKL), which is necessary for osteoclast activation and survival. Prior trials comparing denosumab with other bisphosphonates led to greater spine and hip BMD gains, but there were no significant differences in fracture rates [52]. When stopping denosumab therapy, it is essential to consolidate therapy with another antiresorptive-containing agent to avoid the risk of increased bone resorption, accelerated BMD loss, and rebound fractures [53,54]. While the exact timing is still uncertain, we recommend introducing the antiresorptive consolidation therapy within 6 months of last denosumab injection [55].

Denosumab has been studied in RA to determine its effects on RA disease activity and damage as well as for the treatment of osteoporosis. Trials have shown that denosumab decreases RA erosions but does not affect joint inflammation or joint space narrowing [56]. In an observational study, denosumab had similar efficacy in increasing systemic BMD in people with osteoporosis with and without RA [57].

PTH analog and romosozumab

PTH analog, teriparatide and abaloparatide, stimulate osteoblast activity resulting in net bone formation [58]. Romosozumab is a monoclonal antibody against sclerostin that stimulates osteoblasts with less concomitant activation of osteoclastic activity resulting in significant BMD gains and proven fracture prevention [59,60]. Both PTH analog and anti-sclerostin therapy may be an attractive target approach to osteoporosis treatment in RA patients when degradation of bone structure and quality is often advanced. They can be considered in patients deemed very high risk for fracture, including those with a new or recent fracture or significant declining BMD on oral bisphosphonates or denosumab [58,60].

Hormone-based therapies

The selective estrogen receptor modulator, raloxifene, helps to prevent vertebral fractures in women and stabilizes bone density, but it has not been shown to improve hip fracture rates [61]. It should also be used cautiously in patients with a higher risk for thromboembolic events. ACR 2017 guidelines suggest it as a treatment option only for postmenopausal women with contraindications to other bone health agents [4]. People with RA may be at increased risk for other secondary causes of bone loss such as hypogonadism due to both chronic GC exposure and chronic inflammation [24]. Testosterone treatment may be indicated in men with documented symptomatic androgen deficiency as it has been found to improve volumetric BMD but should not be used alone as an osteoporosis agent as there is no current long-term anti-fracture efficacy data [62]. Treatment courses and monitoring of therapies are not within the scope of this review. We recommend the society guidelines discussed above to help inform these important decisions [3,4,13,45,46].

Conclusions

Early case detection and screening in RA patients is critical, especially in those with high ACPA positivity, prolonged RA disease duration, significant GC exposure, or history of low trauma fracture. While there is a need for more RA-specific studies and RA-focused bone health guidelines, we advocate for the clinician to risk stratify based on existing guidelines to aid in shared decision-making with patients and choosing the appropriate osteoporosis agent for fracture prevention.

Practice points

1. Bone mineral density (BMD) screening rates are low in RA and must be considered in those with RA features that elevate osteoporosis risk: high ACPA positivity, long RA disease duration, and high glucocorticoid (GC) exposure.
2. Treatment of underlying RA disease activity while minimizing GC exposure and improving physical function are important first steps to address osteoporosis and minimize fracture risk in the RA population.
3. Similar to the general population, the severity of BMD, FRAX assessment, and falls risk should guide the selection of the osteoporosis medication in individuals with RA.

Research agenda

1. Evidence-based osteoporosis guidelines specific to people with RA are essential to improve osteoporosis detection and treatment rates.
2. It is important to study new osteoporosis agents in RA populations to inform RA-specific treatment guidelines.

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Declaration of competing interest

None.

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