



Therapeutic Options

UPDATE ON OSTEOPOROSIS

Osteoporosis is a skeletal disorder characterized by decreased bone strength.¹ The most significant consequence of osteoporosis is an increased risk of fragility fractures,* which are associated with high morbidity and mortality, as well as increased social and economic costs.^{1,3} The majority of cases of osteoporosis occur in postmenopausal women, and disease prevalence and fracture risk increase with age.¹ Estimates suggest that osteoporosis affects 4% of women aged 50 to 59 years and 52% of those 80 years or older.¹ Two-thirds of associated fragility fractures occur after age 75.¹ Unfortunately, available data suggest that most patients with a fragility fracture do not receive therapies to prevent further fractures.³

PATHOPHYSIOLOGY & RISK FACTORS

Normal bone is in a constant state of remodelling, where osteoclast-mediated bone resorption is balanced by osteoblast-mediated bone formation.¹ When bone resorption occurs at a rate that exceeds bone

formation, bone mass is lost and fracture risk increases.¹ In women, the drop in circulating levels of 17β -estradiol at menopause contributes to the few years of rapid bone loss seen at this time.¹

An assessment for osteoporosis and fracture risk factors is recommended for women and men over age 50 to identify those at high risk for fractures.³ Risk factors that warrant bone mineral density (BMD) testing according to current Osteoporosis Canada guidelines³ are summarized in Table 1.

DIAGNOSIS & RISK STRATIFICATION

A diagnosis of osteoporosis can be made clinically, based on the presence of a fragility fracture, or technically, based on results of BMD testing.¹ When BMD testing is indicated (see Table 1), dual-energy x-ray absorptiometry (DXA) is the preferred technique.¹ To standardize values from different bone densitometry tests, results are often reported as a T-score,[†] expressed in standard deviation units.¹ When the T-score

is less than or equal to -2.5 at the total hip, femoral neck, or posterior-anterior lumbar spine, the World Health Organization (WHO) criterion for osteoporosis in a postmenopausal woman or man over age 50 is met.¹ It is notable, however, that most postmenopausal women with fractures do not have BMD values consistent with osteoporosis based on the WHO criterion.¹

A patient's 10-year risk of major osteoporotic fracture (i.e., fracture of the hip, vertebra [clinical], forearm, or proximal humerus) can be classified as low ($< 10\%$), moderate ($10\text{--}20\%$), or high ($> 20\%$) using multivariate clinical assessment tools.^{3,4} Web-based fracture risk assessment tools for the Canadian population are available from the WHO (FRAX[®]; see www.sheffield.ac.uk/FRAX/tool.jsp?country=19) and Osteoporosis Canada (see <http://www.osteoporosis.ca/multimedia/FractureRiskTool/index.html#/Calculator>). The WHO tool considers more risk factors than the Osteoporosis Canada tool and is therefore more accurate when

* A fragility fracture occurs spontaneously or after minor trauma that would not be sufficient to fracture normal bone (e.g., a fall from standing height).²

† T-scores are calculated by comparing a patient's current BMD to the mean peak BMD of an average, young adult population of the same gender.¹

Table 1 – Indications for bone mineral density testing³

Adults ≥ 50 years	Adults < 50 years
<ul style="list-style-type: none"> • Age ≥ 65 years (women and men) • Clinical risk factors for fracture (menopausal women, men aged 50–64 years) <ul style="list-style-type: none"> ○ Fragility fracture after age 40 ○ Prolonged use of glucocorticoids* ○ Use of other high-risk medications† ○ Parental hip fracture ○ Vertebral fracture or osteopenia on radiography ○ Current smoking ○ High alcohol intake‡ ○ Low body weight (< 60 kg) or major weight loss (> 10% of body weight at age 25) ○ Rheumatoid arthritis ○ Other disorders strongly associated with osteoporosis§ 	<ul style="list-style-type: none"> • Prior fragility fracture • Prolonged use of glucocorticoids* • Use of other high-risk medications† • Hypogonadism or premature menopause (age < 45 years) • Malabsorption syndrome • Primary hyperparathyroidism • Other disorders strongly associated with rapid bone loss and/or fracture§
<p>* At least 3 months cumulative therapy in the previous year at a prednisone-equivalent dose ≥ 7.5 mg daily. † Examples of medications that may contribute to bone loss are provided in Appendix A of reference #4 (see References, below, for URL). ‡ Generally defined as ≥ 3 standard drinks daily;^{3,4} a standard drink is approximately 44 mL [1.5 oz] of 40% spirits, 355 mL [12 oz] of 5% beer, or 148 mL [5 oz] of 12% wine.^{4,5} § Examples of secondary causes of bone loss are provided in Table 2 of reference #1 (see References, below, for URL).</p>	

one or more of the additional risk factors (e.g., smoking, high alcohol intake, parental hip fracture) is present.³ The WHO tool can also be used in the absence of BMD test results. Notwithstanding results from the online tools, the Osteoporosis Canada guidelines suggest that individuals with a T-score for the lumbar spine or total hip ≤ -2.5 should be considered to have at least moderate risk.³

MANAGEMENT

Nonpharmacological Approaches

General lifestyle practices advised for all individuals at risk of fracture include:

- maintaining a healthy weight;
- eating a balanced diet that ensures adequate calcium and vitamin D intake;
- participating in appropriate exercise to improve strength and balance;
- not smoking;
- avoiding excessive alcohol intake; and
- undertaking measures to prevent falls.^{1,3}

These approaches are all that is usually required for those at low risk of fracture³ (see Diagnosis & Risk Stratification, above), but they also form the necessary foundation for pharmacologic approaches to prevent or manage osteoporosis.¹

Pharmacotherapy

The main therapeutic options for osteoporosis can be classified as antiresorptive agents (e.g., bisphosphonates, estrogens, selective estrogen receptor modulators [SERMs], denosumab, and calcitonin), which slow the

rate of bone resorption, or anabolic agents (e.g., teriparatide), which stimulate bone formation.^{3,6} Antifracture efficacy data and other pertinent information about commonly used medications are presented in Table 2. Further information is provided under the subheadings below.

Generally speaking, pharmacotherapy should be offered to all patients at high risk of fracture (see Diagnosis & Risk Stratification, above), including any individual who has had a previous hip or vertebral fragility fracture or more than one fragility fracture (regardless of site).³ Individuals at moderate risk of fracture should be considered for pharmacotherapy, taking into consideration additional risk factors (see Box 1) and patient preference.³ Individuals at low risk of fracture are unlikely to benefit from pharmacotherapy; risk for such individuals should be reassessed periodically.^{3,7}

Medications for osteoporosis have been shown to reduce the risk of vertebral fracture by 30% to 70% in menopausal women, depending on the agent and level of adherence.³ The reduction in nonvertebral fractures is lower and varies by site.³ Based on a lack of prospective, head-to-head clinical trials, data are insufficient to conclusively demonstrate superior fracture risk reduction for one class of agents over another or, in the case of the bisphosphonates, for one particular agent over another.^{1,4,8} Nonetheless, there is general consensus from international

guidelines that agents that have been shown to decrease vertebral, nonvertebral, and hip fractures should be used preferentially over agents that demonstrate efficacy only for vertebral fractures.⁸

Box 1 – Factors warranting consideration of pharmacotherapy for individuals at moderate risk of fracture³

- Additional vertebral fracture(s) (identified clinically or by radiography)
- Previous wrist fracture in individuals aged > 65 and those with T-score ≤ -2.5
- Lumbar spine T-score << femoral neck T-score
- Rapid bone loss
- Men undergoing androgen-deprivation therapy for prostate cancer
- Women undergoing aromatase inhibitor therapy for breast cancer
- Long-term or repeated use of systemic glucocorticoids (oral or parenteral) not meeting conventional criteria for recent prolonged use
- Recurrent falls (≥2 in the past 12 months)
- Other disorders strongly associated with osteoporosis, rapid bone loss or fractures

Table 2 – Some medications for osteoporosis^{1,3,4,6,10,11}

Drug	Antifracture Efficacy*			Usual Dosage‡	Comments
	V	H	NV†		
Bisphosphonates					
Alendronate	✓	✓	✓	10 mg once daily or 70 mg once weekly	<ul style="list-style-type: none"> • Superiority of one bisphosphonate over another has not been conclusively demonstrated • Alendronate and risedronate tablets should be swallowed whole with a full glass of water 30 minutes before first food of day; patients must not lie down for at least 30 minutes after dosing • Zoledronic acid may be considered for high-risk patients unable to tolerate oral therapy or those with poor adherence
Etidronate	✓	–	–	1 tablet once daily§	
Risedronate	✓	✓	✓	5 mg once daily or 35 mg once weekly or 150 mg once monthly	
Zoledronic acid	✓	✓	✓	5 mg IV once yearly	
Calcitonin peptides					
Calcitonin salmon	✓	–	–	200 IU intranasally once daily	<ul style="list-style-type: none"> • Antifracture efficacy evidence is limited; consider as an alternative when other more effective drugs cannot be used • Effective for decreasing acute pain associated with vertebral fractures
Estrogens					
Conjugated estrogens	✓	✓	✓	0.625 mg once daily	<ul style="list-style-type: none"> • Primarily indicated to manage moderate to severe menopausal symptoms; when symptoms are controlled or cease, continued therapy can be considered for bone effects, weighing benefits and risks against those of other therapies • Not recommended for the sole indication of osteoporosis prevention • Prescribe with a progestin for women with an intact uterus
RANKL inhibitor					
Denosumab	✓	✓	✓	60 mg SC every 6 months	<ul style="list-style-type: none"> • May be considered for patients unable to tolerate oral therapy or those with poor adherence
Selective estrogen receptor modulator					
Raloxifene	✓	–	–	60 mg once daily	<ul style="list-style-type: none"> • May be considered for postmenopausal women unable to tolerate bisphosphonates who have no history of thromboembolic disease
Synthetic parathyroid hormone					
Teriparatide	✓	–	✓	20 mg SC once daily	<ul style="list-style-type: none"> • Consider for patients at increased risk of fracture or those with lack of response to other therapies • May decrease pain associated with vertebral fractures • Discontinue bisphosphonates before starting treatment • Gains in BMD decline once treatment is discontinued; consider antiresorptive therapy after completing treatment to maintain gains • Maximum recommended lifetime exposure is 24 months
<p><i>BMD = bone mineral density; H = hip; IV = intravenously; NV = nonvertebral; RANKL = receptor activator of nuclear factor kappa-B ligand; SC = subcutaneously; V = vertebral</i></p> <p>* Efficacy listed applies to postmenopausal women.^{4,10} For men, there is some evidence of decreased vertebral fractures with alendronate and risedronate, and some evidence of decreased vertebral and nonvertebral fractures with zoledronic acid.⁴</p> <p>† In clinical trials, nonvertebral fractures are a composite endpoint including hip, femur, pelvis, tibia, humerus, radius, and clavicle.¹⁰</p> <p>‡ Doses listed are for oral administration unless otherwise indicated.</p> <p>§ Etidronate products approved for osteoporosis are supplied with calcium carbonate; 90-day cycles are comprised of etidronate disodium 400 mg once daily for 14 days followed by calcium carbonate 1250 mg once daily for 76 days.⁴</p>					

According to current Osteoporosis Canada guidelines, first-line therapies for menopausal women include alendronate, risedronate, zoledronic acid, and denosumab for prevention of all fracture types, and raloxifene for prevention of vertebral fractures.³ Hormone therapy is a first-line alternative for menopausal women also requiring treatment for vasomotor symptoms.³ For men, first-line therapies for fracture prevention include alendronate, risedronate, and zoledronic acid.³ Testosterone therapy is not recommended for osteoporosis in men.³

Regardless of which medication is selected, treatment adherence must be encouraged since evidence shows that poor adherence is associated with a significantly increased fracture risk compared with optimal adherence.⁹

It is notable that osteoporosis in premenopausal women is uncommon and usually associated with a secondary cause.¹² As such, evaluation and treatment of the underlying cause of osteoporosis remains the focus of management in most cases.⁷ Bisphosphonates may be appropriate for premenopausal women with fractures and/or an ongoing source of bone loss;[‡] however, caution is recommended in women of childbearing potential due to the prolonged resident time (i.e., years) of these agents in bone and the lack of data on pregnancy outcomes.⁷

Practical considerations

Combination or sequential therapy

At present, combination antiresorptive drug therapy is not generally recommended.^{1,3} While additive effects on BMD have been demonstrated with some combinations (e.g. alendronate or risedronate plus estrogen; raloxifene plus alendronate), proof of fracture reduction is lacking.^{1,3,13} A potential concern is that combining agents may oversuppress bone turnover, leading to poor bone quality and increased fracture risk.¹

Definitive recommendations for or against combining antiresorptive and anabolic agents cannot be made based on available evidence.¹ Certain antiresorptive-anabolic

combinations (e.g., raloxifene plus teriparatide) may improve BMD, whereas alendronate may lessen the anabolic response to teriparatide if given before or concurrently with teriparatide.¹³ In all instances, fracture data are lacking.¹³

After a course of anabolic therapy, an antiresorptive agent (e.g., a bisphosphonate) is generally recommended to maintain or enhance the benefits achieved.¹³

Duration of therapy

The optimal duration of antiresorptive therapy for osteoporosis is not known, but needs to be long term for most women.^{1,3} Although “drug holidays” (e.g., one to two years off therapy) after five to ten years of treatment have been suggested by some experts,^{14,15} the Osteoporosis Canada guidelines do not support this practice for patients at high risk.³

Calcium & vitamin D supplementation

As noted above, adequate intake of calcium and vitamin D is recommended for all individuals at risk of fracture. The total daily calcium intake suggested by North American¹ and Canadian³ osteoporosis guidelines for all individuals over age 50 is 1200 mg. Given the recent controversy surrounding potential adverse cardiovascular effects of calcium supplements, some experts have suggested that lower intakes (e.g., 800–1000 mg/day) may be sufficient with adequate vitamin D replacement.¹⁶ In any case, calcium intake from nutritional sources should be emphasized since it produces similar benefits on BMD and does not appear to be associated with negative cardiovascular effects.¹⁶ If supplementation is required, products containing 500 mg elemental calcium per dose taken after meals have been suggested by some experts to minimize potential risk.¹⁷

Adults over age 50 should receive supplementation with at least 20–25 µg (800–1000 IU) of vitamin D₃ daily, although higher doses may be required to achieve optimal vitamin D status (i.e., serum 25-hydroxyvitamin D > 75

nmol/L).¹⁹ Doses up to 50 µg (2000 IU) are considered safe and do not require monitoring; if higher doses are necessary, monitoring of serum levels is appropriate.¹⁹

MONITORING

Treatment-induced changes in BMD do not always correlate well with reductions in fracture risk.¹ In addition, fracture risk reduction generally occurs much more quickly than meaningful changes in BMD.¹ Accordingly, repeat BMD testing for most patients receiving osteoporosis therapy is not warranted until after one to three years.³ Treatment is generally considered successful if BMD has improved or remained unchanged; in such instances, further testing appears to be of little value.^{1,3}

Statistically insignificant decreases in BMD may be related to testing variance. On the other hand, marked decreases in BMD warrant consideration of secondary causes of bone loss and evaluation of medication adherence.^{1,3}

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‡ Alendronate, risedronate, and zoledronic acid are approved for the treatment of glucocorticoid-induced osteoporosis.¹⁸

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