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# Osteoporosis in Menopause

This clinical practice guideline has been prepared by the Menopause and Osteoporosis Working Group, reviewed by the Clinical Practice Gynaecology and Family Physician Advisory Committees, and approved by the Executive and Council of the Society of Obstetricians and Gynaecologists of Canada.

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**Key Words**: Osteoporosis, prevention, treatment, diagnosis, bone mineral density, dual energy x-ray absorptiometry, bone turnover markers, vertebral fractures, fragility fractures, antiresorptive, hormone therapy, selective estrogen-receptor modulator, bisphosphonates, calcitonin, anabolic, bone forming agent

## Abstract

**Objective:** To provide guidelines for the health care provider on the prevention, diagnosis, and clinical management of postmenopausal osteoporosis.

**Outcomes:** Strategies for identifying and evaluating high-risk individuals, the use of bone mineral density (BMD) and bone turnover markers in assessing diagnosis and response to management, and recommendations regarding nutrition, physical activity, and the selection of pharmacologic therapy to prevent and manage osteoporosis.

**Evidence:** Published literature was retrieved through searches of PubMed and The Cochrane Library on August 30 and September 18, 2012, respectively. The strategy included the use of appropriate controlled vocabulary (e.g., oteoporosis, bone density, menopause) and key words (e.g., bone health, bone loss, BMD). Results were restricted to systematic reviews, practice guidelines, randomized and controlled clinical trials, and observational studies published in English or French. The search was limited to the publication years 2009 and following, and updates were incorporated into the guideline to March 2013. Grey (unpublished) literature was identified through searching the websites of health technology assessment and health technology assessment-related agencies, clinical practice guideline collections, clinical trial registries, and national and international medical specialty societies.

**Values:** The quality of the evidence was rated using the criteria described by the Canadian Task Force on Preventive Health Care (Table 1).

**Sponsors:** The Society of Obstetricians and Gynaecologists of Canada.

### RECOMMENDATIONS

#### For Postmenopausal Women

1.  Health care providers should be aware that the goals of osteoporosis management include assessment of fracture risk and prevention of fracture. (I-A)

2.  Health care providers should understand that a stable or increasing bone mineral density reflects a response to therapy in the absence of low-trauma fracture or height loss due to vertebral-compression fracture. A progressive decrease in bone mineral density, with the magnitude of bone loss being greater than the precision error of the density assessment, indicates a lack of response to current therapy. Management should be reviewed and modified appropriately. (I-A)

**Table 1. Key to evidence statements and grading of recommendations, using the ranking of the Canadian Task Force on Preventive Health Care**

| Quality of evidence assessment* | Classification of recommendations† |
|---|---|
| I: Evidence obtained from at least one properly randomized controlled trial | A. There is good evidence to recommend the clinical preventive action |
| II-1: Evidence from well-designed controlled trials without randomization | B. There is fair evidence to recommend the clinical preventive action |
| II-2: Evidence from well-designed cohort (prospective or retrospective) or case–control studies, preferably from more than one centre or research group | C. The existing evidence is conflicting and does not allow to make a recommendation for or against use of the clinical preventive action; however, other factors may influence decision-making |
| II-3: Evidence obtained from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of treatment with penicillin in the 1940s) could also be included in this category | D. There is fair evidence to recommend against the clinical preventive action |
|  | E. There is good evidence to recommend against the clinical preventive action |
| III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees | L. There is insufficient evidence (in quantity or quality) to make a recommendation; however, other factors may influence decision-making |

*The quality of evidence reported in these guidelines has been adapted from The Evaluation of Evidence criteria described in the Canadian Task Force on Preventive Health Care.[89]

†Recommendations included in these guidelines have been adapted from the Classification of Recommendations criteria described in the Canadian Task Force on Preventive Health Care.[89]

3. Health care providers should identify the absolute fracture risk by integrating the key risk factors for fracture; namely, age, bone mineral density, prior fracture, and glucocorticoid use. These risk factors allow estimation of fracture risk using the tool of the Canadian Association of Radiologists and Osteoporosis Canada. (I-A)

4. The Fracture Risk Assessment tool of the World Health Organization (FRAX) has now been validated in a Canadian population and may also be used and incorporates additional risk factors; namely, low body mass index, parental history of fracture, smoking status, alcohol intake, and the presence of secondary causes of osteoporosis. (I-A)

5. Health care providers should be aware that a fragility fracture markedly increases the risk of a future fracture and confirms the diagnosis of osteoporosis irrespective of the results of the bone density assessment, (I-A) and that the presence of a low-trauma fracture of a vertebra or hip or more than 1 fragility fracture confirms a high fracture risk regardless of the bone mineral density. (I-A)

6. Treatment should be initiated according to the results of the 10-year absolute fracture risk assessment. (I-A)

## ABBREVIATIONS

| | |
|---|---|
| AFF | atypical femoral fracture |
| BMD | bone mineral density |
| ET | estrogen therapy |
| FIT | Fracture Intervention Trial |
| HR | hazard ratio |
| HT | hormone therapy |
| ONJ | osteonecrosis of the jaw |
| RANKL | receptor activator of nuclear factor kappa-B ligand |
| RCT | randomized controlled trial |
| SERM | selective estrogen-receptor modulator |
| WHI | Women's Health Initiative |

### Calcium and Vitamin D

7. Adequate calcium and vitamin D supplementation is key to ensuring prevention of progressive bone loss. For postmenopausal women a total daily intake of 1200 mg of elemental calcium from dietary and supplemental sources and daily supplementation with 800 to 2000 IU of vitamin D are recommended. Calcium and vitamin D supplementation alone is insufficient to prevent fracture in those with osteoporosis; however, it is an important adjunct to pharmacologic intervention with antiresorptive and anabolic therapy. (I-B)

### Hormone Therapy

8. Hormone therapy should be prescribed for symptomatic postmenopausal women as the most effective option for menopausal symptom relief. (I-A) It represents a reasonable choice for the prevention of bone loss and fracture in this patient population. (I-A)

9. Physicians may recommend low- and ultralow-dosage estrogen therapy to symptomatic women for relief of menopausal symptoms (I-A) but should inform their patients that, despite the fact that such therapy has demonstrated a beneficial effect in osteoporosis prevention, (I-A) no data are yet available on reduction of fracture risk.

### Bisphosphonates

10. Alendronate, risedronate, and zoledronic acid are valuable first-line agents of choice in the treatment of postmenopausal osteoporosis and should be considered to decrease the risk of vertebral, non-vertebral, and hip fractures. (I-A)

11. Etidronate is a weak antiresorptive agent and is not recommended as a first-line agent of choice for the treatment of osteoporosis. (I-D)

### RANKL Inhibitor

12. Denosumab is an effective antiresorptive agent, shown to reduce the risk of vertebral, non-vertebral, and hip fractures, (I-A) and should be considered as a first-line agent of choice in the treatment of postmenopausal osteoporosis in women at a high fracture risk. (I-A)

### Selective Estrogen-Receptor Modulators

13. Treatment with raloxifene may be considered to decrease the risk of vertebral fractures, bearing in mind that this agent has not been shown to be effective in reducing the risk of non-vertebral or hip fractures. (I-A)

### Parathyroid Hormone

14. Treatment with teriparatide should be considered to decrease the risk of vertebral and non-vertebral fractures in postmenopausal women with severe osteoporosis (I-A) and should also be considered in postmenopausal women experiencing bone loss or a new fracture despite antiresorptive therapy. (I-A)

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## INTRODUCTION

Osteoporosis is defined as an impairment in bone strength due to an abnormal quantity and/or quality of bone. Quantity is evaluated by measuring BMD. Quality is affected by many factors, including the degree of mineralization, the rate of bone remodelling, the connectivity of the bony trabeculae, the quality of the collagen fibres, and the health of the bone cells. The 3 types of bone cells are osteoblasts, osteoclasts, and osteocytes. The osteocytes function as "mechanostats", sensing the degree of microdamage and triggering remodelling in areas of stress and strain, thus allowing continual renewal, repair, and replacement of bone. This process of remodelling maintains bone strength.

Adequate calcium and vitamin D intake is necessary to attain and maintain normal bone quantity and quality and thus achieve optimal bone strength. Early assessment of skeletal health and then initiation of appropriate calcium and vitamin D supplementation and an exercise program are essential in the prevention and treatment of osteoporosis. Individuals at increased risk for fracture should also be offered pharmacologic therapy in order to reduce the fracture risk. Absolute fracture risk is identified by integrating age and BMD with other key risk factors for fracture including prior fracture history and use of glucocorticoid therapy. The decision to treat is based on the risk of fracture, and the quantification of absolute fracture risk enables targeting of treatment to those at greatest risk.

## RISK ASSESSMENT AND MANAGEMENT

Bone strength is determined by both bone quantity and bone quality. Bone densitometry provides information on BMD, which is a reflection of bone quantity. Bone quality is determined by a number of factors, including the rate of remodelling, bone mineralization, function of the bone cells, and quality of the collagen fibres. It is necessary to identify risk factors for fracture that may be present and the risk of falls. The timed "get up and go" test is valuable in assessing gait stability and is a reflection of fall risk. Risk factors for osteoporosis have been identified (Table 2),[1] and the presence of risk factors in a postmenopausal woman justifies bone densitometry.[2]

In 2005 Osteoporosis Canada recommended identifying absolute fracture risk by integrating the key risk factors for fracture; namely, age, BMD, prior fracture, and glucocorticoid use.[3] The 10-year risk of fragility fractures is thus determined (Figure)[1] and defined as high if it is greater than 20%, moderate if it is 10% to 20%, and low if it is less than 10%.[4] The additional effect of a pre-existing fragility fracture or glucocorticoid use moves the patient 1 risk category higher. These guidelines were based on Swedish data and have been recalibrated using Canadian hip fracture data. The version developed by the Canadian Association of Radiologists and Osteoporosis Canada[4] has now been validated in 2 Canadian cohorts and has close to 90% agreement with the FRAX[5] score (the FRAX tool can be downloaded from the Osteoporosis Canada website, http://www.osteoporosis.ca). The presence of a vertebral or hip fracture or more than 1 fragility fracture increases the fracture risk to high. Fracture risk is evaluated on the basis of femoral neck BMD and age and is modified by the presence of prior fragility fracture or the use of glucocorticoid therapy (7.5 mg for 3 months or longer); these modifiers increase the fracture risk to the next risk category.[1] A BMD T-score of −2.5 or less at either the lumbar spine or the femoral neck denotes at least a moderate risk of fracture.[1] Height should be measured annually, and a decrease in measured height of more than 2 cm should be further evaluated by radiographs of the thoracic and lumbar spine with exclusion of vertebral fractures.[6]

A more comprehensive calculation of the 10-year absolute fracture risk, now available from the World Health Organization, incorporates additional risk factors: parental history of hip fracture, current tobacco smoking, rheumatoid arthritis or other secondary causes of bone loss, and alcohol intake of 3 or more units daily.[5]

It is recommended that absolute fracture risk be calculated using the tool of either the Canadian Association of Radiologists and Osteoporosis Canada or FRAX and the decision to treat be based on the absolute fracture risk. Younger individuals at a low risk of fracture are appropriately managed with lifestyle changes and strategies designed to prevent bone loss.

Osteoporosis is diagnosed in a postmenopausal woman on the basis of a BMD T-score of less than −2.5 at the

**Table 2. Risk factors for osteoporosis: indications for measuring BMD**

| Older adults (age ≥ 50 years) | Younger adults (age < 50 years) |
|---|---|
| Age ≥ 65 years (both women and men) | Fragility fracture |
| Clinical risk factors for fracture (menopausal women and men age 50 to 64 years) | Prolonged use of glucocorticoids* |
|     Fragility fracture after age 40 years | Use of other high-risk medications† |
|     Prolonged use of glucocorticoids* | Hypogonadism or premature menopause (age < 45 years) |
|     Use of other high-risk medications | Malabsorption syndrome |
|     Parental hip fracture | Primary hyperparathyroidism |
|     Vertebral fracture or osteopenia identified on radiography | Other disorders strongly associated with rapid bone loss and/or fracture |
|     Current smoking | |
|     High alcohol intake | |
|     Low body weight (< 60 kg) or major weight loss (> 10% of body weight at age 25 years) | |
|     Rheumatoid arthritis | |
|     Other disorders strongly associated with osteoporosis | |

*At least 3 months' cumulative therapy in the previous year at a prednisone-equivalent dose ≥ 7.5 mg daily.

†For example, aromatase inhibitors or androgen deprivation therapy.

Reproduced with permission of the Canadian Medical Association from Papaioannou A et al.[1]

lumbar spine, hip (femoral neck or total hip), or radius (distal third). Clinically it is diagnosed in a postmenopausal woman in the presence of a low-trauma fracture. In a premenopausal woman osteoporosis is diagnosed only in the presence of fragility fractures; BMD alone cannot be used for diagnosis.[7] In premenopausal women a normal BMD is defined as being within 2 standard deviations of the age-matched reference mean. Comparison with the age-matched reference range is represented by the Z score, and in premenopausal women Z scores should be used instead of T scores. Low bone density is defined as a BMD Z score 2 or more standard deviations below the mean age-matched reference value.[7]

Pharmacologic therapy is considered in postmenopausal women after exclusion of secondary causes of low bone density. If the 10-year absolute fracture risk is greater than 20% (high), then drug therapy is advised. In those with a moderate risk (10% to 20%), management decisions are individualized. Those with a low fracture risk (< 10%) can be treated conservatively after exclusion of secondary causes of bone loss with prevention strategies based on ensuring adequate calcium and vitamin D supplementation. It is also important to emphasize regular exercise and reduced consumption of alcohol (fewer than 2 drinks/d) and coffee (fewer than 4 cups/d). Smoking cessation should also be strongly advised.

Failure of therapy is confirmed by the development of a low-trauma fracture or significant bone loss despite pharmacologic therapy for 2 years. In these individuals it is necessary to ensure that there are no secondary causes of bone loss. It is also important to ensure adequate adherence to therapy.[8]

## ADVANCES IN PHARMACOLOGIC THERAPY

In addition to adequate calcium, vitamin D, and exercise, options for the prevention and treatment of osteoporosis include antiresorptive and anabolic agents.[9]

Antiresorptive (anticatabolic) agents inhibit osteoclast activity and reduce bone turnover.[9,10] The various agents have different mechanisms of action. Bisphosphonates reduce the rate of bone turnover, providing a longer time for bone to mineralize. Bisphosphonate therapy is thus associated with modest increases in BMD. Estrogen acts through the estrogen receptors on both osteoblasts and osteoclasts, suppressing receptor activator of nuclear factor ϰB ligand (RANKL)-induced osteoclast differentiation and thereby decreasing bone remodeling.[11] Raloxifene, a SERM, can bind to estrogen receptors, with tissue-specific agonist or antagonist effects. Raloxifene decreases bone remodelling in addition to its extraskeletal effects. Osteoclastic bone resorption is also inhibited by calcitonin acting on calcitonin receptors. Denosumab is a monoclonal antibody

to RANKL (receptor activator of nuclear factor ϰB) and binds to RANKL, lowering values to premenopausal levels. This results in a decrease in the formation, function, and survival of osteoclasts.

Antiresorptive agents are effective in reducing fracture risk by approximately 30% to 68% in postmenopausal women. However, fractures may still occur, and anabolic therapy can complement antiresorptive therapy in the prevention of further fractures. Anabolic therapy can result in new bone formation, with increases in cortical thickness and trabecular connectivity, leading to major improvements in the quality and quantity of bone. Anabolic therapy can increase the production of new bone matrix by enhancing osteoblast function. Teriparatide (recombinant human parathyroid hormone, amino acid sequence 1 through 34) decreases the release of sclerostin from osteocytes. Sclerostin is a protein that decreases bone formation by inhibiting the Wnt signalling pathway in the osteoblast. With a decrease in this inhibitor of bone formation, there is an increase in new bone formation. Teriparatide, 20 μg daily, has been shown to reduce the risks of vertebral and non-vertebral fragility fractures by approximately 65% and 53%, respectively, over 18 months in postmenopausal women with osteoporosis.[12] Teriparatide is the only anabolic agent available in Canada.

## CALCIUM AND VITAMIN D SUPPLEMENTATION

The effectiveness of calcium and vitamin D supplementation in preventing hip fractures was evaluated in the WHI.[13] The trial involved 36 282 postmenopausal women who daily received either 1000 mg of elemental calcium as calcium carbonate and 400 IU of vitamin D, or a placebo, for an average of 7 years. Patients were allowed to take additional daily supplements of up to 1000 mg of calcium and 600 IU of vitamin D; approximately 38% of subjects took more than 1200 mg of elemental calcium daily. Personal use of bisphosphonates, calcitonin, SERMs, and ET was also permitted. The calcium and vitamin D study arm overlapped with the HT arm; thus, approximately 51% of women were receiving estrogen.

Treatment compliance was poor: by the end of the study, only 59% of the women were taking 80% or more of their supplements. As compared with those taking placebo, the women taking 1000 mg of calcium and 400 IU of vitamin D daily showed a 1.06% increase in hip BMD ($P < 0.01$). In the treatment-compliant group, the HR for hip fracture was 0.71 (95% CI 0.52 to 0.97), representing a statistically significant 29% reduction in hip fracture risk among the women taking 80% or more of their calcium and vitamin D supplements. Estrogen use was associated with a 42%

**Assessment of basal 10-year risk of fracture with the 2010 tool of the Canadian Association of Radiologist and Osteoporosis Canada.**
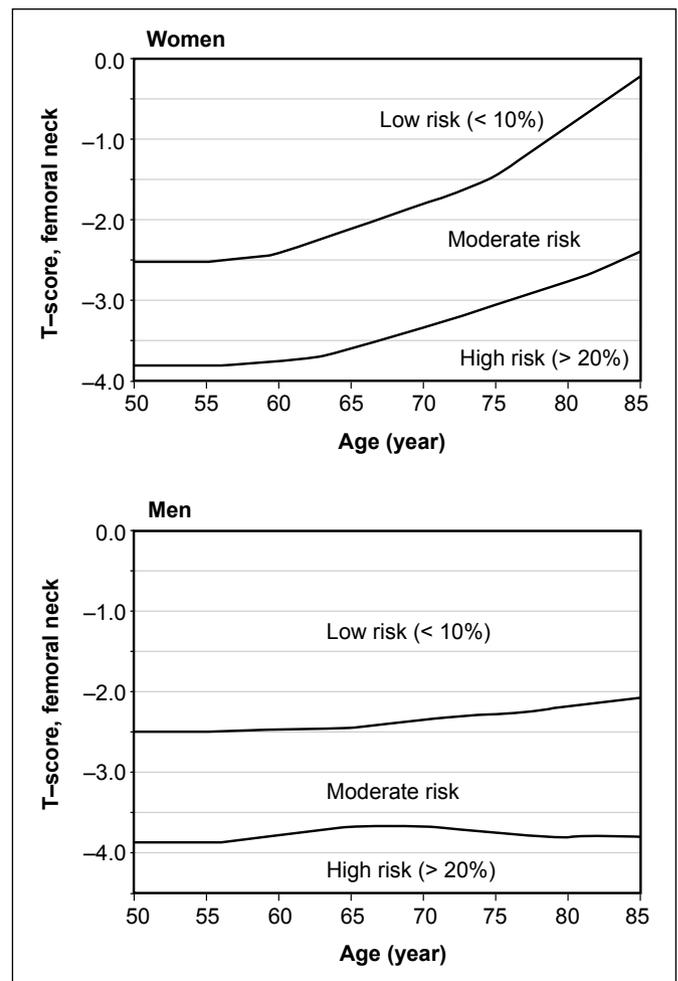


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The T-score for the femoral neck should be derived from the National Health and Nutrition Education Survey III reference database for white women. Fragility fracture after age 40 or recent prolonged use of systemic glucocorticoids increases the basal risk by one category (ie, from low to moderate or moderate to high). This model reflects the theoretical risk for a hypothetical patient who is treatment-naive; it cannot be used to determine risk reduction associated with therapy. Individuals with fragility fracture of a vertebra or hip and those with more than one fragility fracture are at high risk of an additional fracture.

reduction in hip fracture risk. A small but significant 17% increase in the risk of renal stones was noted in the treatment group as compared with the placebo group: the HR was 1.17 (95% CI 1.02 to 1.34). Inadequate blood levels of vitamin D were also noted in the WHI study and may have contributed to the findings. In the nested case–control study, the mean serum 25-hydroxy vitamin D level at baseline was 46.0 nmol/L in the women who had sustained hip fractures as compared with 48.4 nmol/L in their control subjects ($P = 0.17$). Vitamin D supplementation of more than 600 IU daily may have reduced the fracture risk, as has been demonstrated in other clinical trials.

Calcium supplements have been linked to a possible increase in the risk of cardiovascular events.[14] A recent 5-year RCT of 1200 mg of elemental calcium carbonate daily versus placebo in 1460 postmenopausal women did not demonstrate any difference in rates of death or hospitalization due to coronary events.[15] In the EPIC study of 23 980 people between the ages of 35 and 64 years followed for 11 years with questionnaires, those with a calcium-enriched diet had a lower risk of myocardial infarction (HR 0.69; 95% CI 0.5 to 0.94), whereas those using a calcium supplement had a higher risk (HR 1.86; 95% CI 1.17 to 2.96).[16]

Data from the WHI among those not using personal calcium or vitamin D supplements at baseline did not show an adverse effect of such supplementation on the risk of myocardial infarction, coronary heart disease, total heart disease, stroke, or overall cardiovascular disease.[17] These RCT data are the best evidence currently available and do not support an increased risk of coronary events with calcium and vitamin D supplementation.

It is recommended that the daily calcium requirement of 1200 mg be met ideally from dietary sources; if this is not possible, then supplements may be safely used. Calcium carbonate and calcium citrate are the supplements of choice.

Ensuring adequate vitamin D supplementation is a key component of the prevention and treatment of osteoporosis. Although it might not be sufficient as the sole means of therapy for osteoporosis, routine supplementation with calcium (1000 mg/d) and vitamin $D_3$ (800 to 2000 IU/d) is still recommended as a mandatory adjunct to the main pharmacologic agents (antiresorptive and anabolic drugs). Vitamin D in doses of 800 IU daily has been shown to be effective in reducing the risk of falls by 49% over a 12-week period of therapy.[18] Vitamin D supplementation at a dose of 10 000 IU once weekly has been suggested for women unable to take daily supplements in areas where

such a preparation is available. Doses of 100 000 IU of vitamin $D_3$ given orally every 4 months have been shown to be effective in reducing the risk of osteoporotic fractures.[19]

Vitamin D levels depend on a number of factors, including dietary intake, sun exposure, skin pigmentation, body mass index, and smoking status.[20] Extraskeletal benefits are currently being evaluated and may include a reduction in the risk of certain malignant diseases as well as autoimmune disorders.

## HORMONE THERAPY

Estrogen has significant antiresorptive effects. Specifically, it enhances the osteoblastic production of osteoprotegerin, which has antiosteoclastic properties because of its ability to bind to RANKL and subsequently to block the RANKL/RANK interaction required for osteoclast recruitment and activation.[21,22] Estrogen also decreases RANKL expression from the osteoblast. In the WHI, a primary prevention trial, the estrogen-only arm demonstrated a 30% to 39% reduction in fracture rates.[23] This trial therefore confirmed the anti-fracture effects of ET suggested by previous clinical trials.[24,25]

The combined estrogen/progestogen arm of the WHI had similar results: an increase in total hip BMD, together with a 34% reduction in hip and vertebral fractures and a 24% reduction in total osteoporotic fractures.[26] In early-postmenopausal women, the combined therapy resulted in increases in BMD of 2% to 3% at the hip and spine over 2 years of therapy.[24] A decline in the markers of bone turnover in response to HT was also seen in early-postmenopausal women.[25]

HT (with estrogen alone or combined with a progestogen) is still considered the most effective therapy for the medical management of menopausal symptoms. Bone protection with HT at a usual dosage is considered an added benefit. Recent studies designed to test various dosages of estrogen for bone protection have shown a linear dose response of the skeleton from the lowest to the highest dosages tested.[24,27,28] These RCTs have shown that low-dosage ET can prevent postmenopausal osteoporosis, and ultralow-dosage ET has beneficial skeletal effects. However, no fracture trial has yet been carried out with low- and ultralow-dosage HT. A low dose is 0.3 mg of conjugated estrogen or its equivalent (e.g., 0.5 mg of micronized estradiol); half this amount is considered ultralow.[29]

## SERM THERAPY

SERMs have demonstrated tissue-specific estrogen-agonistic or estrogen-antagonistic effects.[30] In the Multiple

Outcomes of Raloxifene Evaluation,[31] patients treated with 60 or 120 mg of raloxifene daily for 4 years demonstrated reductions of 36% and 43%, respectively, in the risk of vertebral fractures. However, no significant effect on the risk of non-vertebral fractures was noted; this may have been the result of multiple factors, including the very low incidence of non-vertebral fractures in the placebo arm of the trial as compared with the incidence rates seen in the RCTs of other antiresorptive agents.

In the Study of Tamoxifen and Raloxifene,[32] which involved 19 747 postmenopausal women at increased risk of breast cancer, the effects of 60 mg of raloxifene daily on reducing the risk of breast cancer were equivalent to those of 20 mg of tamoxifen daily over 5 years. Both drugs reduced the risk of breast cancer by approximately 50%. Raloxifene had a better overall safety profile than tamoxifen, with 36% fewer uterine cancers and 29% fewer deep vein thromboses.

The RUTH study[33] was conducted in postmenopausal women (mean age 67.5 years) with coronary artery disease or with risk factors for this condition. The primary outcome was coronary events. A second primary endpoint was invasive breast cancer. Among the 10 101 women randomly assigned to 60 mg of raloxifene daily or placebo for a median of 5.6 years raloxifene reduced the risk of invasive breast cancer by approximately 50% and the risk of vertebral fractures by 35%. There was an increase of approximately 50% in the risk of venous thromboembolism and an increase of 49% in the risk of fatal stroke, with no effect on overall stroke risk. This impact on the risk of stroke was not well understood and was an unexpected finding.

Tissue-selective estrogen complexes, which combine a SERM with 1 or more estrogens, constitute a new class of agents in development for the treatment of women with menopausal symptoms and at risk of osteoporosis. The goal of this combination is to provide relief of menopausal symptoms and prevent bone loss while protecting the breast and the endometrium. Bazedoxifene with conjugated estrogens is the first such agent in clinical development.[34] Dosages of 20 mg of bazedoxifene with either 0.45 or 0.625 mg of conjugated estrogens have been shown in phase-III clinical trials to significantly reduce vasomotor symptoms[35] and vulvovaginal atrophy[36] in postmenopausal women aged 40 to 65 years and to prevent bone loss in those women at risk for osteoporosis.[37] The US Food and Drug Administration recently approved this combination for the treatment of moderate to severe vasomotor symptoms associated with menopause in women who have not undergone hysterectomy, as well as for the prevention of postmenopausal osteoporosis.

## BISPHOSPHONATE THERAPY

Nitrogen-containing bisphosphonates (alendronate, risedronate, and zoledronic acid) provide antiresorptive effects by binding to the calcium hydroxyapatite crystal at sites of bone resorption, where the bone matrix is exposed.[38] The bisphosphonate is buried under the newly formed bone, where it lies inert and has no skeletal effects. During bone resorption the drug is released from the bone matrix and ingested by osteoclasts. It inhibits farnesyl diphosphate synthase (FDPS), a key enzyme in the cholesterol synthesis pathway involved in post-translational modification of important signalling molecules (Ras, Rac, Rho, and Rab). This inhibition disrupts several pathways involved in cytoskeletal organization, cell survival, and cell proliferation, leading to osteoclast deactivation and apoptosis.[39] The result is reduced bone turnover and enhanced bone mineralization because of the extended time available for mineral accumulation. With the normalization of bone remodelling to premenopausal levels, overall bone strength is improved.[39,40] However, adherence to oral bisphosphonate therapy is mandatory to achieve a reduction in fracture risks: low adherence may compromise therapeutic effectiveness.[41]

### Alendronate

Alendronate, taken orally, has been approved for the prevention of osteoporosis at a daily dose of 5 mg and for the treatment of osteoporosis at a daily dose of 10 mg or a weekly dose of 70 mg.

Alendronate reduces the risk of vertebral fractures in postmenopausal woman with and without previous vertebral fractures, as has been demonstrated in the FIT study.[42–44] Several trials have shown that alendronate use reduces bone resorption and improves BMD.[44,45] A combined analysis of the data for 3658 patients in the FIT osteoporotic cohort that had a pre-existing fracture or a femoral neck BMD T-score of −2.5 or less at baseline demonstrated a significant decrease in the incidence of symptomatic vertebral fractures of 55% ($P = 0.003$). The incidence of hip fractures was reduced by 63% at 18 months ($P = 0.014$) and by 54% at 36 months ($P = 0.005$).[31]

The FIT Long-term Extension Study found that increases in BMD continued at the lumbar spine and hip through 10 years of alendronate treatment, with an associated fracture risk reduction.[44] Bone biopsies performed after 10 years of alendronate treatment revealed double fluorescent tetracycline label in all samples, indicating ongoing bone remodelling and an absence of "frozen" bone.[44] In this study, patients who had completed 5 years of alendronate therapy were assigned to receive either alendronate or

placebo for an additional 5 years. The frequency of clinical vertebral fractures was reduced by 55% in those receiving 10 years of alendronate treatment in comparison with those who had received 5 years of alendronate therapy followed by 5 years of placebo. No differences were observed in the frequency of nonvertebral fractures or radiographic vertebral fractures with bisphosphonate therapy continued beyond 5 years.[46]

## Risedronate

Risedronate maintains bone mass and preserves bone microarchitecture,[47] and it reduces the risk of vertebral and non-vertebral fractures.[48–50] In the Vertebral Efficacy with Risedronate Therapy trials 5 mg of risedronate daily reduced the incidence of new fractures within 6 months of the start of therapy and significantly lowered the risk of new vertebral fractures within 1 year.[48–50] The reduction in risk was maintained for up to 7 years of treatment.[51] In a study of 9331 elderly women at high risk, risedronate reduced the risk of non-vertebral fractures after 3 years of treatment and also reduced the risk of hip fractures.[52]

Studies involving early-postmenopausal women demonstrated that 5 mg of risedronate daily increased the BMD at the lumbar spine by more than 5% during 2 years of treatment ($P < 0.05$) as compared with both baseline and placebo.[53,54] In addition, key clinical trials have shown that reductions in vertebral fracture risk with risedronate are independent of increases in BMD.[55]

Various oral dosage regimens of risedronate are approved for the prevention and treatment of osteoporosis: 5 mg daily, 35 mg weekly, or 150 mg monthly. Delayed-release risedronate can be taken with food in doses of 35 mg weekly and is as effective and as well tolerated as risedronate 5 mg daily.[56]

## Zoledronic acid

Zoledronic acid is the most potent bisphosphonate available.[57,58] It contains 2 nitrogen atoms in the R2 side chain. The intravenous administration of 4 mg doses has been approved for the prevention and treatment of metastatic bone disease and hypercalcemia related to malignant disease. Zoledronic acid, 5 mg intravenously on an annual basis, has been approved in Canada for the treatment for Paget's disease and postmenopausal osteoporosis.

The phase-III RCT Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly (HORIZON) Pivotal Fracture Trial (PFT) evaluated the effects of zoledronic acid, given as a single 5-mg intravenous infusion annually, on fracture incidence in men and women 50 years of age or older who had already sustained a low-trauma hip fracture.[59] Compared with placebo, zoledronic acid reduced the 3-year risk of vertebral fracture by 70% (RR 0.30; 95% CI 0.24 to 0.38) and the 3-year risk of hip fracture by 41% (HR 0.59; 95% CI 0.42 to 0.83). Increases in BMD were significantly greater and height loss reduced in the group receiving zoledronic acid.

The long-term effects of zoledronic acid on BMD and fracture risk over 6 years were evaluated in the extension trial of the HORIZON_PFT study:[60] 1233 postmenopausal women who had received zoledronic acid for 3 years in the core study were randomly assigned to receive 3 additional years of zoledronic acid ($n = 616$) or placebo ($n = 617$). The femoral-neck BMD was stable in those receiving the additional therapy and dropped slightly in those switched to placebo (between-treatment difference 1.04%; 95% CI 0.4% to 1.7%, $P = 0.0009$); however, the BMD remained above pretreatment levels in the placebo group. The incidence rate of new morphometric vertebral fractures was lower in the group receiving 6 years of zoledronic acid in comparison with the group switched to placebo after 3 years (OR 0.51; $P = 0.035$). The rates of other new fractures did not differ between the 2 groups.

It appears that long-term therapy confers ongoing reduction in fracture risk and maintenance of BMD even when therapy is stopped after 3 years. Individuals at a moderate risk of fracture could therefore be given a "drug holiday" and have treatment interrupted, with monitoring of the BMD. Since a reduction in the risk of morphometric vertebral fractures was seen in those at high risk of fracture, in this patient population drug therapy should be continued beyond 3 years.

## Advantages and disadvantages

A major advantage of oral bisphosphonate therapy is ease of administration and excellent tolerability. The most common side effects are abdominal pain and dysphagia. However, in the RCTs conducted to date, the incidence rates of upper gastrointestinal side effects with alendronate and risedronate have been comparable to those of placebo.[61]

Intravenous administration of bisphosphonates has a number of advantages, including less frequent dosing and less potential for gastrointestinal side effects as compared with oral administration. Intravenous therapy also has assured compliance if the patient attends the physician's office for the annual infusion.

Recently, reports of mandibular or maxillary osteonecrosis as a rare complication of bisphosphonate use have been published.[62] ONJ is an avascular bone necrosis that may

occur in patients at risk for this condition. Most of the reports have been associated with frequent high-dose intravenous administration of pamidronate or zoledronic acid in patients with a history of breast cancer or myeloma. Many of these patients were also receiving concomitant chemotherapy, radiation therapy, or both, which are risk factors for avascular bone necrosis. The condition has been most commonly reported in high-risk individuals after dental surgery, such as tooth extraction.[63] The condition has seldom been reported with alendronate and risedronate use[62] and has not been seen in any of the clinical trials conducted to date, which represent prospective data for more than 100 000 patients treated with aminobisphosphonates for an average of 3 years. In a retrospective chart review, ONJ was identified in 0.825% of 4000 cancer patients treated with zoledronic acid, pamidronate, or both.[64] The HORIZON_PFT study found that the incidence of ONJ was similar in the treatment and placebo groups: 1 case in each group.[59] The cases were validated by an adjudication committee. Both cases resolved.

A search of 4 other RCTs with zoledronate did not reveal any other cases of ONJ, and the incidence of ONJ from RCTs has been reported to be less than 1 in 14 200 patient treatment-years.[65]

The incidence of ONJ in Canada in the population of patients with osteoporosis is less than 1 in 100 000 and appears to be similar to or only slightly higher than the background incidence in the general population.[66] In the oncology patient population the incidence appears to be higher and to be related to dose and duration of intravenous bisphosphonate therapy or the use of high-dose denosumab therapy.[67]

Current international guidelines recognize ONJ as a very rare condition, limited mostly to the oncology population receiving high-dose intravenous bisphosphonate or denosumab therapy.[67] Prospective data in oncology and non-oncology populations are needed to better understand the underlying pathophysiology of ONJ so that appropriate decisions can be made regarding prevention, diagnosis, and management,[68] as well as to determine the true incidence. It is important for all Canadians to visit their dentist every 6 months to ensure that dental hygiene is maintained, as this is a cornerstone in the prevention and treatment of ONJ.

AFFs have been reported with long-term use of bisphosphonates.[69] These subtrochanteric fractures are atypical in that they have a short oblique or transverse fracture line with thickened cortices. Typical subtrochanteric fractures are comminuted, with a spiral fracture line, and

usually the cortices are thin.[70] The thickened cortices seen in AFFs reflect increased callus formation at the periosteum, similar to the radiographic features of a stress fracture. Magnetic resonance imaging demonstrates marrow edema, and increased tracer uptake is seen on bone scans. In 75% of patients prodromal pain in the thigh or groin is present and precedes the fracture by weeks or months. Patients on long-term bisphosphonate therapy should be questioned about this type of discomfort, and if it is present plain radiography should be done to exclude an AFF. As these fractures may be bilateral, it is important to evaluate the contralateral femur as well. If the plain films are normal, then a bone scan or magnetic resonance imaging should be done in a search for evidence of a stress fracture. If there is no such evidence, then the bisphosphonate or denosumab therapy can be continued. If there is evidence of a stress fracture, then the drug therapy must be stopped. The pain will usually lessen as the AFF heals. There is evidence that teriparatide is of value in the healing of these fractures.[71–74]

To satisfy the 2013 case definition of the American Society for Bone and Mineral Research,[70] an AFF must have at least 4 of the 5 following major features.

1. The fracture is associated with minimal or no trauma, as in a fall from a standing height or less.

2. The fracture line originates at the lateral cortex and is substantially transverse in its orientation, although it may become oblique as it progresses medially across the femur.

3. Complete fractures extend through both cortices and may be associated with a medial spike; incomplete fractures involve only the lateral cortex.

4. The fracture is non-comminuted or minimally comminuted.

5. Localized periosteal or endosteal thickening of the lateral cortex is present at the fracture site ("beaking" or "flaring").

None of the following minor features are required but when present can support the diagnosis of an AFF.

1. Generalized increase in cortical thickness of the femoral diaphysis.

2. Unilateral or bilateral prodromal symptoms, such as dull or aching pain in the groin or thigh.

3. Bilateral incomplete or complete femoral diaphyseal fractures.

4. Delayed fracture healing.

AFFs have been noted to occur with long-term use of bisphosphonates, usually for 5 to 7 years, and the risk

appears to decrease by 70% per year after discontinuation of use.[75] In this study all hip fractures occurring in Sweden in 2008 were reviewed; 12 777 were in women 55 or more years of age, and 1351 of these women experienced a femoral shaft fracture, 59 of which were atypical. Approximately 80% of the women with the AFFs had been on bisphosphonate therapy, and only 13 of the 59 had never used bisphosphonates. The risk of an AFF was 0.09/10 000 person-years for women not on bisphosphonate therapy and 5.5/10 000 person-years for those on such therapy.

The number needed to harm with bisphosphonate use is estimated to be 1/2000 person-years of use.[76] The risk of an AFF appears to be higher with longer use and drops significantly with interruption of therapy.

At this time there appears to be an association between long-term bisphosphonate or denosumab use and the development of an AFF. It is not clear whether this is a causal association, as these fractures have been known to occur in the absence of drug therapy. Proposed mechanisms for these fractures include oversuppression of remodelling with long-term bisphosphonate or denosumab use.[70]

### Drug holidays

Drug holidays from long-term bisphosphonate therapy are possible, as these drugs have long-term skeletal retention, and the BMD appears to be stable when therapy is stopped after 5 years of use. Interruption of bisphosphonate therapy after 5 years therefore appears to be an attractive option for those at moderate risk of fracture: it may allow bone remodelling to recover and may reduce the risk of possible long-term harmful effects of bisphosphonate therapy, such as the risk of AFFs. In those at high risk (those who have previously had a fragility fracture or after 5 years of therapy have a femoral-neck T-score of less than −2.5), therapy should not be stopped, as the benefit of ongoing therapy in such individuals is far greater than the potential risks. Further reductions in fracture risk are seen with ongoing treatment up to 10 years. Reductions in the risk of clinically recognized vertebral fractures have been seen with 10 years of alendronate therapy compared with 5 years, and reductions in the risk of morphometric vertebral fractures have been seen with 6 years of zoledronic acid therapy compared with 3 years.[60]

## CALCITONIN THERAPY

Calcitonin, a hormone produced in the thyroid gland, inhibits osteoclastic bone resorption. Its poor oral absorption necessitates either subcutaneous or intranasal administration. Administration of 200 IU by nasal spray was approved in Canada for the treatment of postmenopausal osteoporosis. Recently, however, the European Medicines Agency[77] reviewed all available postmarketing safety data for nasal-spray calcitonin as well as information from experimental cancer studies and found a 0.7% to 2.4% increase in the rate of cancer among those using this therapy long term. This risk of cancer may not be causal and may simply be an association, but because calcitonin is not effective in lowering the risk of non-vertebral or hip fractures, the risk/benefit ratio does not support the use of calcitonin for fracture reduction in postmenopausal osteoporosis. For this reason, calcitonin has been withdrawn from the market by Health Canada and is no longer available as a therapeutic option for the treatment of postmenopausal osteoporosis.

## DENOSUMAB THERAPY

Denosumab is a fully human monoclonal antibody against RANKL; it binds to human RANKL, thus preventing osteoclast activation and consequently reducing bone resorption. In the estrogen-deficient woman there is upregulation of RANKL, resulting in an increase in osteoclast formation, function, and survival, which leads to significant bone loss after menopause. By binding to RANKL, denosumab reduces binding to the RANK receptor on osteoclasts, thereby reducing the rate of bone remodelling. Denosumab is cleared through the reticuloendothelial system rather than the kidneys. Unlike bisphosphonates it can be used in those with stage IV chronic kidney disease and has been shown to be effective in reducing fracture risk in this patient population.[78]

The FREEDOM Study was a phase-III registration study conducted in 7808 postmenopausal women randomly assigned to denosumab, 60 mg subcutaneously every 6 months, or placebo for 3 years. The primary endpoint was morphometric vertebral fractures, whose incidence rate after 3 years was 68% lower ($P < 0.0001$) in the denosumab group compared with the placebo group; the incidence rates of non-vertebral fractures and hip fractures were 20% ($P < 0.01$) and 40% ($P < 0.04$), respectively, lower in the denosumab group.[79] Extension data for another 3 years showed ongoing fracture-risk reduction, and safety data out to 6 years demonstrated a side-effect profile similar to that of placebo with the exception of an increased risk of dermatitis or eczema (in 10.8% versus 8.2%; $P < 0.0001$).[80] Long-term extension data were presented recently: ongoing therapy with denosumab over 8 years was associated with further rises in BMD at the lumbar spine and hip, and a further reduction in fracture risk has been observed at vertebral and non-vertebral skeletal sites.[81]

Denosumab, administered by subcutaneous injection twice yearly, has been approved for use in postmenopausal women at high fracture risk and in those who are intolerant to bisphosphonate therapy or in whom bisphosphonate therapy has failed.

## THERAPY WITH ANABOLIC AGENTS

Until recently, pharmaceutical treatment of post-menopausal osteoporosis was limited to the use of antiresorptive agents. The availability of anabolic agents represents a major advance, as these agents substantially improve the quality and the quantity of bone, significantly increasing bone strength.

### Teriparatide

In an RCT involving postmenopausal women with fragility fractures, subcutaneous administration of teriparatide, 20 µg daily, led to a 9% increase in lumbar-spine BMD and improved femoral-neck and whole-body BMD after about 18 months.[12] The risks of vertebral and non-vertebral fragility fractures were reduced by approximately 65% and 53%, respectively. Evidence for the anabolic effects of teriparatide on bone microarchitecture has been found in biopsy specimens, which have shown dramatic increases in the thickness, density, and number of trabeculae and increases in cortical thickness and bone size.[82] A reduction in back pain has also been noted with teriparatide use.

Teriparatide is well tolerated, with only minor adverse events, such as nausea, headaches, and transient mild hypercalcemia.[83] A dose- and duration-dependent relation-ship between teriparatide and osteosarcoma was noted in rats receiving nearly lifelong exposure to high doses, 5 µg/kg or more daily,[84] which are much higher than the daily dose used in humans, 20 µg (approximately 0.28 µg/kg). Osteosarcoma has not been seen in studied monkeys. To date, more than 1 million people have been treated with teriparatide, and an increased risk of osteosarcoma has not been seen.

## EMERGING FORMS OF THERAPY

### Odanacatib

Bone remodelling approximately doubles after menopause for about 5 to 7 years, after which it stabilizes.[85] In the postmenopausal years, increases in bone resorption are accompanied by increases in bone formation; however, bone resorption exceeds bone formation, and progressive bone loss occurs. Odanacatib is a new antiresorptive agent that is currently in a phase-III clinical trial of use in women with postmenopausal osteoporosis.

This molecule inhibits cathepsin K, a lysosomal enzyme present in osteoclasts, and thus decreases bone resorption. However, signalling between osteoclasts and osteoblasts continues, and osteoblast function appears to be preserved. This seems to be a unique effect of odanacatib, as other antiresorptive agents decrease bone formation. In the phase-II clinical study odanacatib was found to significantly increase BMD at the lumbar spine (11.9%) and at the femoral neck (9.8%) from baseline.[86] Markers of bone resorption were reduced, whereas markers of bone formation were relatively well maintained. Efficacy in reducing the fracture rate is being evaluated in the phase-III clinical trial.

### Antisclerostin monoclonal antibodies (blosozumab and romosozumab)

Sclerostin is a signalling protein secreted by osteocytes that inhibits the Wnt and bone morphogenetic protein pathways in the osteoblast, which decreases osteoblast proliferation and function and leads to decreased bone formation. The antisclerostin monoclonal antibodies bind to sclerostin and thereby lead to increased bone formation. In a phase-II 12-month RCT in 419 postmenopausal women, treatment with romosozumab, 210 mg monthly, resulted in a significant 11.3% increase in BMD at the lumbar spine as compared with a decrease of 0.1% with placebo and increases of 4.1% and 7.1% with alendronate and teriparatide, respectively.[87] Significant increases in BMD were also noted at the total-hip and femoral-neck sites. The drug was very well tolerated with the exception of mild local reactions at the injection site. Romosozumab is being further evaluated in a phase-III clinical trial.

## CONTRAINDICATIONS TO THERAPY

In premenopausal women it is necessary to ensure that the diagnosis is based on the presence of fragility fractures or bone-biopsy evidence of osteoporosis with microarchitectural deterioration. Osteoporosis cannot be diagnosed solely on the basis of a low BMD in premenopausal women. A BMD Z score of up to −2 is considered normal for premenopausal women. A BMD of ≤ −2 is classified as lower than expected for age. In the absence of a fragility fracture this may not be abnormal and may simply reflect low peak bone mass. Such individuals should be carefully evaluated, with exclusion of secondary causes of low BMD. It is recommended that the BMD be followed, and if it is stable in the absence of fragility fractures, then pharmacologic therapy is not indicated and may be harmful.[88]

Certain drugs are contraindicated in the presence of impaired renal function. Bisphosphonates are renally cleared, with approximately 50% of the drug being deposited into the skeleton and the remaining 50%

## Recommendations

### For Postmenopausal Women

1. Health care providers should be aware that the goals of osteoporosis management include assessment of fracture risk and prevention of fracture. (I-A)

2. Health care providers should understand that a stable or increasing bone mineral density reflects a response to therapy in the absence of low-trauma fracture or height loss due to vertebral-compression fracture. A progressive decrease in bone mineral density, with the magnitude of bone loss being greater than the precision error of the density assessment, indicates a lack of response to current therapy. Management should be reviewed and modified appropriately. (I-A)

3. Health care providers should identify the absolute fracture risk by integrating the key risk factors for fracture; namely, age, bone mineral density, prior fracture, and glucocorticoid use. These risk factors allow estimation of fracture risk using the tool of the Canadian Association of Radiologists and Osteoporosis Canada. (I-A)

4. The Fracture Risk Assessment tool of the World Health Organization (FRAX) has now been validated in a Canadian population and may also be used and incorporates additional risk factors; namely, low body mass index, parental history of fracture, smoking status, alcohol intake, and the presence of secondary causes of osteoporosis. (I-A)

5. Health care providers should be aware that a fragility fracture markedly increases the risk of a future fracture and confirms the diagnosis of osteoporosis irrespective of the results of the bone density assessment, (1-A) and that the presence of a low-trauma fracture of a vertebra or hip or more than 1 fragility fracture confirms a high fracture risk regardless of the bone mineral density. (I-A)

6. Treatment should be initiated according to the results of the 10-year absolute fracture risk assessment. (I-A)

### Calcium and Vitamin D

7. Adequate calcium and vitamin D supplementation is key to ensuring prevention of progressive bone loss. For postmenopausal women a total daily intake of 1200 mg of elemental calcium from dietary and supplemental sources and daily supplementation with 800 to 2000 IU of vitamin D are recommended. Calcium and vitamin D supplementation alone is insufficient to prevent fracture in those with osteoporosis; however, it is an important adjunct to pharmacologic intervention with antiresorptive and anabolic therapy. (I-B)

### Hormone Therapy

8. Hormone therapy should be prescribed for symptomatic postmenopausal women as the most effective option for menopausal symptom relief (I-A). It represents a reasonable choice for the prevention of bone loss and fracture in this patient population. (I-A)

9. Physicians may recommend low-and ultralow-dosage estrogen therapy to symptomatic women for relief of menopausal symptoms (I-A) but should inform their patients that, despite the fact that such therapy has demonstrated a beneficial effect in osteoporosis prevention, (I-A) no data are yet available on reduction of fracture risk.

### Bisphosphonates

10. Alendronate, risedronate, and zoledronic acid are valuable first-line agents of choice in the treatment of postmenopausal osteoporosis and should be considered to decrease the risk of vertebral, non-vertebral, and hip fractures. (I-A)

11. Etidronate is a weak antiresorptive agent and is not recommended as a first-line agent of choice for the treatment of osteoporosis. (I-D)

### RANKL Inhibitor

12. Denosumab is an effective antiresorptive agent, shown to reduce the risk of vertebral, non-vertebral, and hip fractures, (I-A) and should be considered as a first-line agent of choice in the treatment of postmenopausal osteoporosis in women at a high fracture risk. (I-A)

### Selective Estrogen-Receptor Modulators

13. Treatment with raloxifene may be considered to decrease the risk of vertebral fractures, bearing in mind that this agent has not been shown to be effective in reducing the risk of non-vertebral or hip fractures. (I-A)

### Parathyroid Hormone

14. Treatment with teriparatide should be considered to decrease the risk of vertebral and non-vertebral fractures in postmenopausal women with severe osteoporosis (I-A) and should also be considered in postmenopausal women experiencing bone loss or a new fracture despite antiresorptive therapy. (I-A)

cleared renally. If the glomerular filtration rate is below 35 mL/min, bisphosphonates should not be given. It may be of value to consider denosumab in this circumstance, as denosumab is not renally cleared.

Oral bisphosphonate therapy should be avoided in individuals with esophageal abnormalities, such as achalasia, stricture, and motility abnormalities.

## REFERRAL

As an aid to health care providers, referral to a bone specialist should be considered in the following situations.

1. Failure of treatment: a fracture or bone loss after 2 years of therapy.

2. Intolerance to existing therapies.

3. Low BMD and progressive bone loss or the presence of fractures in a premenopausal woman.

4. Feeling of the physician or the patient that a second opinion would be of value in management.

## SUMMARY

Osteoporotic fractures result in significantly increased mortality rates and are associated with significant morbidity. Effective options for the prevention and treatment of osteoporosis are available in Canada. Anabolic therapy now complements antiresorptive therapy and increases our ability to reduce fracture risk significantly. New anabolic molecules and antiresorptive options will become available in Canada in the next 5 years, and treatment strategies integrating antiresorptive therapy and anabolic agents are expected to be published shortly.

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