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Osteoporosis in 2024: Frequency, Monitoring and Treatment

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Introduction

Osteoporosis is a chronic condition characterized by decreased bone mineral density (BMD) and deterioration of bone architecture, leading to an increased risk of fractures. It is the most common metabolic bone disease globally. It is estimated that more than two million Canadians aged 40 years and older have osteoporosis. Approximately 80% of Canadians who have sustained a fracture due to osteoporosis do not receive appropriate care, leaving them at an elevated risk for subsequent fractures, deconditioning, and premature death.[1] Many clinical practice guidelines exist on the management of osteoporosis and fracture prevention. Several of them have separate definitions for patients deemed very high and high risk for fracture and, as such, have specific criteria for the use of anabolic and antiresorptive treatments.

Patients with Rheumatic Diseases

Patients with rheumatic diseases are at an elevated risk of osteoporosis due to inflammation and immobility, predisposing them to bone loss. Many autoinflammatory diseases and autoimmune diseases result in the dysregulation of the RANKL-RANK pathway or the upregulation of Dickkopf-related protein 1 (Dkk-1) and sclerostin, both of which inhibit the Wnt/β-catenin pathway.[2,3] Upregulation of RANK-L and downregulation of the Wnt signalling are highly associated with deleterious effects on bone health. Furthermore, given that corticosteroids are common medications used in many rheumatic diseases, clinicians should be vigilant for the risks of their patients developing glucocorticoid-induced osteoporosis. Rheumatologists and family physicians should recognize the increased risk of osteoporosis in their patients with rheumatic diseases and ensure they have timely access to diagnostic assessments as well as pharmacotherapy when necessary.

What Should We Start With?

Patients with rheumatic diseases should undergo a fracture risk assessment, which consists of the following steps:

1. A detailed history of the patient's chronic conditions, comorbidities, health status (i.e., diet, smoking, alcohol consumption), fall risk, and medications that contribute to osteoporosis.
2. A physical examination to evaluate subclinical vertebral fractures, as well as frailty and sarcopenia, both of which are highly associated with bone loss.[4,5]
3. Diagnostic studies to exclude secondary causes of osteoporosis, as well as BMD measurement combined with fracture risk stratification tools such as FRAX and CAROC.

A list of secondary causes of osteoporosis from the Osteoporosis Canada 2023 Guidelines is provided in **Table 1**. Patients undergoing osteoporosis evaluation should have baseline measurements of height, rib-to-pelvic distance, and occiput-to-wall distance taken. If there is a history of height loss greater than 6 cm, a prospect of height loss of at least 2 cm, less than 2 fingerbreadths between the rib-to-pelvis distance, or a greater than 5 cm distance from occiput to-wall measurement on physical examination, consider further investigation with x-rays of the spine, including para-spinal views, to rule out vertebral compression fractures.

Baseline investigations to evaluate for secondary causes of osteoporosis include the following: calcium corrected for albumin, phosphate, renal function, liver function tests, thyroid-stimulating hormone, and serum protein electrophoresis (SPEP) for patients with vertebral

Drugs	Endocrine Disorders	Gastrointestinal & Nutritional Disorders
• Glucocorticoid steroids • Aromatase inhibitors • Anticonvulsants (particularly phenytoin, phenobarbital) • GnRH agonists and antagonists • Androgen-deprivation agents • Cancer chemotherapy • Immunosuppressants (eg. cyclosporine)	• Hyperparathyroidism Hyperthyroidism • Hypercortisolism/Cushing's syndrome • Diabetes mellitus (Type 1 & Type 2) • Prolonged premature hypogonadism • Acromegaly	• Inflammatory bowel disease • Celiac disease • Bariatric surgery • Pancreatic insufficiency • Other malabsorptive syndromes • Primary biliary cholangitis • Chronic liver disease • Eating disorder • Malnutrition • Parenteral nutrition • Vitamin D and/or calcium deficiency
Rheumatologic Disorders	**Genetic Disorders**	**Other Disorders**
• Rheumatoid arthritis • Other inflammatory arthritis disorders • Systemic lupus erythematous	• Osteogenesis imperfecta Hypophosphatasia • Other genetic causes of osteomalacia	• Multiple myeloma • Other marrow-related disorders • Idiopathic hypercalciuria • Chronic kidney disease/renal failure • Chronic obstructive pulmonary disease • Organ transplantation • Multiple sclerosis Parkinson's disease • Other neuromuscular disorders • Prolonged immobilization • Paget's disease • Acquired causes of osteomalacia

Table 1. Secondary causes of osteoporosis; a*dapted from Osteoporosis Canada Guidelines (2023).*

fractures, as well as 25-hydroxy vitamin D if risk factors for insufficiency are present or there is consideration for starting antiresorptive therapy.

Choice and Duration of Pharmacotherapy

Numerous treatment options are available for osteoporosis management and fracture prevention (**Figure 1**). Antiresorptive therapies, including bisphosphonates (i.e., alendronate, risedronate and zoledronic acid), denosumab, venlafaxine, and menopausal hormone therapy, are among the options, as well as anabolic therapies such as teriparatide or romosozumab.

Bisphosphonates

The 2023 Osteoporosis Canada guidelines currently recommend bisphosphonates as first-line treatment for osteoporosis and fracture prevention in postmenopausal females and males aged 50. Bisphosphonates are widely utilized for osteoporosis treatment and fracture prevention in Canada, with the first publications on their effects dating back to 1969. With over 50 years of data on their use in various metabolic bone disorders, they have demonstrated a proven record of success and efficacy.

However, a universal recommendation may not be suitable for all patients, particularly those with rheumatic conditions or secondary causes of osteoporosis. Patients at high risk (e.g., FRAX Hip Fracture Risk ≥3%, FRAX Major Osteoporotic Fracture (MOF) Risk ≥20%, prior

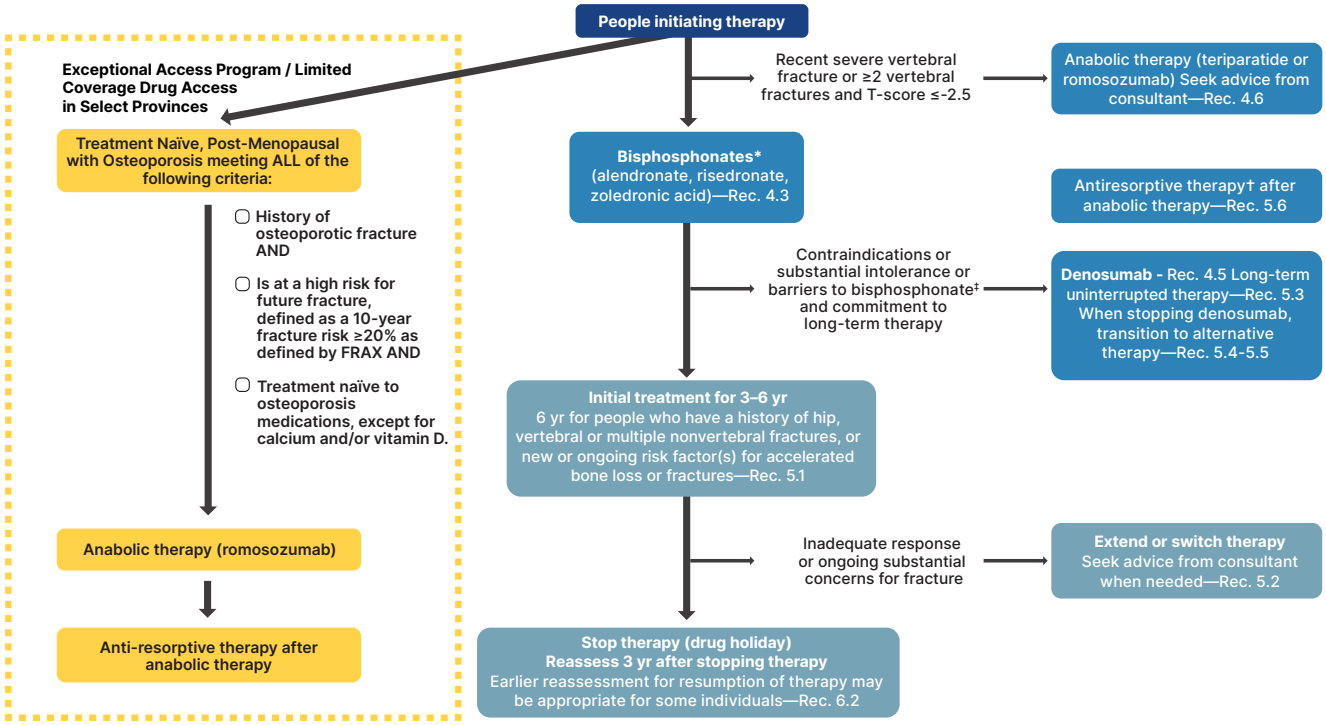

Figure 1. Pharmacotherapy for osteoporosis; *adapted from Osteoporosis Canada Guidelines (2023)*.

spine or hip fracture, or FRAX MOF risk between the upper assessment threshold and very high-risk threshold) or very high risk (e.g., multiple fractures, fracture within the last 12 months, BMD ≤-3.0, fracture while on osteoporosis therapy, FRAX hip fracture risk ≥4.5%, FRAX MOF risk ≥30%) should be considered for alternative antiresorptive therapies (e.g., denosumab) versus anabolic treatments.[6-10]

A systematic review, network meta-analysis, and meta-regression analysis of randomized clinical trials in 2023, involving over 80,000 patients from 69 trials, found that bisphosphonates, parathyroid hormone receptor agonists, and romosozumab all demonstrated a protective effect for clinical fracture prevention. However, bone anabolic treatments were more effective irrespective of baseline risk indicators. Management plans for patients with rheumatic diseases and low bone mass should be individualized and tailored according to the patient's comorbidities and risk profile. Several notable studies comparing newer treatment modalities to bisphosphonates are outlined below.

Denosumab vs Alendronate

A study conducted in 2023 compared the effectiveness of denosumab (n = 90,805) versus alendronate (n = 392,682) among postmenopausal women in the U.S .Medicare program. The study, which focused on treatment naïve patients initiating pharmacotherapy between 2012 and 2018, revealed that the use of denosumab, compared to that of alendronate, resulted in a 36% reduction in hip fractures (RR = 0.64, 95% CI: 0.39–0.90), a 43% reduction in non-vertebral fractures (RR = 0.57; 95% CI: 0.42–0.71), and a 39% reduction in major osteoporotic fractures (RR = 0.61; 95% CI: 0.48–0.74).[11] Overall, the study found that patients who remained on denosumab for extended periods experienced greater reductions in fracture risk compared to those who remained on alendronate, with statistical differences observed as soon as 1 year after pharmacotherapy.

Teriparatide vs Risedronate

The VERO Study (2017) enrolled 680 postmenopausal women with at least 2 moderate or 1 severe vertebral fracture and a BMD T-Score ≤-1.5 in a 24-month double-blind randomized controlled trial. Participants were assigned in a 1:1 ratio to compare the effectiveness of teriparatide vs risedronate in patients with severe osteoporosis. By the end of the 24-month period, the use of teriparatide, compared to risedronate, resulted in a 56% reduction in new vertebral fractures (RR 0.44; 95% CI 0.29–0.68) as well as a lower cumulative incidence of clinical fractures (4.8% vs 9.8%, [HR 0.48; 95% CI 0.32–0.74], P = 0.0009).[12] This demonstrated that teriparatide is associated with a significant reduction in the incidence of vertebral and clinical fractures compared to risedronate.

Romosozumab vs Alendronate

The ARCH Study (2017) enrolled 4093 postmenopausal women with osteoporosis and a fragility fracture in a 24-month double-blinded randomized controlled trial, in a 1:1 ratio, to compare the effectiveness of a regimen initiating romosozumab (12 months) and transitioning to alendronate (12 months) vs treatment with alendronate alone (24 months). By the end of the 24-month period, the romosozumab-to-alendronate group, compared to the alendronate-alone group, showed a 48% lower risk of new vertebral fractures (6.2% [127 of 2046 patients] vs 11.9% [243 of 2047 patients], P<0.001) and a 27% lower risk of clinical fractures (non-vertebral and symptomatic vertebral fracture) (9.7% [198 of 2046 patients] vs 13.0% [266 of 2047 patients], P<0.001).[13] During the first year of treatment, serious cardiovascular adverse events were observed more often with romosozumab compared to alendronate (2.5% [50 of 2040 patients] vs 1.9% [38 of 2014 patients]). Therefore, consideration should be given to the patient's cardiovascular risk profile before considering this treatment. It is contraindicated in patients with a history of previous myocardial infarction or stroke.

What to Monitor in Patients with Osteoporosis

During each follow-up assessment, it is recommended to reassess the risk for fracture, patient adherence to pharmacotherapy, and whether treatment needs to be continued or modified. Ideally, BMD measurements should be repeated three years after initiating pharmacotherapy, but shorter intervals may be necessary for patients with secondary causes of osteoporosis, new fractures or clinical risk factors associated with rapid bone loss. Patients with rheumatic diseases are at an elevated risk for bone loss compared to the general population, so repeat BMD testing every 1–2 years may be considered for this group.

Pharmacotherapy should be re-evaluated, and consideration given to a drug holiday at 5–6 years for patients taking oral bisphosphonates due to the risk of cumulative exposure and the development of atypical femoral fractures. If there is an inadequate response or if there are ongoing concerns for future fractures, extending or switching treatment modalities may be necessary, with guidance from a specialist in osteoporosis, if required. Patients with contraindications or potential intolerance to bisphosphonates should be considered for denosumab or anabolic therapy depending on their fracture risk. For those on denosumab, long-term uninterrupted therapy is recommended. The treatment duration for anabolic therapies (romosozumab and teriparatide) is 1 year, after which the patient should transition to an antiresorptive agent (either bisphosphonates or denosumab) to maintain bone density gains.

Conclusion

Osteoporosis is a disease that clinicians should closely monitor, especially in those with autoimmune rheumatic diseases. Several treatment options exist for fracture prevention. However, it is essential to carefully evaluate the patient's comorbidities, medications and risk profile to determine the appropriateness of the chosen pharmacotherapy based on the patient's circumstances.

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