Prevention of osteoporosis-related fractures among postmenopausal women and older men

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The case

A 73-year-old woman with controlled hypertension sees you for a routine visit. Five months ago, she broke her humerus after tripping over a bag of groceries. She has completely recovered. Although she fell 4 times in the last year, this was her first fracture. She does not smoke, drinks alcohol occasionally and enjoys line-dancing twice weekly. Her medications include a calcium-channel blocker and a thiazide diuretic. She has never taken corticosteroids. Her weight is 67 kg, height 165 cm and body mass index 25. Her blood pressure is 135/80 mm Hg, with no evidence of orthostatic drop. Measurement of bone mineral density with the use of dual-energy x-ray absorptiometry reveals T scores of –2.2 at the lumbar spine and –2.1 at the femoral neck. What would your approach be to the management of this patient?

Key points

- Assessment of a patient's absolute risk of osteoporosis-related fractures, based on his or her clinical risk factors and bone mineral density, should guide management.
- The presence of a fragility fracture increases the risk of further fractures and should be considered in the assessment.
- Lifestyle modification and pharmacologic therapy should be determined on an individual basis to enhance adherence to the treatment plan.

Osteoporosis is a common disorder characterized by deterioration of bone microarchitecture, skeletal fragility and increased risk of fracture.[1] The prevalence of osteoporosis increases with age, from 6% at 50 years to 50% after the age of 80.[2] An estimated 50% of women and 20% of men over the age of 50 will have an osteoporosis-related fracture.[1] Osteoporosis is responsible for lasting disability, impaired quality of life and increased mortality.[1,3] Individuals who have an osteoporosis-related fracture are at high risk of recurrent fractures.[4–6]

In this review, we will address the approach to managing osteoporosis in postmenopausal women and older men. Although the prevention of falls should not be ignored, its evaluation is beyond the scope of this article and we refer readers to recent systematic reviews.[7,8]

How should osteoporosis be diagnosed?

Osteoporosis may be diagnosed in postmenopausal women and in men aged 50 years and older if the measurement of bone mineral density in the lumbar spine, total hip or femoral neck is at least 2.5 standard deviations below that of a young control (T score –2.5 or less).[9] Each decrease in standard deviation is associated with a 2-fold increase in the relative risk of osteoporosis-related fractures.[1]

The measurement of bone mineral density, however, identifies only a small component of the risk of fracture.[10] There is an emerging consensus based on results from clinical trials and observational studies that individuals at high risk of osteoporosis-related fractures are best identified through an assessment of clinical risk factors in addition to measurement of bone mineral density.[6,11–14] Risk factors include smoking, excessive alcohol intake, low body mass index, glucocorticosteroid use, rheumatoid arthritis, previous fragility fracture and a parental history of hip fracture.[11] Siminoski and colleagues developed a tool that combines a patient's age, sex, bone mineral density, prevalence of low-trauma fractures and use of corticosteroids to predict his or her 10-year absolute risk of any osteoporosis-related fracture (Table 1).[15] Three categories of risk are assigned for each sex: low (< 10% absolute risk), moderate (10%–20%) and high (> 20%). Other tools for assessing risk of fracture use similar approaches.[16,17] The WHO developed the Fracture Risk Assessment Tool (FRAX; www.shef.ac.uk/FRAX). This tool is based on individual patient models that integrate the risks associated with clinical risk factors as well as bone mineral density at the femoral neck (Table 1).[17] Both the FRAX tool and the one proposed by Siminoski and colleagues have been validated in clinical cohorts.[11,18] In the hypothetical case at the beginning of the article, the patient's age, her recent fragility fracture and her bone mineral density all point to her being at high risk of recurrent fracture (10-year absolute risk > 20%).

Some experts recommend that a limited workup be done to exclude secondary causes of osteoporosis such as multiple myeloma, endocrine disorders (hyperthyroidism, hyperparathyroidism, hypercortisolism), liver disorders and malabsorption

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syndromes. Such a workup may include a complete blood count, measurement of serum calcium, total alkaline phosphatase, serum creatinine and liver transaminase levels and serum protein electrophoresis.[19,20] In the FIT study (Fracture Intervention Trial), the prevalence of abnormal laboratory test results among women with osteoporosis was similar to that among women without the condition except for a low level of thyroid stimulating hormone (< 0.5 UI/mL);[21] therefore, measuring the thyroid stimulating hormone level may be informative in women. Because the prevalence of vitamin D insufficiency is increased in older individuals, serum 25-hydroxy-vitamin D levels should be measured in patients with low dietary intake of vitamin D and poor exposure to sunlight.[22]

How should osteoporosis be managed?

We searched MEDLINE and the Cochrane Database of Systematic Reviews for articles published from 1997 to January 2008. We identified studies that focused on the treatment of osteoporosis in postmenopausal women and in men over the age of 50 years. We further identified additional studies by searching the website of the Canadian Agency for Drugs and Technologies in Health and performed a manual search of reference lists of studies identified through MEDLINE. We limited our search to meta-analyses, systematic reviews and most recent randomized trials conducted in English. A complete description of our methods can be found in Appendix 1 (available at www.cmaj.ca/cgi/content/full/cmaj.080709/DC1).

General recommendations

The primary goal of treatment is to reduce the risk of fracture through lifestyle modification and proven pharmacologic interventions (Box 1). Based on economic models, clinical guidelines recommend treating individuals at high risk of fractures, such as those with a prior low-trauma fracture.[25,26] Although 90% of fractures are related to falls, evidence that programs for the prevention of falls are effective in reducing the number of falls and fall-related injuries is limited.[7,27,28] Pharmacologic therapies should be considered in people at high risk of fractures, such as those with a 10-year absolute risk above 20% for any osteoporotic fracture or a 10-year probability of hip fracture of 3%.[19,25,29,30] Patients found to be at moderate risk might also benefit from pharmacologic therapy. Specific decisions about treatment should be made on an individual basis.

Box 1: General recommendations for the maintenance of musculoskeletal health in postmenopausal women and older men

- Weight-bearing exercise that includes impact (e.g., walking, jogging or aerobics): 30 minutes, 3 times weekly
- Adequate calcium intake: 1200–1500 mg/d[20,23,24]
- Adequate vitamin D intake: ≥ 800 IU/d[20,23,24]
- Smoking cessation
- Moderate alcohol intake: < 3 drinks per day*

*One drink is equivalent to 285 mL of beer, 120 mL of wine or 30 mL of spirits.[17]

Lifestyle modification

Bone responds to dynamic loading. Both observational and clinical trials of exercise therapy have documented that regimens of moderate weight-bearing exercise in adulthood have a small but beneficial effect on bone strength.[31,32]

Individuals who smoke should be encouraged to quit. Alcohol intake in excess of 3 drinks per day is detrimental to bone health and should be discouraged.[19,20,30]

Table 1: Risk factors assessed by 2 tools available for the evaluation of a patient's 10-year absolute risk of osteoporosis-related fracture*

Risk factor assessed	Tool developed by Siminoski et al[15]	Fracture Risk Assessment Tool (FRAX)†
Sex	Yes	Yes
Age, yr	50–85	40–90
Body mass index	No	Yes
Measurement of bone mineral density	Lowest T score	T score for femoral neck
Prevalent fractures	After age 40	No age cut-off
Use of corticosteroids	≥ 3 mo in last year	Current use, or > 3 mo at dose of ≥ 5 mg/d of prednisolone or equivalent
Alcohol intake (> 3 drinks daily‡)	No	Yes
Parent with fractured hip	No	Yes
Current smoking	No	Yes
Presence of rheumatoid arthritis	No	Yes
Secondary osteoporosis	No	Yes

*Both tools predict the 10-year absolute risk of major osteoporotic fractures for individuals who are not receiving pharmacologic therapy.
†Tool developed by the World Health Association.[17]
‡One drink is equivalent to 285 mL of beer, 120 mL of wine or 30 mL of spirits.

Calcium and vitamin D supplementation

Vitamin D and calcium play an essential role in the regulation of calcium and overall bone health.[33] Several meta-analyses have examined the effect of various doses of calcium and vitamin D, alone or in combination, on bone mineral density and fractures among postmenopausal women and elderly men.[23,24,34–37] Most of them suggest that calcium and vitamin D should be given in combination for optimal results.[24] The largest meta-analysis included 29 randomized controlled trials (total 63 897 men and women over age 50) and evaluated the effects of calcium alone or in combination with vitamin D on fracture outcomes.[23] Calcium and vitamin D in combination were associated with a risk reduction of 12% in fractures at any site (risk ratio 0.88, 95% confidence interval [CI] 0.83–0.95). The reduction in risk was greatest among elderly individuals

who were most adherent to therapy and among those who received at least 1200 mg of calcium and 800 IU of vitamin D daily (number needed to treat = 53). The effect of supplemental vitamin D, with or without calcium, on the risk of falls was found to be marginally beneficial in elderly populations (odds ratio [OR] 0.89, 95% CI 0.80–0.99).[24,38,39]

Pharmacologic therapy

The choice of pharmacologic therapy should be based on an individualized assessment of the patient's risk factors and preferences. Agents considered as first-line therapy are those whose efficacy in preventing fractures has clearly been documented (Table 2).

Bisphosphonates

Bisphosphonates are pyrophosphate analogues with a high affinity to bone mineral surfaces.[40] Through inhibition of osteoclastic activity, they reduce bone remodelling, improve bone mineral density and are associated with reduced rates of fracture among women and men, although less well documented in the latter group.[41] Alendronate (70 mg once weekly) and risedronate (typically 35 mg once weekly) are the most commonly used bisphosphonates worldwide. The most important benefit of bisphosphonates lies in the prevention of vertebral, nonvertebral and hip fractures in people who have low bone mineral density (T score −2.5 or lower) or prevalent fractures, or both.[41–43]

One recent meta-analysis evaluated the effect of cyclical etidronate therapy (400 mg/d for 2 weeks followed by calcium carbonate daily for 10 weeks; this cycle is repeated continuously) on the prevention of fractures.[42,44] Eleven studies were included in the review (total 1248 postmenopausal women). Among women at high risk, cyclical etidronate therapy was associated with a risk reduction of 47% in vertebral fractures compared with placebo (pooled relative risk [RR] 0.53, 95% CI 0.32–0.87; number needed to treat ranged from 167 to 19 across the range of fracture risk [whether women were at low or high risk of fractures based on bone mineral density and the presence of clinical risk factors] for 5 years of treatment). There was no significant reduction in nonvertebral or hip fractures.

Meta-analyses of the effect of alendronate for the prevention of fractures are numerous, the results of which are similar to those of a recent Cochrane analysis.[45–48] The Cochrane review included 11 trials in which participants (total 12 068 women with postmenopausal osteoporosis) were randomly assigned to receive either alendronate (10 mg/d) or placebo.[48] Alendronate was associated with significant reductions in vertebral fractures (RR 0.55, 95% CI 0.43–0.69; number needed to treat = 200 to 20 across the range of fracture risk for 5 years of treatment), nonvertebral fractures (RR 0.84, 95% CI 0.74–0.94; number needed to treat = 50 to 16), wrist fractures (RR 0.50, 95% CI 0.34–0.73) and hip fractures (RR 0.47, 95% CI 0.26–0.85; number needed to treat = 500 to 22). When used in women at low risk of fractures (participants with a low bone mineral density but no prevalent fragility fractures), only the risk of vertebral fractures was found to be reduced (RR 0.55, 95% CI 0.45–0.69), although the absolute risk of fracture in this population is low.

Seven trials (total 14 049 postmenopausal women) were included in a meta-analysis evaluating the effect of risedronate relative to placebo.[49] Participants at high risk of fractures who were given risedronate (5 mg/d) experienced significant risk reductions in vertebral fractures (RR 0.61, 95% CI 0.50–0.76; number needed to treat = 214 to 23 across the range of fracture risk for 5 years of treatment), nonvertebral fractures (RR 0.80, 95% CI 0.72–0.90; number needed to treat = 58 to 18) and hip fractures (RR 0.74, 0.59–0.94; number needed to treat = 962 to 44). Risk estimates among women at low risk of fractures showed no statistically significant effect of risedronate on fractures. Other systematic reviews reached similar conclusions.[41,50]

We identified 2 large clinical trials that compared yearly infusion of 5 mg of zoledronic acid with placebo: one involved postmenopausal women at high risk of fractures[51] and the other, women and men with a recent hip fracture.[52] The use of zoledronic acid was associated with a risk reduction in vertebral fractures (RR 0.30, 95% CI 0.24–0.38; number needed to treat = 14) and nonvertebral fractures (RR 0.75, 95% CI 0.64–0.87; number needed to treat = 38). The risk of hip fracture was decreased in both trials, although the difference was statistically significant only in the first trial (hazard ratio 0.59, 95% CI 0.42–0.83; number needed to treat = 98).[51] Surprisingly, zoledronic acid was also found to decrease mortality by 28% compared with placebo in the study involving patients with a recent hip fracture (number needed to treat = 29).[52]

We were unable to find a meta-analysis of ibandronate. In a randomized trial involving 2946 postmenopausal women, ibandronate (2.5 mg/d) was associated with a relative risk

Table 2: Effect of pharmacologic therapy compared with placebo on risk of fracture among postmenopausal women

Drug	Effect of therapy on risk of fracture (level of evidence*)		
	Vertebral fracture	Nonvertebral fracture	Hip fracture
Bisphosphonate			
Etidronate	Reduced (1a)	No effect (1a)	No effect (1a)
Alendronate	Reduced (1a)	Reduced (1a)	Reduced (1a)
Risedronate	Reduced (1a)	Reduced (1a)	Reduced (1a)
Zoledronic acid	Reduced (1a)	Reduced (1b)	Reduced (1b)
Raloxifene	Reduced (1a)	No effect (1a)	No effect (1a)
Calcitonin	Reduced (1a)	No effect (1b)	–
Teriparatide	Reduced (1a)	Reduced (1a)	No effect (1b)

*Levels of evidence, as defined by the Oxford Centre for Evidence-based Medicine (www.cebm.net), are as follows: 1a = evidence from systematic reviews with homogeneity of randomized control trials; level 1b = evidence from randomized clinical trials.

reduction of 50% to 60% in vertebral fractures after 3 years of treatment (number needed to treat = 20). However, the incidence of nonvertebral fractures was similar between the treatment and control groups.[53,54]

The evaluation of oral bisphosphonate therapy in men is sparse. A meta-analysis of alendronate identified 2 trials that included 375 men.[55] Treatment with alendronate reduced the risk of vertebral fractures (OR 0.44, 95% CI 0.23–0.83). However, there was no evidence of effect on other types of fracture.

The most common adverse events reported with the use of oral bisphosphonate therapy are related to gastrointestinal intolerance, reported in up to 10% of trial participants.[42] This often disappears with optimal adherence to the dosing regimen.[56] There are occasional reports of esophageal ulceration and bone pain.[41] Osteonecrosis of the jaw has been reported primarily in patients with cancer who received large cumulative doses of bisphosphonates intravenously. The incidence of this condition is estimated to be less than 1 in 100 000 person-treatment years among patients who receive oral bisphosphonate therapy.[57] Flu-like symptoms, reported in up to 10% of patients following infusion of zoledronic acid, are most prominent after the initial dose and are usually self-limited.[51] In one trial, the incidence of atrial fibrillation was reported to be higher among the participants given zoledronic acid than among those given placebo (1.3% v. 0.5%; number needed to harm = 125).[51] Reanalysis of the data for 6459 women enrolled in the alendronate trials documented a trend toward an increased risk of atrial fibrillation.[58] Karam and colleagues examined data for 15 000 individuals enrolled in 3 clinical trials of risedronate.[59] They found no increase in the incidence of atrial fibrillation. Observational studies of large administrative databases have resulted in conflicting data.[60,61] The American Food and Drug Administration (FDA) recently reviewed data for 19 687 patients given bisphosphonate therapy and 18 358 given placebo who had been monitored in trials for 6 months to 3 years.[62] The occurrence of atrial fibrillation was rare in each study, with most studies reporting 2 or fewer events. Across all of the studies, no clear association between overall exposure to bisphosphonates and the rate of serious or nonserious atrial fibrillation was observed. In addition, increasing the dose or duration of bisphosphonate therapy was not associated with an increased rate of atrial fibrillation. Health care professionals should not alter their prescribing patterns for bisphosphonates. Patients should not stop taking their bisphosphonate medication.

Raloxifene

Raloxifene, a selective estrogen-receptor modulator, has estrogenic activity in some tissues (e.g., bone) and antagonist effects in others (e.g., breast).[63] Daily use of raloxifene (60 mg/d) increases bone mineral density and has been shown to diminish the risk of estrogen-receptor–positive invasive breast cancer by 55% to 90%.[64] In a meta-analysis of 7 trials in which postmenopausal women were given raloxifene or placebo, raloxifene was associated with a risk reduction in vertebral fractures (RR 0.60, 95% CI 0.50–0.70; number needed to treat = 2381 to 99 across the range of fracture risk for 2 years of treatment).[65] There was little effect of raloxifene on the risk of other fractures. The RUTH (Raloxifene Use for The Heart) study, involving postmenopausal women at high risk of cardiovascular disease, showed that raloxifene had no effect on the risk of cardiovascular death, coronary artery disease or stroke.[66] Raloxifene, like estrogen, is associated with an increased risk of venous thromboembolism (OR 2.08, 95% CI 1.47–3.02).[41] In practice, raloxifene is generally well tolerated, with transient occurrence of hot flashes and leg cramps in less than 10% of patients.[65]

Calcitonin

Calcitonin, a peptide secreted by the C cells of the thyroid, inhibits osteoclastic function. In a meta-analysis, nasal calcitonin therapy was shown to reduce the risk of vertebral fractures among postmenopausal women at high risk of osteoporotic fractures (RR 0.46, 95% CI 0.25–0.87).[67] The effect size in the largest trial was more modest (RR 0.79, 95% CI 0.62–1.00) than that reported in 3 smaller trials, which raises concerns about publication bias.[68] Calcitonin has not been shown to reduce the risk of fractures at other sites. In men, one study documented a small reduction in the risk of vertebral fracture after 1 year of therapy.[69] A meta-analysis of 5 trials involving 246 patients documented an analgesic effect of calcitonin for acute pain of recent vertebral compression fracture within 1 week after starting therapy (weighted mean difference compared with placebo 3.08, 95% CI 2.64–3.52).[70] Calcitonin is available as a nasal spray of 200 IU/d, and is well tolerated.

Teriparatide

Teriparatide, a synthetic recombinant hormone consisting of the first 34 amino acids of the human parathyroid hormone, has anabolic properties through its effect on bone formation.[71] It is injected subcutaneously daily (20 μg). Two systematic reviews have documented the effect of teriparatide compared with placebo on the risk of fractures among postmenopausal women.[72,73] Cranney and colleagues reported a risk reduction in vertebral fractures (RR 0.35, 95% CI 0.22–0.55; number needed to treat = 11 for 21 months of treatment) and nonvertebral fractures (RR 0.65, 95% CI 0.43–0.98; number needed to treat = 29) with teriparatide therapy.[72] Vestergaard and colleagues pooled results of studies of different preparations of parathyroid hormone and found a positive effect on fracture risk.[73] We found no data for men. Adverse events most commonly noted with the use of teriparatide included pain at the injection site, nausea, headache (in 3% of patients), leg cramps (in 2%–8%) and mild hypercalcemia (in 10%), which responds to a reduction in calcium intake.[74] The cost of teriparatide is several fold higher than that of other therapies.

Hip protectors

Hip protectors are padded undergarments designed to decrease the impact of a fall.[75] Two meta-analyses documented a relative risk reduction in hip fractures of 23% to 60%, depending on the study methodology, among residents in nursing homes.[76,77] No effect was observed among elderly people living in the community. A recent trial was unable to demonstrate a benefit in reducing the risk of hip fractures

among nursing home residents.[75] Although not associated with adverse events, the use of hip protectors incurs additional labour expenditures and is often met with modest adherence.[78] The efficacy of hip protectors appears unconfirmed, in particular among people living in the community.

Gaps in knowledge

Data on the efficacy of pharmacologic and nonpharmacologic strategies to prevent osteoporosis-related fractures are lacking for men and frail elderly people, in particular those in long-term care institutions. Head-to-head efficacy trials of agents are also lacking. Additional investigations are warranted to better understand the modifiers of vitamin D effect, to delineate optimal duration of antiresorptive therapy and to develop agents that enhance bone formation. Also, interdisciplinary collaboration and research are needed to study exercise in combination with pharmacologic therapy, effective strategies to prevent falls and the effect of multifaceted interventions on clinical outcomes.

The case revisited

The physician assesses the patient's risk factors for fracture and prescribes oral bisphosphonate therapy with alendronate (70 mg once weekly). He recommends adequate supplementation with calcium (≥ 1200 mg/d) and vitamin D (≥ 800 IU/d) and an increase in the frequency of weight-bearing physical activity. There is currently no evidence to support the use of hip protectors outside the nursing home setting. He discusses the importance of adherence to therapy on fracture outcomes with the patient and asks her to return for a follow-up visit in 3 to 6 months to evaluate tolerance and adherence to the alendronate therapy.

The physician makes a note in the patient's file to measure her bone mineral density again in 2 years. If it continues to decrease, he will investigate causes of bone loss, including nonadherence to therapy, malabsorption of the medication, and secondary causes of osteoporosis. He will consider referring the patient to a specialist if the patient has a serious intolerance or contraindication to oral drug therapies, if there is progressive bone loss despite therapy or if there are recurrent fractures.[20,79]

Conclusion

Pharmacologic agents for the treatment of osteoporosis are effective in preventing fractures in postmenopausal women and elderly men at high risk (10-year absolute risk of any osteoporosis-related fracture > 20%). All of the proposed interventions are cost-effective compared with no treatment in postmenopausal women. However, the gains associated with each intervention are strongly related to the age of the patient, the presence of fracture and the agent used.[26] Practice guidelines recommend pharmacologic intervention in men and women who have had a fragility fracture and whose T score is −1.5 or lower.[20,29] Oral bisphosphonate therapy would be considered first-line therapy in the management of osteoporosis. Because not all agents are covered by drug benefit formularies, clinicians should determine which ones are covered in their own setting. Measurement of bone mineral density should be repeated 2 years after initiating treatment to monitor the effectiveness of treatment.[20,80]

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