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Therapeutic Options

FOCUS ON OSTEOPOROSIS

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BACKGROUND

Osteoporosis is a skeletal disorder that affects millions of people across the globe. When bone strength is compromised due to low bone mineral density (BMD) and bone tissue destruction, osteoporosis predisposes patients to an increased risk of fracture.[1,2] In Canada, approximately 2.2 million people over 40 years of age have osteoporosis. In this population, approximately 130,000 fractures occur yearly, resulting in substantial morbidity and mortality.[2] A low BMD is one of several risk factors for fracture; however, appropriate screening, assessment and management should evaluate all clinical characteristics of the disease. This article will discuss the importance of osteoporosis screening and risk assessment and provide an overview of treatment options, focusing on patients older than 50 years of age.[3]

ETIOLOGY & PATHOPHYSIOLOGY

Healthy bone physiology involves constant remodelling, as osteoclasts remove old bone (resorption) while osteocytes and osteoblasts form new bone. Osteoporosis develops when there is more bone resorption than formation. The imbalance between these processes typically occurs with increasing age, but age-related bone loss is milder than that seen in osteoporosis.[2] Women have a higher risk of osteoporosis compared to men.[4] Women have lower bone density to begin with, and remodelling and bone loss tend to accelerate with menopause which contribute to an increased risk of osteoporosis in postmenopausal females.[2,4] Bones most often affected by osteoporosis are the spine, hip and wrist.[1,4,5]

Osteoporosis can result in fragility fractures, which are fractures occurring from low trauma such as a fall from standing height.[2,3,5] These fractures lead to increased chronic pain, morbidity and mortality. In menopausal women over 50 years of age, fragility fractures account for 80% of all fractures. Fractures of the hip or vertebrae are associated with an increased risk of subsequent death. Although there is a high incidence of fragility fractures in Canada, less than 20% of women and 10% of men are given preventive therapy.[3]

RISK FACTORS AND SCREENING

Women and men over 50 years of age should be assessed for osteoporosis and absolute risk of fracture using an integrated approach.[3] A detailed history assessing all clinical factors including height loss, fall history, back pain, fracture history, medical conditions, and medications can aid in the assessment of osteoporotic fracture risk.[2,3] See Table 1 for clinical risk factors for fracture, and Table 2 for medications that may increase fracture risk.

There are currently two risk assessment tools used for osteoporosis screening in Canada: the Canadian Association of Radiologists and Osteoporosis Canada (CAROC) tool and the Fracture Risk Assessment (FRAX) tool of the World Health Organization (WHO). Each tool estimates a patient's 10-year risk (percentage-wise) of a major fracture (spine, hip, forearm, or proximal humerus) due to osteoporosis. Clinical practice guidelines use these tools (which incorporate age, sex, BMD and several other clinical risk factors) to categorize the 10-year fracture risk as low (<10%), moderate (10-20%) or high (>20%). The fracture rates predicted by both tools tend to be similar in both women and men, although FRAX has been shown to be slightly superior to CAROC.[2,3] The choice of assessment tool is based on convenience and personal preference; neither is recommended for use in patients already on osteoporosis therapy.[3]

SIGNS & SYMPTOMS

The preferred method of assessing bone mass is through dual x-ray absorptiometry of the hip and spine to measure BMD. This BMD measurement indicates the quantity of bone mineral but does not identify other components of bone strength such as the structural properties or non-mineral material that may represent bone quality. The focus of diagnosing and managing osteoporosis no longer relies solely on BMD, but instead evaluates all clinical factors to assess fragility fracture risk. In some cases the risk may be present without low BMD; for example, after menopause or 50 years of age, a hip or vertebral fracture automatically places the patient in the high-risk category regardless of BMD (unless it occurs due to high trauma such as a car accident).[2]

Typically, limited laboratory investigations are needed, as osteoporosis is defined as a BMD of 2.5 or more standard deviations below the average BMD of a normal young female adult, or a T-score of $\leq$-2.5 (a normal T-score is $\geq$-1.0).[2,3] X-rays are used to detect fractures but may also indicate reduced BMD (osteopenia); this finding should be confirmed with a BMD measurement.[2]

Table 1: Clinical risk factors for fracture.[2,3,4]

Age*	Conditions Associated with Increased Fracture Risk
≥ 65 years of age	No other conditions required; increased fracture risk due to age
Men 50–64 years of age, Menopausal/ postmenopausal women	• Fragility fracture after 40 years old • Parent with hip fracture • Current smoker • High alcohol consumption • Low body weight or major weight loss • Vertebral fracture or osteopenia on x-ray • Rheumatoid arthritis or other disorders associated with osteoporosis
Any age	• Fragility fracture • Renal disease • Organ transplant • Gastric/bariatric surgery, malabsorption syndrome • Hyperthyroidism • Primary hyperparathyroidism • Cushing syndrome • Hypogonadism, premature menopause (under 45 years) • Other disorders linked to rapid bone loss/fracture

Table 2: Examples of medications associated with increased fracture risk.[2,3]

- Androgen deprivation therapy
- Anticoagulants
- Antiepileptics
- Antiretrovirals
- Aromatase inhibitors
- Chemotherapy
- Cyclosporine
- Drugs with increased fall risk in the elderly, such as sedatives
- Loop diuretics
- PPIs
- Prolonged corticosteroid use*
- SSRIs
- Thiazolidinediones

PPIs=proton pump inhibitors;
SSRIs=selective serotonin reuptake inhibitors

* Usually considered as the dose equivalent to prednisone >7.5mg/day for a minimum of 3 months (cumulative) in the past year. Corticosteroid-induced osteoporotic effects are often dose and duration dependent.

PHARMACOTHERAPY

Therapy for osteoporosis can be categorized into prevention and treatment. The goals of therapy include avoiding fractures, loss of independence and disability while preserving or improving BMD.[2] Treatment for osteoporosis should be offered to all postmenopausal women and men over 50 years of age with T-scores ≤-2.5 or with previous hip or spine fracture; to all patients with T-scores between -1 and -2.5 and a FRAX hip fracture risk of at least 3% or a FRAX major fracture risk of at least 20%; and to patients with fragility fractures.[1,3] Based on risk assessment values, patients in both moderate- and high-risk categories (10-year fracture risk ≥10%) should be offered medication.[6] In low-risk patients, medication is unnecessary but lifestyle interventions may be beneficial.[3,6]

Osteoporosis pharmacotherapy aims to alter the bone remodelling process by either reducing remodelling and slowing bone breakdown or stimulating the formation of bone.[2] Medications are thus categorized as antiresorptive agents (decrease bone remodelling) or anabolic agents (stimulate the formation of bone).[2,3] Depending on the agent chosen and patient adherence, pharmacologic therapy can decrease the risk of vertebral fracture by 30-70%.[3] In addition, adequate calcium and vitamin D intake helps preserve bone mass in all age groups.[2]

ANTIRESORPTIVE AGENTS

These agents reduce the depth and rate of bone resorption while bone formation continues normally, thereby increasing BMD.[2] **Bisphosphonates** are the foundation of treating osteoporosis in both postmenopausal women and men.[2,7] They inhibit osteoclast activity and induce osteoclast apoptosis. A risk associated with the use of bisphosphonates is the occurrence of atypical femoral fractures (AFF). When taken for 2-4 years, bisphosphonates have been associated with 11 AFFs per 100,000 patients per year; however, a typical hip fracture occurs in 750-4200 per 100,000 high-risk patients per year, thus demonstrating their benefit usually outweighs this risk.[2] Since AFF risk increases with a longer duration of bisphosphonate use (but declines rapidly upon discontinuation), a "drug holiday" may be suggested to patients at lower risk of osteoporotic fractures after 3-5 years of therapy. A drug holiday may not be appropriate for patients at high risk of fractures, and longer courses (6-10 years) are usually considered for these patients.[1,2]

Denosumab, the first biologic approved for osteoporosis, is a human monoclonal antibody that inhibits the RANK ligand to reduce osteoclast formation, survival and function for approximately 6 months after one dose. It is considered first line therapy for osteoporosis. **Raloxifene**, a selective estrogen receptor modulator (SERM), has estrogen-like activity in the bone, increasing BMD by approximately 3% and decreasing new vertebral fractures by approximately 40%.[2] As raloxifene acts as an estrogen antagonist in the breast and decreases the relative risk of estrogen-receptor-positive breast cancer by 76%, it can be used for osteoporosis prevention and treatment in postmenopausal women with high breast cancer risk.[1,2] **Hormone therapy (estrogen or estrogen/progesterone)** may be an option for osteoporosis prevention in women when treatment for menopausal vasomotor symptoms is also desired.[2]

ANABOLIC AGENTS

These agents enhance bone formation and may also be termed "osteoanabolic". **Teriparatide** is a parathyroid hormone analog that stimulates bone formation more than bone resorption, resulting in greater bone mass and strength. It also enhances trabecular connectivity and thickness as well as cortical bone thickness. Overall, it has shown a 50% decrease in vertebral and non-vertebral fractures and is effective for corticosteroid-induced osteoporosis treatment. Its cost limits use as a first line option, but in patients with severe osteoporosis, it should still be considered for initial therapy. **Romosozumab,** a humanized monoclonal antibody, inhibits sclerostin, ultimately enhancing the pathways of bone formation.[2] Sclerostin inhibition also results in decreased bone resorption, and is therefore both antiresorptive and anabolic. However, the drug has a black box warning for patients with history of cardiovascular disease (stroke or myocardial infarction) and should be avoided in these patients.[1,2] See Table 3 for osteoporosis medications available in Canada, and Table 4 for treatment choices based on patient population.

Table 3: Therapeutic options for the management of osteoporosis in Canada.[1,2,6,7,8,9]

3a: Antiresorptive Agents					
MEDICATION	**PLACE IN THERAPY**	**DOSE**	**ADMINISTRATION**	**SIDE EFFECTS**	**COMMENTS**
BISPHOSPHONATES					
Alendronate* (Fosamax®, generics)	**First line** Reduces risk of all fractures	**Prevention:** 5 mg PO once daily **Treatment:** 10 mg PO once daily, or 70 mg PO once weekly	Must be taken on an empty stomach with a full glass of water, at least 30 minutes before first food or drink of the day or other medications; must not lie down for 30 min after taking	Minor GI upset, heartburn, altered taste, night leg cramps Rare allergic reactions, AFFs, ONJ	There are no trials directly comparing alendronate and risedronate to identify if one is superior for fracture prevention Bisphosphonate relative risk reduction of osteoporotic fracture ranges from 40-60% Due to extremely poor intestinal absorption, dosing instructions must be adhered to strictly, which is often a major adherence problem with oral bisphosphonates Avoid in patients who have esophageal disorder, unable to follow dosing instructions, are hypocalcemic or have renal insufficiency May consider discontinuation after 5 years, or longer course (10 years) if patient is high-risk
Risedronate (Actonel®, Actonel DR®, generics)	**First line** Reduces risk of all fractures	**Prevention or treatment:** 5 mg PO once daily, or 35 mg PO once weekly, or 150 mg PO once monthly	Regular release tablet: same instructions as alendronate above Delayed release (DR) tablet: take with breakfast		
Zoledronic acid (Aclasta®, generics)	**First line** Usually reserved for patients who cannot tolerate GI effects of oral agents, cannot follow dosing or not responding to oral agent	**Prevention or treatment:** 5 mg IV once yearly (prevention requires single dose only)	Infusion over 15-30 minutes Patients should be well hydrated (500 mL of water) before and after infusion	Acute-phase reaction in 10-20% of patients 24-72 hours after infusion (may last up to 3-4 days): fever, joint/muscle pain, skin reactions, lymphopenia May cause hypocalcemia Rarely: atrial fibrillation, atypical thigh fracture, ONJ	Recent meta-analysis ranks slightly ahead of oral bisphosphonates Avoid use in patients with hyocalcemia Avoid in patients with CrCl <30 mL/min Adherence less of an issue compared to oral bisphosphonates May consider discontinuation after 3 years, or treat up to 6 years if high-risk
RANK LIGAND INHIBITOR					
Denosumab (Prolia®)	**First line** Increases BMD, reduces incidence of vertebral, nonvertebral, and hip fractures in menopausal women with OP (similar BMD changes seen in men as well)	**Treatment:** 60 mg SC once every 6 months	Keep injection refrigerated	Eczema, serious infections Infrequent AFF and ONJ; rare hypocalcemia	Not contraindicated in renal insufficiency but avoid in significant renal insufficiency Avoid in patients with hypocalcemia Not retained in the skeleton (unlike bisphosphonates) thus increases in BMD may be lost after discontinuation; bisphosphonates may be used post-treatment to alleviate this BMD loss May consider discontinuation after 5-10 years More expensive than bisphosphonates
SELECTIVE ESTROGEN RECEPTOR MODULATOR					
Raloxifene (Evista®, generics)	Prevents postmenopausal bone loss BMD increased by approximately 3%, new vertebral fractures reduced by approximately 40% Useful in post-menopausal women who cannot use bisphosphonates or denosumab, or are at high risk of breast cancer	**Prevention or treatment:** 60 mg PO daily		Hot flashes, leg cramps Similar VTE and PE risk as estrogen	Has been shown to significantly decrease relative risk of ER+ breast cancer Only initiate once menopause has started, as it may aggravate hot flashes Avoid in patients with VTE history and hot flashes

3b: Anabolic Agents					
MEDICATION	**PLACE IN THERAPY**	**DOSE**	**ADMINISTRATION**	**SIDE EFFECTS**	**COMMENTS**
PARATHYROID HORMONE ANALOG					
Teriparatide (Forteo®, Osnuvo™, generics)	Vertebral and nonvertebral fractures reduced by approximately 50% Useful in postmenopausal women with high fracture risk or who cannot use other agents	**Treatment:** 20 mcg SC daily, for 24 months (lifetime exposure)	Patient should be sitting or lying down for administration Keep injection refrigerated	Dizziness, nausea, hypercalcemia, leg cramps Risk of orthostatic hypotension	Limited use first line due to cost; should be considered as initial therapy in patients with severe OP and fractures Gains in bone density are lost rapidly once therapy is stopped; denosumab or bisphosphonate usually recommended after treatment Avoid use in patients with metabolic bone disease, Paget's disease, increased ALP or who have had previous skeletal irradiation Limited data regarding use in renal/hepatic impairment
SCLEROSTIN INHIBITOR					
Romosozumab (Evenity™)	Enhances pathways of bone formation and reduces bone resorption Useful in postmenopausal women with high fracture risk	**Treatment:** 210 mg SC (2 injections of 105 mg given consecutively) once per month, for 12 months No lifetime exposure limit; doses may be continued or restarted	Must also receive calcium and vitamin D supplementation during treatment Keep injections refrigerated	Headache, arthralgia, mild injection site reactions; potential for ONJ and AFF Black box warning against using in patients with history of CVD (MI or stroke)	Increase in BMD may be lost after discontinuing; may need to follow treatment with antiresorptive therapy Avoid in patients with hypocalcemia

3c: Nutritional Supplements					
MEDICATION	**PLACE IN THERAPY**	**DOSE**	**ADMINISTRATION**	**SIDE EFFECTS**	**COMMENTS**
Calcium (Caltrate®, Tums®, generics)	Appropriate calcium and vitamin D intake (whether dietary or as a supplement) recommended for all patients Vitamin D increases calcium absorption in the intestine	Total intake (diet + supplements): <50 years = 1000 mg elemental calcium PO daily >50 years = 1200 mg elemental calcium PO daily Divide supplement doses >500 mg to improve absorption	Calcium carbonate: take with or after meals** Calcium citrate absorption is not affected by food May reduce absorption of some medications; space administration apart by 2 hours (bisphosphonates, iron, levothyroxine, ciprofloxacin, tetracycline)	Nausea, constipation Less likely: hypercalcemia, hypercalciuria, renal stones/calcification (nephrolithiasis associated with calcium supplements but not with dietary calcium) High supplement doses may be associated with an increased risk of MI	Dietary intake should always be encouraged first; at least half of calcium intake preferred from diet In patients taking PPIs/H2 blockers calcium carbonate is poorly absorbed; calcium citrate is preferred in these patients Calcium supplements up to 1000 mg daily, increased dietary calcium, and vitamin D supplements have all been shown not to increase all-cause or CV mortality
Vitamin D (generics)		Patients over 50 years of age at risk for OP: 800–2000 units PO daily Healthy adults at lower risk of deficiency: 400–1000 units PO daily Generally, 1000 units of vitamin D daily is recommended for prevention		Possible renal stones/calcification, hypercalcemia, hypercalciuria (at high doses)	Increases absorption of calcium Cholecalciferol (vitamin D3) preferred over ergocalciferol (vitamin D2) Measure serum 25-hydroxyvitamin D after 3–4 months of supplementation (optimal level ≥75 nmol/L)

* Also available as alendronate/vitamin D (Fosavance®, generics) combination pill: alendronate 70 mg + vitamin D3 (2800 units or 5600 units) PO once weekly.

** Calcium carbonate needs an acidic environment for best absorption.

AFF=atypical femoral fracture; ALP=alkaline phosphatase; BMD=bone mineral density; CrCl=creatinine clearance; CV=cardiovascular; CVD=cardiovascular disease; DR=delayed release; ER+=estrogen-receptor positive; GI=gastrointestinal; H2 blockers= histamine H2-receptor antagonists; IV=intravenous(ly); L=litre(s); mg=milligram(s); MI=myocardial infarction; min=minutes; mL=millilitre(s); nmol=nanomole(s); ONJ=osteonecrosis of the jaw; OP=osteoporosis; PE=pulmonary embolism; PO=by mouth; PPIs=proton pump inhibitors; RANK=receptor activator of nuclear factor kappa-B; SC=subcutaneously; VTE=venous thromboembolism

Table 4. Preferred therapeutic choices for osteoporosis in various patient populations.[1,3,6]

Patient Population	Consider for First Line Therapy
Menopausal women requiring osteoporosis treatment	Alendronate Risedronate Zoledronic acid Denosumab Raloxifene
Menopausal women requiring osteoporosis treatment in addition to treatment for vasomotor symptoms	Hormone therapy
Postmenopausal women with high fracture risk, other therapy failed/cannot use other agents	Teriparatide
Postmenopausal women with high risk of breast cancer	Raloxifene
Men requiring osteoporosis treatment	Alendronate Risedronate Zoledronic acid Denosumab
Hypogonadal osteoporosis in men	Teriparatide
Men on androgen-deprivation therapy	Denosumab
Corticosteroid-induced osteoporosis	Alendronate Risedronate Zoledronic acid
Corticosteroid-induced osteoporosis with high risk of fracture	Teriparatide

KEY POINTS

- The decision to prescribe osteoporosis therapy in patients >50 years of age should encompass a thorough evaluation of all clinical factors predisposing a patient to fracture, in addition to BMD.
- First line options for osteoporosis include bisphosphonates, denosumab, hormone therapy (in women) and teriparatide.[2]
- For severe cases of osteoporosis (such as very low BMD or multiple fragility fractures), an anabolic agent may be considered for initial therapy.[2]
- Cessation of anabolic therapy is often followed by a rapid decline in BMD gains, requiring a course of antiresorptive therapy (e.g., bisphosphonates, denosumab).

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