

Canadian Consensus Conference on Osteoporosis, 2006 Update

Jacques P. Brown, MD, FRCPC and
Quebec QC

Michel Fortier, MD, FRCSC
Quebec QC

Abstract

Objective—To provide guidelines for the health care provider on the 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—MEDLINE and the Cochrane database were searched for articles in English on subjects related to osteoporosis diagnosis, prevention, and management from March 2001 to April 2005. The authors critically reviewed the evidence and developed the recommendations according to the *Journal of Obstetrics and Gynaecology Canada's* methodology and consensus development process.

Values—The quality of evidence is rated using the criteria described in the report of the Canadian Task Force on the Periodic Health Examination. Recommendations for practice are ranked according to the method described in this report.

Sponsors—The development of this consensus guideline was supported by unrestricted educational grants from Berlex Canada Inc., Lilly Canada, Merck Frosst, Novartis, Novogen, Novo Nordisk, Proctor and Gamble, Schering Canada, and Wyeth Canada.

Keywords

Osteoporosis; prevention; treatment; diagnosis; bone mineral density; dual energy X-ray absorptiometry; bone turnover markers; vertebral fractures; fragility fractures; antiresorptive;

OSTEOPOROSIS GUIDELINES COMMITTEE

Heather Frame, MD, CFPC, Winnipeg MB
André Lalonde, MD, FRCSC, Ottawa ON
Alexandra Papaioannou, MD, FRCPC, Hamilton ON
Vyta Senikas, MD, FRCSC, Ottawa ON
Chui Kin Yuen, MD, FRCSC, Winnipeg MB

PROJECT COORDINATOR

Elke Henneberg, Communications Message & More Inc., Sutton QC

TRANSLATION

Chantal Capistran, hons. B.A., SOGC

DOCUMENT MANAGEMENT

Jackie Oman, SOGC

hormone therapy; selective estrogen receptor modulator; bisphosphonates; calcitonin; anabolic; bone forming agent

INTRODUCTION

Osteoporosis is a systemic skeletal disorder characterized by a low BMD and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk.¹ The condition is usually painless until a fracture occurs. Because of its association with fractures, osteoporosis is a major public health hazard with high morbidity, mortality, and social costs. Recent advances in measuring BMD have provided strategies to assess the presence and extent of early and asymptomatic osteoporosis.

EPIDEMIOLOGY

Osteoporosis is a major public health problem in Canada and its prevalence is increasing as the population ages.² According to results from BMD assessments in the Canadian Multicentre Osteoporosis Study (CaMOS), the prevalence of osteoporosis in Canadian women aged 50 years and over was 12.1% at the lumbar spine and 7.9% at the femoral neck, with a combined prevalence of 15.8%.³ The prevalence of osteoporosis increases with age from approximately 6% at 50 years of age to over 50% above 80 years of age.⁴ In light of these statistics and the aging of the population, it comes as no surprise that osteoporosis will be an even greater problem in the future.

Based on fracture data, it has been estimated that approximately 1 in 4 women and 1 in 8 men in Canada have osteoporosis.^{5,6} The public health and clinical importance of osteoporosis lies in the fractures that occur. Conservative estimates have suggested that a 50-year-old Caucasian woman has a remaining lifetime fragility fracture risk of 40% (for hip, vertebra, or wrist).⁷

SOGC Clinical Tip

Osteoporosis Canada (former Osteoporosis Society of Canada) recommends that all postmenopausal women older than 50 years be assessed for the presence of risks factors for osteoporosis.

Social and Medical Outcomes of Fracture

The medical and social consequences of fractures make osteoporosis an important public health problem. About 20% of women and 40% of men die within 1 year after a hip fracture.⁸ It has been estimated that 50% of women who sustain a hip fracture become functionally dependent in their daily activities, and 19% require long-term nursing home care because of the fracture.⁸ Vertebral fractures appear to be associated with similar 5-year mortality.⁹⁻¹¹ Only one-third of all vertebral fractures are clinically diagnosed.¹² In addition to health care costs, vertebral fractures cause back pain, loss of height, depression, and low self-esteem.¹³ Wrist and other fractures have considerable morbidity that is not usually captured in

osteoporosis cost estimates. The total costs of osteoporosis are difficult to assess and are based on many assumptions. It is estimated that the total acute care costs attributable to osteoporosis in Canada (hospitalization, outpatient care, and drug therapy) approached \$1.3 billion in 1993.³

It is also well-known that the burden of illness associated with hip fracture extends beyond the initial hospitalization. The levels of health services used were assessed in a study of women aged 50 years and over who had been admitted to an acute care facility for hip fracture in the Hamilton-Wentworth region in Ontario from April 1, 1995 to March 31, 1996.¹⁴ The mean 1-year cost of hip fracture for the 504 study patients was \$26 527 (95% confidence interval [CI], \$24 564–\$28 490). One-year costs were significantly ($P < 0.001$) different for patients who returned to the community (mean = \$21 385), versus those who were transferred (mean = \$44 156) or readmitted (mean = \$33 729) to long-term care facilities. Initial hospitalization represented 58% of the 1-year cost for the community-dwelling patients, compared with 27% of the cost for the long-term care residents. Only 59.4% of the community-dwelling patients resided in the community 1 year following fracture, and 5.6% of patients who survived their first fracture experienced a subsequent hip fracture. Annual economic implications of hip fracture in Canada are \$650 million and are expected to rise to \$2.4 billion by 2041.¹⁴

BONE HEALTH

Osteoporosis is a disease with its roots in childhood as bone size, strength, and mineralization peak in one's 20s. Those with the highest peak bone mass have an advantage as reductions in bone density occur with advancing age and menopause. Peak bone mass, while largely genetically determined, is not always met. This can be a result of inadequate calcium and vitamin D intake, poor nutrition, lack of physical exercise, smoking, and other environmental, physiologic, and lifestyle factors. Refer to Table 11.1 for calcium and vitamin D recommendations.

RECOMMENDATIONS

- 1 The goals of osteoporosis management should be fracture risk assessment and prevention of fracture (IB). BMD should not be viewed as the only indicator for management success because therapy may or may not be associated with significant increases in BMD. (IA)
- 2 Physicians should be aware that a prevalent vertebral or non-vertebral fragility fracture markedly increases the risk of future fracture. (IA)
- 3 Fragility fracture after the age of 40, being over 65 years of age, low BMD, and family history of osteoporotic fracture (especially maternal hip fracture) should be recognized as the key risk factors for fragility fractures. Systemic glucocorticoid use of more than 3 months duration should be considered as another major risk factor. (IA)
- 4 Evaluation of osteoporosis in postmenopausal women should include the assessment of clinical risk factors for low BMD and BMD testing. (IB)

- 5 Central (hip and spine) measurements by DXA should be used for both risk assessment (IA) and follow-up (IB), as they provide the most accurate and precise measurements of BMD.
- 6 Further evidence should be collected to determine the role of peripheral BMD measurements (e.g., ultrasound or DXA measurements in the radius, phalanx, or heel) in clinical practice. (II-2D)
- 7 Postmenopausal women with historical height loss greater than 6 cm, prospective height loss greater than 2 cm, kyphosis, or acute incapacitating back pain syndrome should be sent for spine radiographs with a specific request to rule out vertebral fractures. (IA)
- 8 Until more data becomes available on other clinical applications, bone turnover markers can be used to rapidly assess adherence and effectiveness of pharmacological interventions. (IB)

Calcium

Adequate dietary calcium intake is necessary for mineralization of the skeleton and attainment of peak bone mass. In postmenopausal women, calcium supplements slow bone loss and improve BMD.¹⁵ Increasing dietary calcium through dairy products has also been associated with increasing BMD.¹⁶ There are many forms of calcium supplements available and while they may differ in qualities such as absorption, calcium carbonate, being least expensive, could be a cost effective option in older populations.¹⁷

Vitamin D

The prevalence of vitamin D deficiency in Canada is high.⁵ The northern latitude makes it difficult to raise vitamin D levels sufficiently in the summer to maintain adequate levels throughout the winter. This is especially true for house-bound and institutionalized people. In elderly men and women with vitamin D insufficiency, vitamin D supplementation probably reduces vertebral fractures and may also impact non-vertebral fractures.^{18,19}

Recent evidence suggests that routine supplementation with calcium (1000 mg/d) and vitamin D₃ (800 IU/d), either alone or in combination, is not effective in reducing the risk of fractures among community-dwelling older women with at least one self-reported risk factor for hip fracture. It is also not effective in preventing further fractures in elderly men and women who had a recent fragility fracture.^{20,21}

Although it might not be sufficient as the sole therapy for osteoporosis, routine supplementation with calcium (1000 mg/d) and vitamin D₃ (800 IU/d) is still recommended as mandatory adjunct therapy to the main pharmacological interventions (antiresorptive and anabolic drugs). Muscle strength, which may reduce the risk of falling, is also affected by vitamin D (dose equivalent to 800 IU/d),¹⁹ but this has been recently challenged. Osteoporosis prevention and treatment requires adequate vitamin D intake.

CALCIUM AND VITAMIN D RECOMMENDATION

- 9 Although it might not be sufficient as the sole therapy for osteoporosis, routine supplementation with calcium (1000 mg/d) and vitamin D₃ (800 IU/d) is still recommended as mandatory adjunct therapy to the main pharmacological interventions (antiresorptive and anabolic drugs). (IB)

Exercise

Physical activity early in life contributes to higher peak bone mass, with resistance and impact exercises showing most benefit.^{22–25} In postmenopausal women, BMD at the spine can be positively affected by aerobics, resistance, and weight-bearing exercise.^{26–28}

Walking also appears to benefit the hip BMD. Walking may be the most cost-effective exercise that is easily accessible to the population.²⁸ Trials of exercise in older community-dwelling women with osteoporosis produce variable results in terms of improved strength and balance.²⁹ Exercise interventions that increase strength and improve balance can reduce falls, but there is not yet evidence of fracture reduction in exercise trials. Women should be encouraged to perform fast walking in a safe environment as a means of improving bone health.

Nutrition

Optimal bone health requires good overall nutrition. Malnutrition is associated with an increased risk of osteoporosis.³⁰ Body mass index (BMI) $< 20 \text{ kg/m}^2$ is associated with increased risk of fracture.³¹ Elderly community-dwelling women are at risk of malnutrition for many reasons. Weight gain in underweight community-dwelling women is associated with increased BMD.³² High protein and high sodium diets increase calcium excretion and increase markers of bone resorption.³³ Weight loss in overweight post-menopausal women with a normal calcium intake may also result in inadequate calcium absorption.³⁴ A caffeine intake of over 4 cups of coffee per day has been associated with an increased risk in hip fracture.³⁵

Osteoporosis has been added to the negative effects of smoking. Smokers have significantly lower bone mass compared with non-smokers. This effect appears to be dose dependent and may be partially reversible by smoking cessation. The negative effect of smoking is even more pronounced at the hip, where it is estimated that smoking increases lifetime fracture risk by 31% in women and 40% in men.³⁶

DEFINITIONS

The WHO has proposed 4 diagnostic categories for postmenopausal Caucasian women combining BMD (or bone mineral content [BMC] measured at any site and osteoporotic fracture in a stratified definition of osteoporosis (Table 11.2).³⁷ The choice of this 2.5 standard deviation cut-off by the WHO was based on epidemiological data showing that over 50% of the individuals who have already sustained a fragility fracture were at or below this level of BMD.

A US National Institutes of Health (NIH) consensus conference defined osteoporosis as "... a skeletal disorder characterized by compromised bone strength predisposing a person to an increased risk of fracture. Bone strength reflects the integration of two main features: bone density and bone quality."³⁸ The only clinically applicable index of bone quality at present is a patient's history of a fragility fracture. Fragility fractures are associated with significant morbidity, increased mortality, and staggering medical expenses. In the absence of methods of measuring bone quality, the diagnosis of osteoporosis tends to be made on the basis of low BMD.

This definition recognizes that there is a strong association between BMD and the likelihood of fracture in untreated postmenopausal women, but that other factors independent of BMD influence fracture risk as well: rate of bone loss, breakdown of bone architecture, ineffective repair of fatigue damage, geometric aspects of skeletal structure such as hip axis length, frequency and type of falls, and life expectancy. Therefore, the WHO definition is important for assessing the number of affected individuals but should not be used as the sole indication for treatment. In fact, treatment could be justified regardless of the BMD level in patients who have already sustained a fragility fracture and in glucocorticoid-treated patients.³⁹ Furthermore, Osteoporosis Canada has recently proposed that an individual's 10-year absolute fracture risk, rather than BMD alone, be used for fracture risk categorization.⁴⁰

ASSESSMENT

Women at Risk of Low Bone Mineral Density

Osteoporosis Canada recommends that all postmenopausal women older than 50 be assessed for the presence of risks factors for osteoporosis.³⁹ There are two stages of assessment in identifying high-risk individuals for osteoporosis: risk factors identifying those who should be assessed with a BMD test, and the risk factors identifying those at risk of osteoporotic (fragility) fracture who should be considered for therapy.³⁹

SOGC Clinical Tip

Among the major factors identifying those who should be assessed with a BMD test, the most relevant are: age > 65 years; fragility fracture after age 40, including wrist, vertebral, and hip fractures; family history of osteoporotic fracture (especially maternal hip fracture); and systemic glucocorticoid therapy of > 3 months.

It is important to assess for the presence of one major or two minor risk factors for osteoporosis (Table 11.3) to identify who should have a BMD test.

There are a number of decision tools that have been developed to aid physicians in selecting patients for BMD testing using a variety of combinations of risk factors.^{41–44} Recent evidence from multiple sources confirms that each tool identifies over 90% of women aged 45 years or older with primary osteoporosis.^{45–47} However, these tools have poor specificity in that a significant portion of identified women (30% to 60%) will have normal BMDs upon testing.^{45–47}

Women at Risk of Fragility Fracture

It is critical to recognize that low BMD is one of the most significant risk factors for predicting future fragility fractures. Equally important is the presence of a previous fragility fracture. Despite availability of different evaluation techniques and diagnostic modalities, it has been estimated that only 5% to 25% of Canadian women with fragility fractures are subsequently investigated for osteoporosis, and only half of those receive treatment.^{48,49}

Fragility fracture is defined as a fracture that occurs spontaneously or following a minor trauma, such as a fall from standing height (e.g., a fall from roller skates or ice skates); a fall from a sitting position; a fall from laying down on a bed or a reclining deck chair from less than a meter high; a fall after having missed 1 to 3 steps in a staircase; a fall after a movement outside of the typical plane of motion; or coughing. Some studies have considered fractures that occur as a result of any fall from a height of less than a meter, such as after having missed 1 to 3 steps in a staircase, as fragility fractures.⁵⁰⁻⁵⁵

Measurement of height loss is a good clinical indicator of vertebral fracture.⁵⁶ Klotzbuecher et al.⁵⁷ performed a meta-analysis of the risk of future fracture, given the history of prior fracture, and concluded that women with prior fracture had a 2- to 10-fold risk of another fracture, compared with those without fracture. This risk was reported to further increase with the number of prior vertebral fractures.

MONITORING: CENTRAL DXA, RADIOGRAPHS, AND BONE TURNOVER MARKERS

Depending on the clinical situation, central DXA scans (lumbar spine and hip) may be repeated in 1 to 3 years. This is usually done to monitor the response to a pharmacologic therapy or to document the stability of bone density in untreated patients at risk for bone loss and to improve adherence to therapy.⁵⁸ Whenever possible, the patient's initial and follow-up scans should be done on the same instrument, using the same procedure. The reader is referred to the recommendations for BMD reporting in Canada, recently published by Osteoporosis Canada.⁴⁰

SOGC Clinical Tip

Depending on the clinical situation, central DXA scans (lumbar spine and hip) may be repeated in 1 to 3 years, on the same instrument, using the same procedure.

Role of Peripheral Bone Mineral Density Testing

Peripheral BMD can be measured by DXA, ultrasound, or single X-ray absorptiometry at several skeletal sites (radius, phalanx, calcaneus, tibia, metatarsal). These technologies are predictive of hip fracture in women over the age of 65, but they cannot be used at the present time for follow-up.^{59,60} Peripheral testing may play an important role for women in underserved areas and in raising awareness about osteoporosis. However, these services may be provided by unregulated practitioners, raising concerns about quality control.

Radiographs

There is renewed interest in vertebral fractures resulting from osteoporosis. The presence of a vertebral fracture increases the risk of a second vertebral fracture at least 4-fold over 3 years.⁶¹ A study of the placebo group in a recent major clinical trial showed that 20% of subjects experiencing a vertebral fracture during the period of observation had a second vertebral fracture within 1 year.⁶² Vertebral fractures are also indicators of increased risk of fragility fractures at other sites, such as the hip.⁶³

Postmenopausal women with historical height loss greater than 6 cm, prospective height loss greater than 2 cm, kyphosis, or acute incapacitating back pain syndrome should be sent for spine radiographs with specific request to rule out vertebral fractures.⁵⁶

SOGC Clinical Tip

Measurement of height loss is a good clinical indicator of vertebral fracture.

Spinal radiographs remain the best method for assessing the presence of vertebral fractures with no satisfactory alternative currently available.⁶⁴ The role of vertebral fracture assessment (VFA) on DXA to define vertebral dimensions without distortion due to parallax is being established.

For the initial assessment of spinal osteoporotic fractures, both the antero-posterior (AP) and lateral projections of both the thoracic and lumbar spines is advised. For follow-up, only the lateral radiographs of the thoracic and lumbar spines are required, as these are the most effective in the detection of osteoporotic fractures.

SOGC Clinical Tip

Antero-posterior (AP) and lateral projections of both the thoracic and lumbar spine radiographs remain the best method for assessing the presence of vertebral fractures with no satisfactory alternative currently available.

Bone Turnover Markers

Bone turnover markers have emerged as powerful tools to help in the management of osteoporosis since they provide information that is different and complementary to BMD measurements.⁶⁵ Because of the coupling between resorption and formation in the remodelling cycle, both markers of bone formation (within 3 to 6 months) and bone resorption (within 1 to 3 months) will decrease or increase in parallel, in response to antiresorptive and anabolic drug therapies. Bone formation markers include serum osteocalcin, bone alkaline phosphatase (BAP), and the C- and N-terminal propeptides of type I collagen (PICP, PINP). Bone resorption markers include urinary hydroxyproline, urinary pyridinoline (PYR), urinary deoxypyridinoline (D-PYR), as well as urinary collagen type I cross-linked N-telopeptide (uNTx), and urinary and serum collagen type I cross-linked C-telopeptide (uCTx and sCTx).

Large prospective population studies in untreated subjects have shown that increased bone remodelling and, more specifically, an increase in bone resorption markers, are associated with increased vertebral and non-vertebral fractures independently of BMD on a group basis, but their measurements cannot yet be recommended to predict fracture risk on an individual basis.^{39,66,67} Currently, bone turnover markers cannot be recommended for the prediction of bone loss.⁶⁸

The ability to monitor treatment with bone turnover markers to rapidly assess adherence and effectiveness of pharmacological interventions represents the most promising clinical application.⁶⁵ Given the paucity of data, the clinical utility of bone turnover marker changes under anabolic agents is yet to be determined. Currently approved osteoporosis therapies are mostly antiresorptive and produce a rapid reduction of bone turnover that reaches nadir levels in 3 to 6 months, followed by a plateau. For the clinician, the primary concern is the early identification of non-responders, that is, of patients who fail to demonstrate the expected decrease in bone remodelling and, therefore, the expected reduction in fracture risk. The optimal threshold of bone marker change that will lead to the maximal fracture reduction is yet to be defined. However, recent findings from a large fracture trial indicate no further anti-fracture benefit with further decreases in bone resorption markers below a decrease of 55% to 60% for uCTx and 35% to 40% for uNTx.⁶⁹ Further research is needed to establish the cut-offs of each bone turnover markers based on the probability of fracture in large clinical trials of each therapeutic regimen.

To reduce the impact of circadian variability on clinical interpretation of bone turnover markers, it is essential that the timing of sample collection is tightly controlled: early morning (serum before 9:00 AM; first or second morning voided urine, with creatinine correction) after an overnight fast.⁶⁸ In addition, it should be noted that abnormal bone turnover marker values may indicate that a fracture has occurred within the previous 3 months, resulting in accelerated local bone metabolism.⁷⁰

Recent developments using an electrochemiluminescence automated method (Elecsys, Roche Diagnostics) to measure N-MID Osteocalcin and PINP (bone formation) and sCTx (bone resorption) with excellent intra- and interassay precisions (CV \approx 5–8%) have improved the ability of bone turnover markers to monitor the individual response to antiresorptive or bone-forming therapies.⁷¹

THERAPEUTICS AGENTS

For a summary of hormonal preparations, refer to chapter 6 of the Canadian Consensus Conference on Menopause, 2006 Update.

SOGC Clinical Tip

Routine supplementation with calcium (1000 mg/d) and vitamin D3 (800 IU/d) is still recommended as mandatory adjunct therapy to the main pharmacological interventions (antiresorptive and anabolic drugs).

For an overview of non-hormonal osteoporosis therapies, refer to Tables 11.4 and 11.5.

Hormone Therapy

Since the publication of results from the 2 hormone randomized controlled clinical trials of the Women's Health Initiative (WHI),^{72,73} guidelines from the Society of Obstetricians and Gynaecologists of Canada (SOGC)⁷⁴ and a position statement from the North American Menopause Society (NAMS),⁷⁵ recommended the use of HT in postmenopausal women for moderate to severe symptoms of menopause.

The estrogen and progestin component of WHI randomized controlled trials is the first trial with definitive data supporting the ability of conjugated equine estrogens and progestins to prevent clinical fractures at the hip, vertebrae, and other sites, in a population of postmenopausal women not selected for osteoporosis based on BMD testing.⁷² Similar results for prevention of fractures were demonstrated in the estrogen component trial of WHI.⁷³

For symptomatic menopausal women choosing HT as a therapeutic option,⁷⁶ osteoporosis prevention can still be considered as a secondary benefit due to the positive effect ovarian hormones have on BMD. This is supported by results of many studies with BMD as the primary measure.⁷⁷⁻⁷⁹ Both oral and transdermal estrogen therapy (ET) decrease bone loss.⁷⁷⁻⁷⁹ Lower doses of estrogen taken in combination with calcium may also prevent BMD loss.⁸⁰ BMD rises in women who begin ET within five years after menopause.⁷⁷⁻⁷⁹ Postmenopausal treatment with unopposed very-low-dose transdermal estradiol (0.014mg/day) has also been shown to increase BMD and decrease markers of bone turnover without causing endometrial hyperplasia.⁸¹ There is no published data for fracture reduction with these lower doses of estrogen.

SOGC Clinical Tip

For symptomatic menopausal women choosing HT as a therapeutic option, osteoporosis prevention can still be considered as a secondary benefit due to the positive effect ovarian hormones have on BMD.

HORMONE THERAPY RECOMMENDATION

- 10 HT should be prescribed to symptomatic postmenopausal women as the most effective therapy for symptom relief (IA) and a reasonable choice for the prevention of bone loss and fracture (IA). The risks should be weighted against the benefits if estrogen therapy is being used solely for fracture prevention. (ID)

Bisphosphonates

Bisphosphonates are naturally occurring analogues of pyrophosphate that bind to hydroxyapatite crystals in bone. There are 3 oral bisphosphonates approved in Canada for the prevention and treatment of osteoporosis: etidronate, alendronate, and risedronate. Etidronate is a non-nitrogen containing bisphosphonate and has largely been replaced by the more potent nitrogen-containing bisphosphonates alendronate and risedronate.⁹⁵

Etidronate—Cyclical etidronate is currently prescribed as 400 mg daily for 14 days followed by 76 days of calcium. A meta-analysis of 13 RCTs (of which 6 were placebo controlled) of cyclical etidronate found BMD increased by 4.06% ($P < 0.01$) at the lumbar spine and 2.35% at the femoral neck ($P < 0.01$). There was evidence for the reduction of vertebral fractures (37% reduction; $P = 0.02$) but not for non-vertebral fractures ($P = 0.97$).^{88,96}

Alendronate—The most commonly prescribed alendronate dose is currently 70 mg once weekly or 10 mg daily. A meta-analysis included 11 randomized placebo-controlled trials of 12 855 postmenopausal women.⁹⁷ These trials were of at least 1-year duration and used daily doses ranging from 5 to 40 mg. BMD increases were dose dependant, particularly for doses 10 mg or greater. Three years of therapy with alendronate resulted in BMD increases of 7.48% ($P < 0.01$) in the lumbar spine and 5.6% ($P < 0.01$) in the total hip. The pooled relative risk reduction for vertebral fractures with doses of 5 mg or greater was 48% ($P < 0.01$); and in those who were treated with doses of 10 mg or greater, the relative risk reduction in non-vertebral fracture was 49% ($P < 0.01$).⁹⁷

In postmenopausal women with a prevalent vertebral fracture from the vertebral fracture arm of the Fracture Intervention Trial (FIT), treatment with alendronate reduced the incidence of hip fractures by 51% ($P = 0.047$) over 3 years.⁹⁸ In a post hoc pooled analysis of the vertebral fracture and clinical fracture arms of FIT, alendronate reduced the relative risk of hip fracture by 53% ($P = 0.005$) over 3 to 4 years in postmenopausal women with a prevalent vertebral fracture or a femoral neck BMD T-score of -2.5 or less.⁹⁹ In this post hoc analysis, alendronate has been found to reduce fractures both in high risk women with vertebral fractures and those with osteopenia.⁹⁹ Furthermore, clinical vertebral fracture rate reduction (59%; $P < 0.001$) was demonstrated as early as one year into the study.⁹⁹ In a more recent post hoc analysis of a subgroup of women who had T-scores of -1.6 to -2.5 , there was a relative risk reduction in clinical and radiographic fractures of 60 ($P = 0.005$) and 43% ($P = 0.002$) respectively, compared with placebo with 3 years of therapy.¹⁰⁰ Fractures appear to remain significantly reduced up to 7 years on therapy, with BMD increases of 11.4% at the lumbar spine.¹⁰¹

SOGC Clinical Tip

Alendronate (Fosamax) has been found to reduce fractures both in high-risk women with vertebral fractures and those with osteopenia. The most commonly prescribed alendronate doses are currently 70 mg once weekly or 10 mg daily.

Risedronate—Risedronate is prescribed either at 35 mg once weekly or 5 mg daily. A meta-analysis of eight randomized placebo-controlled trials of 14 832 postmenopausal women with osteoporosis examined the efficacy of risedronate in doses ranging from 2.5 to 5 mg daily in trials of at least 1-year duration. A dose-dependant improvement was associated with the 5 mg dose. BMD increased by 4.54% at the lumbar spine ($P < 0.01$) and 2.75% ($P < 0.01$) at the femoral neck. Patients taking 5 mg of risedronate daily demonstrated

relative risk reduction of 38% ($P=0.01$) in vertebral fractures and of 32% ($P<0.01$) in non-vertebral fractures, compared with those taking placebo.¹⁰²

A significant reduction in new vertebral fractures in high-risk women with osteoporosis and vertebral fractures (61–65%) has been observed within the first year of therapy in the VERT trials.^{103,104} These risk reductions have subsequently been demonstrated in individuals with and without vertebral fractures.¹⁰⁵ In addition, non-vertebral fractures were reduced by 74% within 1 year of risedronate therapy.¹⁰⁶ A post hoc analysis of the VERT trials has also demonstrated risedronate efficacy at reducing relative risk for clinical vertebral fractures (80% reduction, $P<0.05$; 1 [0.1%] risedronate patient versus 12 [1.0%] placebo patients) in just 6 months.¹⁰⁷

A similar post hoc analysis combining BMD and VERT trials demonstrated a significant reduction in relative risk for non-vertebral fractures (66% reduction, $p<0.05$) as early as 6 months.¹⁰⁶

BMD continues to increase with long-term use. The mean increase from baseline in lumbar spine BMD over 5 years was 9.3% ($P<0.001$).¹⁰⁸ The relative risk of new vertebral fractures was significantly reduced with risedronate treatment in years 4 and 5 by 59% ($P=0.01$). The mean increase from baseline in lumbar spine BMD over 7 years was 11.5% ($P<0.05$).¹⁰⁹

In a large RCT designed to determine hip fracture efficacy, risedronate was shown to reduce hip fracture rates in those with low femoral neck BMD by 40% ($P=0.009$) and prior vertebral fractures by 60% ($P=0.003$).¹¹⁰ Nonskeletal clinical risk factors (other than low BMD) did not identify a population that benefited from treatment, although it did identify a population at increased risk of hip fracture.

SOGC Clinical Tip

A significant reduction in new vertebral fractures in high-risk women with osteoporosis and vertebral fractures has been observed within the first year of therapy with risedronate (Actonel). Risedronate is prescribed either at 35 mg once weekly or 5 mg daily.

Tolerability and Safety—Adverse effects from bisphosphonates are rare, and in a meta-analysis of cyclical etidronate,⁹⁶ alendronate,⁹⁷ and risedronate,¹⁰² there was no difference in withdrawals, compared with placebo for adverse events. The most frequent concerns associated with cyclical etidronate are diarrhea, nausea, and, rarely, osteomalacia if cyclical therapy is not used.

Nitrogen containing bisphosphonates (alendronate and risedronate) may be associated with gastrointestinal side effects in patients with prior upper gastrointestinal disease, concomitant nonsteroidal anti-inflammatory drug use, and those already using antireflux medications.^{111,112}

Once weekly bisphosphonates may reduce adverse effects and increase adherence. Once weekly alendronate (70 mg) and risedronate (35 mg) have been found to be equivalent to

daily dosing at the lumbar spine, hip, and total body BMD.^{113–115} Increasing age and the presence of non-vertebral fractures have been found to be independent predictors of adherence in postmenopausal women.¹¹⁶

To minimize the risk for esophagitis, patients must take bisphosphonates on an empty stomach with a full glass of water, then remain upright and avoid food, beverage, and other medications for 30 minutes. Patients who have mechanical problems of the esophagus, renal dysfunction (creatinine clearance < 30 mL/min), hypersensitivity to the drug, or suffer from hypocalcemia should avoid bisphosphonates.⁹⁵

BISPHOSPHONATES RECOMMENDATIONS

- 11 Treatment with alendronate or risedronate should be considered to decrease vertebral, non-vertebral, and hip fractures. (IA)
- 12 Treatment with etidronate can be considered to decrease vertebral fractures. (IB)

NEWER AGENTS, COMBINATION THERAPY

Selective Estrogen Receptor Modulators

SERMs consist of a group of structurally diverse compounds that are distinguished from estrogen by their ability to interact with estrogen receptors, but act either as an estrogen agonist or antagonist depending on the particular environment. A receptor changes its shape when a SERM binds to it, and its particular shape determines which gene it will activate. Subsequently, the activated genes will produce proteins that regulate different processes in the body, such as bone remodelling. Presently, raloxifene is the only SERM approved in Canada for the management of osteoporosis. Raloxifene exhibits agonist effects on the bone and cardiovascular system and antagonist effects on the breast and uterus.

The anti-fracture efficacy of raloxifene is well established by the Multiple Outcomes of Raloxifene Evaluation (MORE) trial, a large RCT of postmenopausal women with or without prevalent vertebral fractures with BMD scores of -2.5 and lower in either the lumbar spine or the hip. Raloxifene is efficacious (vertebral fracture reduction of 30% in women with and 55% in women without prevalent fractures in 3 years),^{82,83} sustainable (50% in fourth year versus 55% in years 0–3),⁸⁴ fast acting (68%, $P = 0.01$, in a 1-year post hoc analysis).⁸⁵ The risk reduction for non-vertebral fractures in the overall MORE population is not significant, but a reduction of 47% ($P = 0.04$) is noted in a post hoc analysis of patients with severe (semi-quantitative grade 3) prevalent vertebral fractures.⁸⁶ In another post hoc analysis of postmenopausal women without baseline vertebral fracture who are osteopenic at the total hip by NHANES III criteria, treatment with 60 mg per day of raloxifene significantly reduced the risk of new vertebral fractures (47% reduction) and new clinical vertebral fractures (75% reduction).⁸⁷

A meta-analysis of seven randomized placebo-controlled trials of raloxifene found BMD increased by 2.51% ($P < 0.01$) at the lumbar spine and 2.11% at the total hip ($P < 0.01$). There was evidence for the reduction of vertebral fractures (40% reduction; $P = 0.01$) but not for non-vertebral fractures ($P = 0.24$).⁸⁸

In the prevention trials, it was reported that fewer women in the raloxifene treatment group progressed from normal to osteopenia, and from osteopenia to osteoporosis.⁸⁹

In addition to its skeletal effects, the MORE trial demonstrates that raloxifene reduces breast cancer by 76% in postmenopausal women with osteoporosis.⁹⁰ The recent results of Continuing Outcomes of Raloxifene Evaluation (CORE), the extension arm of the MORE trial, confirm that the breast cancer reduction effect in osteoporotic women lasts up to 8 years, with a reduction rate of 66%.⁹¹

Unlike the HERS and WHI trials, which indicated an increased risk of cardiovascular events, the MORE trial did not demonstrate harmful effects of raloxifene on the cardiovascular system. In fact, in a subset of women at high risk of cardiovascular diseases, it may have a beneficial effect.⁹²

Until more results are published in the STAR and RUTH trials, raloxifene is not recommended for prevention of breast cancer or cardiovascular diseases.

SOGC Clinical Tip

Because of its vertebral fracture efficacy data and its additional extraskeletal benefits, raloxifene (Evista) 60 mg daily is recommended to prevent and treat osteoporosis in younger, asymptomatic postmenopausal women.

Tolerability and Safety—The side effects of raloxifene are minimal, with increased incidence of leg cramps and hot flashes (especially in the younger postmenopausal women). The incidence of deep venous thrombosis doubles, but the absolute incidence is small. Venous thromboembolism is a serious side effect associated with raloxifene, although it is reported infrequently: 1.44 and 3.32 events per 1000 woman-years for placebo and raloxifene 60 mg per day.⁹⁰ The magnitude of the relative risk is similar to that observed with both HRT or HT7^{2,93} and tamoxifen.⁹⁴ Patients are advised to stop using raloxifene a few days prior to major surgeries or long-haul international travel.

SELECTIVE ESTROGEN RECEPTOR MODULATORS RECOMMENDATION

- 13** Treatment with raloxifene should be considered to decrease vertebral fractures. (IA)

Calcitonin

Calcitonin is a hormone, produced in the thyroid gland, which is effective in specifically inhibiting osteoclastic bone resorption. Poor oral absorption necessitates either subcutaneous or intranasal administration. Nasal spray calcitonin 200 IU is approved for the treatment of postmenopausal osteoporosis.¹²⁹ BMD stabilizes at the lumbar spine and at the hip, similar to the effect of calcium and vitamin D.¹²⁹

A meta-analysis of 30 RCTs (of which 15 were placebo controlled) of calcitonin found a significant relative risk reduction of 21% ($P=0.05$) in vertebral fractures but not in non-vertebral fractures ($P=0.12$).⁸⁸

In the PROOF study, nasal salmon calcitonin significantly reduced vertebral fractures by 33% to 36% using a daily dose of 200 IU in postmenopausal women with and without prior vertebral fracture.¹²⁹ No anti-fracture effect has been shown with 100 IU or 400 IU doses, and there is no significant reduction in rates of non-vertebral or hip fracture. Some women report the side effect of rhinorrhea. Nasal spray calcitonin has a possible analgesic effect that may be useful in managing the pain of acute vertebral compression fractures. Nasal spray dosing is convenient and flexible.

SOGC Clinical Tip

Nasal spray calcitonin 200 IU (Miacalcin) is approved for the treatment of postmenopausal osteoporosis and has a possible analgesic effect that may be useful in managing the pain of acute vertebral compression fractures.

WHEN TO INITIATE THERAPY

Previous guidelines from the Osteoporosis Society of Canada (now called “Osteoporosis Canada”) advised to consider pharmacologic intervention based on an individual’s lowest BMD T-score not adjusted for age, as a marker of relative fracture risk and a threshold that varies based on the absence or presence of fragility fracture and other risk factors for fracture.³⁹

Although this was major progress compared with the thresholds derived from the WHO, there were still several weaknesses associated with that system:

1. On its own, a T-score is not the optimal diagnostic parameter for clinical decision making.¹³⁰
2. More than half of the osteoporotic fractures occurred in women with a BMD-T score of -1.0 to -2.5 , in a large longitudinal observational study in the US.¹³¹
3. Absolute fracture risk can vary substantially within any WHO category due to modification of risk by other factors such as age and sex.¹³²

Therefore, the OSC now proposes that age, sex, fracture history, and glucocorticoid use be incorporated into the assessment of fracture risk.⁴⁰ Additional clinical variables may be included in the absolute fracture risk estimate in the future when the methods are more firmly established and validated. The OSC recommends using the lowest BMD T-score to determine a person’s 10-year absolute fracture risk: combined risk for fractures of the hip, spine, forearm, and proximal humerus⁴⁰ (Table 11.6).

There are 3 categories for absolute risk: low (less than 10%), moderate (10% to 20%), and high (over 20%). Fragility fracture after age 40 or glucocorticoid use increase risk

categorization to the next level: from low risk to moderate risk, or from moderate risk to high risk.

Co-therapy with bisphosphonates should be initiated in women (with or without HT) receiving or planning to receive a daily dose of prednisone of > 7.5 mg (or equivalent) for more than 3 months.³⁹ Pharmacological intervention should be considered in women at high risk of fracture, particularly those known to have low BMD or prevalent fragility fracture. However, not all clinical risk factors for fracture are amenable to pharmacotherapy. For example, in a non-osteoporotic individual with high risk of falling, a fall prevention program could be preferred to pharmacotherapy.

In low-risk women, the therapeutic intervention could be limited to counselling about bone hygiene, that is, nutrition (adequate calcium and vitamin D through diet and/or supplements), physical exercise, and risk-factor modification (smoking, alcohol, weight).

In moderate-risk women, pharmacological intervention could be considered on the basis of a woman's perception of a serious threat arising from the disease (e.g., strong family history of osteoporotic fracture), or on the basis of the extra skeletal benefits associated with some therapeutic options such as raloxifene; either of these will lead to an improved persistence.

LENGTH OF THERAPY

This issue is simple for teriparatide, the only anabolic agent currently available in Canada. According to its labelling, the duration of treatment with teriparatide is limited to 18 months in Canada. However, for the antiresorptives, there is no current definitive answer to this question. Anti-fracture efficacy has been evaluated in placebo-controlled trials of 3,^{82,96,97,102,103,104} 4,^{84,97,102} or 5 years duration.^{72,73,108,133}

The antiresorptive drugs appear to be safe up to 5,^{72,73} 7,¹⁰⁹ 8,⁹¹ and 10 years¹³⁴ for HT, risedronate, raloxifene, and alendronate, respectively. Except for a rapid loss of hip fracture protection after estrogen discontinuation,¹³⁵ no fracture data are available after discontinuation of any of the other antiresorptive drugs.

CALCITONIN RECOMMENDATION

- 14** Treatment with calcitonin can be considered to decrease vertebral fractures and to reduce pain associated with acute vertebral fractures. (IB)

Parathyroid Hormone

Parathyroid hormone (PTH) and its analogues represent a new class of anabolic agents for the treatment of severe osteoporosis. Unlike current antiresorptive agents, which act primarily by inhibiting bone resorption and remodelling to increase bone mass, PTH directly stimulates osteoblast activities and markedly increases bone formation to a greater extent than bone resorption.

Teriparatide (recombinant human PTH(1–34), the only approved drug in this class, is an analog of parathyroid hormone which has shown a significant relative risk reduction in vertebral (65%; $P < 0.001$) and non-vertebral fractures (53%; $P = 0.02$).¹¹⁷

Teriparatide is administered as a daily subcutaneous injection of 20 mcg and is approved for therapy of up to 18 months. This regimen increased lumbar spine BMD by 9.7% ($P < 0.001$), total hip BMD by 2.6% ($P < 0.001$), and femoral neck BMD by 2.8% ($P < 0.001$).¹¹⁷

Jiang et al. conducted a histomorphometric study of paired bone biopsies from the teriparatide clinical trial. Women receiving teriparatide had significant increases in cancellous bone volume and cancellous trabecular number and connectivity density, as well as an increase in cortical thickness.¹¹⁸

This unique improvement of bone microarchitecture illustrates the bone forming properties of teriparatide and distinguishes it from the maintenance observed with bisphosphonates.¹¹⁹

Because of its cost and its unique anabolic property, teriparatide is usually reserved for patients with severe osteoporosis.

SOGC Clinical Tip

Teriparatide (Forteo) is administered as a daily subcutaneous injection of 20 mcg and is approved for therapy of up to 18 months. It is recommended for patients with prior fragility fractures; patients with very low BMD, below -3 to -3.5 ; or patients who continue to fracture or to lose BMD while taking antiresorptive therapy.

Tolerability and Safety

No major adverse reactions have been associated with teriparatide. Compared with placebo, teriparatide 20 μg per day has a higher incidence of nausea, dizziness, and leg cramps.

Hypercalcemia is an occasional occurrence, but is rarely clinically significant.¹¹⁷

Teriparatide produced osteosarcoma in rats who received the drug at doses 3 to 58 times higher than the human therapeutic dose for virtually their entire lifespan, that is, from the age of 8 weeks to 2 years.¹²⁰ Reported osteosarcomas in Fischer 344 rats are unlikely to predict an increased risk for osteosarcoma subsequent to the therapeutic use of teriparatide in women with severe osteoporosis at the dosage recommended in the product monograph, namely 20 μg per day subcutaneously for 18 months.

Teriparatide should not be used in patients with metabolic bone diseases other than osteoporosis (osteomalacia, primary or secondary hyperparathyroidism, Paget's disease of the bone, hypercalcemia), in patients with cancer or are at risk for bone metastasis, or in patients who have previously undergone bone radiation therapy. Teriparatide is also contraindicated in children and adolescents as well as during pregnancy and while breastfeeding. Known allergy to the product or its excipient also contraindicates its use. Safety of teriparatide use in the presence of renal impairment has not been established and, consequently, is not recommended.

PARATHYROID HORMONE RECOMMENDATION

- 15 Treatment with teriparatide should be considered to decrease vertebral and non-vertebral fractures in postmenopausal women with severe osteoporosis. (IA)

Combination Therapy

Combination of Antiresorptives—The addition of bisphosphonate therapy (alendronate, risedronate, and cyclic etidronate) to long-term ET in women has been shown to improve bone density; when alendronate is added to ET, BMD increases by 3% after 2 years.^{121,122} Other combination therapies (e.g., calcitonin and estrogen, raloxifene and alendronate), also increase bone density. However, fracture data are lacking. Because of the additional cost and side effects and the lack of fracture efficacy, combination therapies are usually not recommended.

Combination of PTH Therapy and Antiresorptives—It appears that bisphosphonates may slightly blunt the effect of PTH therapy if they are given concurrently or preceding PTH therapy.¹²³ There is good evidence that giving bisphosphonates after a course of PTH therapy will enhance and maintain the bone mass.¹²⁴ Estrogen and raloxifene do not appear to have the blunting effect on PTH therapy.^{125–128} Fracture data are lacking and combination therapies are usually not recommended. Sequential therapies preceding or following PTH treatment are useful in maintaining and enhancing bone mass.

When HT is used for symptomatic treatment of postmenopausal women, the addition of bisphosphonates or PTH is indicated in the following situations: significant bone loss despite use of HT; glucocorticoid therapy (at least 7.5 mg prednisone/day, or equivalent, for at least 3 months); and osteoporotic fracture in a woman on HT.

COMBINATION THERAPY RECOMMENDATION

- 16 Although combination of antiresorptive therapies may be synergistic in increasing BMD, the anti-fracture effectiveness has not been proven; therefore, it is not recommended. (ID)

SUMMARY

Osteoporosis and its consequent increase in fracture risk is a major health concern for postmenopausal women, and has the potential to reach epidemic proportions. Low BMD, clinical risk factors for fragility fractures, indices of vertebral fracture such as height loss and kyphosis, and radiographic vertebral fractures are combined in a new paradigm to estimate the 10-year fracture risk and develop treatment protocols for the most at risk women.

Well-designed RCTs have proven the efficacy of drugs such as bisphosphonates, calcitonin, estrogen and progestin therapy, SERMs, and recombinant human PTH (1–34) to treat osteoporosis. These studies also proved undoubtedly that drug therapies for osteoporosis can reduce risk of fractures and improve quality of life. However, the studies' beneficial results are obtained under ideal conditions; but in real life, effectiveness (efficacy in real practice)

matters more than efficacy. Compliance with and adherence to a specific drug may influence effectiveness. Finally, adequate calcium and vitamin D through diet and/or supplements are essential adjuncts to osteoporosis prevention and treatment.

CONCLUSION

In this document, we have outlined clinical decision making to manage postmenopausal women: diagnosis, risk assessment, appropriate investigations, non-pharmacologic and pharmacologic treatments, and monitoring of response to therapy.

We hope this information will assist you in your clinical practice, particularly in selecting the appropriate postmenopausal women to be tested and treated for osteoporosis, as well as the investigations and therapeutic options best suited for postmenopausal patients with osteoporosis.

References

1. Consensus development conference: diagnosis, prophylaxis, and treatment of osteoporosis. *Am J Med.* 1993; 94:646–50. [PubMed: 8506892]
2. Papadimitropoulos EA, Coyte PC, Josse RG, Greenwood CE. Current and projected rates of hip fracture in Canada. *Can Med Assoc J.* 1997; 157:1357–63. [PubMed: 9371065]
3. Tenenhouse A, Joseph L, Kreiger N, Poliquin S, Murray TM, Blondeau L, et al. CaMos Research Group. Canadian Multicentre Osteoporosis Study. Estimation of the prevalence of low bone density in Canadian women and men using a population-specific DXA reference standard: The Canadian Multicentre Osteoporosis Study (CaMos). *Osteoporos Int.* 2000; 11:897–904. [PubMed: 11199195]
4. Looker AC, Orwoll ES, Johnston CC Jr, Lindsay RL, Wahner HW, Dunn WL, et al. Prevalence of low femoral bone density in older US adults from NHANES III. *J Bone Miner Res.* 1997; 12:1761–8. [PubMed: 9383679]
5. Hanley DA, Josse RG. Prevention and management of osteoporosis: consensus statements from the Scientific Advisory Board of the Osteoporosis Society of Canada. *Can Med Assoc J.* 1996; 155:921–3. [PubMed: 8837540]
6. Jackson SA, Tenenhouse A, Robertson L. the CaMos Study Group. Vertebral fracture definition from population-based data: preliminary results from the Canadian Multicentre Osteoporosis Study (CaMos). *Osteoporos Int.* 2000; 11:680–7. [PubMed: 11095171]
7. Melton LJ, Chrischilles EA, Cooper C, Lane AW, Riggs BL. Perspective. how many women have osteoporosis? *J Bone Miner Res.* 1992; 7:1005–10. [PubMed: 1414493]
8. Chrischilles EA, Butler CD, Davis CS, Wallace RB. A model of lifetime osteoporosis impact. *Arch Intern Med.* 1991; 151:2026–32. [PubMed: 1929691]
9. Cauley JA, Thompson DE, Ensrud KC, Scott JC, Black DM. Risk of mortality following clinical fractures. *Osteoporos Int.* 2000; 11:556–61. [PubMed: 11069188]
10. Cooper C, Atkinson EJ, Jacobsen SJ, O’Fallon WM, Melton LJ. Population-based study of survival after osteoporotic fractures. *Am J Epidemiol.* 1993; 137:1001–5. [PubMed: 8317445]
11. Center JR, Nguyen TV, Schneider D, Sambrook PN, Eisman JA. Mortality after all major types of osteoporotic fracture in men and women: an observational study. *Lancet.* 1999; 353:878–82. [PubMed: 10093980]
12. Cooper C, Atkinson EJ, O’Fallon WM, Melton LJ III. Incidence of clinically diagnosed vertebral fractures: a population-based study in Rochester, Minnesota, 1985–1989. *J Bone Miner Res.* 1992; 7:221–7. [PubMed: 1570766]
13. Gold DT. The clinical impact of vertebral fractures: quality of life in women with osteoporosis. *Bone.* 1996; 18:185S–189S. [PubMed: 8777086]

14. Wiktorowicz ME, Goeree R, Papaioannou A, Adachi JD, Papadimitropoulos E. Economic implications of hip fracture: health service use, institutional care and cost in Canada. *Osteoporos Int.* 2001; 12:271–8. [PubMed: 11420776]
15. Shea B, Wells G, Cranney A, Zytaruk N, Robinson V, Griffith L, et al. Osteoporosis Methodology Group; Osteoporosis Research Advisory Group. Calcium supplementation on bone loss in postmenopausal women. *Cochrane Database Syst Rev.* 2004; (1):CD004526. Review. [PubMed: 14974070]
16. McCabe LD, Martin BR, McCabe GP, Johnston CC, Weaver CM, Peacock M. Dairy intakes affect bone density in the elderly. *Am J Clin Nutr.* 2004; 80(4):1066–74. [PubMed: 15447921]
17. Heaney RP, Dowell SD, Bierman J, Hale CA, Bendich A. Absorbability and cost effectiveness in calcium supplementation. *J Am Coll Nutr.* 2001; 20(3):239–46. [PubMed: 11444420]
18. Papadimitropoulos E, Wells G, Shea B, Gillespie W, Weaver B, Zytaruk N, et al. Meta-analyses of therapies for postmenopausal osteoporosis. VIII: meta-analysis of the efficacy of vitamin D treatment in preventing osteoporosis in postmenopausal women. *Endocr Rev.* 2002; 23:560–9. [PubMed: 12202471]
19. Trivedi DP, Doll R, Khaw KT. Effect of four monthly oral vitamin D₃-cholecalciferol supplementation on fractures and mortality in men and women living in the community: randomized double blind controlled trial. *BMJ.* 2003; 326:469–72. [PubMed: 12609940]
20. Porthouse J, Cockayne S, King C, Saxon L, Steele E, Aspray T, et al. Randomized controlled trial of supplementation with calcium and cholecalciferol (vitamin D₃) for prevention of fractures in primary care. *BMJ.* 2005; 330:1003–6. [PubMed: 15860827]
21. Grant AM, Avenell A, Campbell MK, McDonald AM, MacLennan GS, McPherson GC, et al. for the Record Trial Group. Oral vitamin D₃ and calcium for the secondary prevention of low-trauma fractures in elderly people—randomised evaluation of calcium or vitamin D, RECORD): a randomised placebo-controlled trial. *Lancet.* 2005; 6736:63013–9.
22. Smith EL. The role of exercise in the prevention and treatment of osteoporosis [review]. *Tap Geriatr Rehab.* 1995; 10:55–63.
23. Jaglal SB, Kreiger N, Darlington G. Past and recent physical activity and risk of hip fracture. *Am J Epidemiol.* 1993; 138:107–18. [PubMed: 8342529]
24. Kerr DA, Prince RL, Morton A, Dick I. Does high resistance weight training have a greater effect on bone mass than low resistance weight training? [abstract, 128]. *J Bone Miner Res.* 1994; 9(suppl 1):S152.
25. Dalsky GP, Stocke KS, Ehsani AA, Slatopolsky E, Lee WC, Birge SJ Jr. Weight-bearing exercise training and lumbar bone mineral content in postmenopausal women. *Ann Intern Med.* 1998; 108:824–8.
26. Kelley GA, Kelley KS, Tran ZV. Exercise and lumbar spine bone mineral density in postmenopausal women: a meta-analysis of individual patient data. *J Gerontol A Biol Sci Med Sci.* 2002; 57:M599–604. [PubMed: 12196498]
27. Chan K, Qin L, Lau M, Woo J, Au S, Choy W, et al. A randomized, prospective study of the effects of Tai Chi Chun exercise on bone mineral density in postmenopausal women. *Arch Phys Med Rehabil.* 2004; 85:717–22. [PubMed: 15129394]
28. Bonaiuti D, Shea B, Iovine R, Negrini S, Robinson V, Kemper HC, et al. Exercise for preventing and treating osteoporosis in postmenopausal women. *Cochrane Database Syst Rev.* 2002; (3):CD000333. Review. [PubMed: 12137611]
29. Carter ND, Khan KM, McKay HA, Petit MA, Waterman C, Heinonen A, et al. Community-based exercise program reduces risk factors for falls in 65-to 75-year-old women with osteoporosis: randomized controlled trial. *Can Med Assoc J.* 2002; 167(9):997–1004. Erratum in: *Can Med Assoc J* 2003;168(2):152. [PubMed: 12403738]
30. Munger RG, Cerhan JR, Chiu BC-H. Prospective study of dietary protein intake and risk of hip fracture in postmenopausal women. *Am J Clin Nutr.* 1999; 69:147–52. [PubMed: 9925137]
31. Kanis JA, Borgstrom F, De Laet C, Johansson H, Johnell O, Jonsson B, et al. Assessment of fracture risk. *Osteoporos Int.* 2005; 16(6):581–9. Epub 2004 Dec 23. [PubMed: 15616758]

32. Hampson G, Martin FC, Moffat K, Vaja S, Sankaralingam S, Cheung J, et al. Effects of dietary improvement on bone metabolism in elderly underweight women with osteoporosis: a randomised controlled trial. *Osteoporos Int.* 2003; 14(9):750–6. Epub 2003 Aug 5. [PubMed: 12904840]
33. Harrington M, Bennett T, Jakobsen J, Ovesen L, Brot C, Flynn A, et al. Effect of a high-protein, high-salt diet on calcium and bone metabolism in postmenopausal women stratified by hormone replacement therapy use. *Eur J Clin Nutr.* 2004; 58(10):1436–9. [PubMed: 15100715]
34. Cifuentes M, Riedt CS, Brodin RE, Field MP, Sherrell RM, Shapses SA. Weight loss and calcium intake influence calcium absorption in overweight postmenopausal women. *Am J Clin Nutr.* 2004; 80(1):123–30. [PubMed: 15213038]
35. Kiel DP, Felson DT, Hannan MT, Anderson JJ, Wilson PWF. Caffeine and the risk of hip fracture: the Framingham study. *Am J Epidemiol.* 1990; 132(4):675–84.
36. Oncken C, Prestwood K, Cooney JL, Unson C, Fall P, Kulldorff M, et al. Effects of smoking cessation or reduction on hormone profiles and bone turnover in postmenopausal women. *Nicotine Tob Res.* 2002; 4(4):451–8. [PubMed: 12521404]
37. World Health Organization. Technical report series. Geneva: WHO; 1994. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis.
38. No authors listed. Osteoporosis Prevention, Diagnosis, and Therapy. NIH Consensus Statement Online. 2000 Mar 27–29; 17(1):1–36. [Accessed on Dec. 2nd, 2005] <http://consensus.nih.gov/2000/2000Osteoporosis111html.htm>.
39. Brown JP, Josse RG. for the Scientific Advisory Council of the Osteoporosis Society of Canada. 2002 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada. *Can Med Assoc J.* 2002; 167:S1–S36. [PubMed: 12427685]
40. Siminoski K, Leslie WD, Frame H, Hodsmann A, Josse RG, Khan A, et al. Recommendations for bone mineral density reporting in Canada. *Can Assoc Radiol J.* 2005; 56(3):178–88. [PubMed: 16144280]
41. Ungar WJ, Josse R, Lee S, Ryan N, Adachi R, Hanley D, et al. The Canadian SCORE questionnaire: optimizing the use of technology for low bone density assessment. Simple Calculated Osteoporosis Risk Estimate *J Clin Densitom.* 2000; 3:269–80. [PubMed: 11090234]
42. Cadarette SM, Jaglal SB, Kreiger N, McIsaac WJ, Darlington GA, Tu JV. Development and validation of the osteoporosis risk assessment instrument to facilitate selection of women for bone densitometry. *Can Med Assoc J.* 2000; 162:1289–94. [PubMed: 10813010]
43. National Osteoporosis Foundation. Osteoporosis: review of the evidence for prevention, diagnosis, and treatment and cost-effectiveness analysis. *Osteoporos Int.* 1998; 8(Suppl 4):7–80.
44. Cadarette SM, Jaglal SB, Murray TM, McIsaac WJ, Joseph L, Brown JP. Evaluation of decision rules for referring women for bone densitometry by dual-energy X-ray absorptiometry. *J Am Med Assoc.* 2001; 286:57–63.
45. Geusens P, Hochberg MC, van der Voort DJ, Pols H, van der Klift M, Siris E, et al. Performance of risk indices for identifying low bone density in postmenopausal women. *Mayo Clin Proc.* 2002; 77:629–37. [PubMed: 12108600]
46. Cadarette SM, McIsaac WJ, Hawker GA, Jaakkimainen L, Culbert A, Zarifa G, et al. The validity of decision rules for selecting women with primary osteoporosis for bone mineral density testing. *Osteoporos Int.* 2004; 15:361–6. [PubMed: 14730421]
47. Richey F, Gourlay M, Ross PD, Sen SS, Radican L, De Ceulaer F, et al. Validation and comparative evaluation of the osteoporosis self-assessment tool—OST in a Caucasian population from Belgium. *Q J Med.* 2004; 97:39–46.
48. Hajcsar EE, Hawker G, Bogoch ER. Investigation and treatment of osteoporosis in patients with fragility fracture. *Can Med Assoc J.* 2000; 163:819–22. [PubMed: 11033708]
49. Papaioannou A, Giangregorio L, Kvern B, Boulos P, Ioannidis G, Adachi JD. The osteoporosis care gap in Canada. *BMC Musculoskelet Disord.* 2004; 5(1):11. [PubMed: 15068488]
50. Ingle BM, Eastell R. Site-specific bone measurements in patients with ankle fracture. *Osteoporos Int.* 2002; 13:342–7. [PubMed: 12030550]
51. Jacobsen D, Sargent J, Atkinson EJ, O’Fallon WM, Melton LJI. Contribution of weather to the seasonality of distal forearm fractures: a population-based study in Rochester, Minnesota. *Osteoporos Int.* 1999; 9:254–9. [PubMed: 10450415]

52. Tromp AM, Smit JH, Deeg DJH, Bouter LM, Lips P. Predictors for falls and fractures in longitudinal aging study Amsterdam. *J Bone Miner Res.* 1998; 13:1932–9. [PubMed: 9844112]
53. Kannus P, Palvanen M, Niemi S, Parkkari J, Jarvinen M. Epidemiology of Osteoporotic Pelvic Fractures in Elderly People in Finland: Sharp Increase in 1970–1997 and alarming projections for the new millennium. *Osteoporos Int.* 2000; 11:443–8. [PubMed: 10912847]
54. Kanis JA, Oden A, Johnell O, Jonsson B, de Laet C, Dawson A. The burden of osteoporotic fractures: a method for setting intervention thresholds. *Osteoporos Int.* 2001; 12:417–27. [PubMed: 11444092]
55. Khan SA, de Geus C, Holroyd B, Russell AS. Osteoporosis follow-up after wrist fractures following minor trauma. *Arch Intern Med.* 2001; 161:1309–12. [PubMed: 11371259]
56. Siminoski K, Jiang G, Adachi JD, Hanley DA, Cline G, Ioannidis G, et al. Accuracy of height loss during prospective monitoring for detection of incident vertebral fractures. *Osteoporos Int.* 2005; 16(4):403–10. Epub 2004 Aug 11. [PubMed: 15309381]
57. Klotzbuecher CM, Ross PD, Landsman PB, Abbott TAI, Berger M. Patients with prior fractures have an increased risk of future fractures: a summary of the literature and statistical synthesis. *J Bone Miner Res.* 2000; 15:721–39. [PubMed: 10780864]
58. Khan AA, Brown JP, Kendler DL, Leslie WD, Lentle BC, Lewiecki EM, et al. The 2002 Canadian bone densitometry recommendations: take-home messages. *Can Med Assoc J.* 2002; 167(10):1141–5. [PubMed: 12427706]
59. Bauer DC, Gluer CC, Cauley JA, Vogt TM, Ensrud KE, Genant HK, et al. Broadband ultrasound attenuation predicts fractures strongly and independently of densitometry in older women. A prospective study. Study of Osteoporotic Fractures Research Group. *Arch Intern Med.* 1997; 157:629–34. [PubMed: 9080917]
60. Hans D, Dargent-Molina P, Schott AM, Sebert JL, Cormier C, Kotzki PO, et al. Ultrasonographic heel measurements to predict hip fracture in elderly women: the EPIDOS prospective study. *Lancet.* 1996; 348:511–4. [PubMed: 8757153]
61. Ettinger B, Black DM, Mitlak BH, Knickerbocker RK, Nickelsen T, Genant HK, et al. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. Multiple Outcomes of Raloxifene Evaluation (MORE) Investigators. *J Am Med Assoc.* 1999; 282(7):637–45.
62. Lindsay R, Silverman SL, Cooper C, Hanley DA, Barton I, Broy SB, et al. Risk of new fracture in the year following a fracture. *J Am Med Assoc.* 2001; 285:320–3.
63. Black DM, Arden NK, Palermo L, Pearson J, Cummings SR. Prevalent vertebral deformities predict hip fractures and new vertebral deformities but not wrist fractures. Study of Osteoporotic Fractures Research Group. *J Bone Miner Res.* 1999; 14:821–8. [PubMed: 10320531]
64. National Osteoporosis Foundation Working Group on Vertebral Fractures. Assessing vertebral fractures. *J Bone Miner Res.* 1995; 10:518–23. [PubMed: 7610921]
65. Miller PD, Baran DT, Bilezikian JP, Greenspan SL, Lindsay R, Riggs BL, et al. Practical clinical application of biochemical markers of bone turnover: consensus of an expert panel. *J Clin Densitom.* 1999; 2(3):323–42. [PubMed: 10548827]
66. Garnero P, Hausherr E, Chapuy MC, Marcelli C, Grandjean H, Muller C, et al. Markers of bone resorption predict hip fracture in elderly women: the EPIDOS prospective study. *J Bone Miner Res.* 1996; 11(10):1531–8. [PubMed: 8889854]
67. Looker AC, Bauer DC, Chesnut CHI, Gundberg M, Hochberg MC, Kleerekoper M, et al. Clinical use of biochemical markers of bone remodeling: current status and future directions. *Osteoporos Int.* 2000; 11:467–80. [PubMed: 10982161]
68. Delmas PD, Eastell R, Garnero P, Seibel MJ, Stepan J. for the Committee of Scientific Advisors of the International Osteoporosis Foundation. The use of biochemical markers of bone turnover in Osteoporosis. *Osteoporos Int.* 2000; (Suppl 6):S2–S17. [PubMed: 11193237]
69. Eastell R, Barton I, Hannon RA, Chines A, Garnero P, Delmas PD. Relationship of early changes in bone resorption to the reduction in fracture risk with risedronate. *J Bone Miner Res.* 2003; 18(6):1051–6. [PubMed: 12817758]

70. Nishizawa Y, Nakamura T, Ohta H, Kushida K, Gorai I, Shiraki M, et al. Guidelines for the use of biochemical markers of bone turnover in osteoporosis–2004. *J Bone Miner Metab.* 2005; 23:97–104.
71. Garnero P, Bianchi F, Cartier M-C, Genty V, Jacob N, Karmel S, et al. Les marqueurs biologiques du remodelage osseux: variations pré-analytiques et recommandations pour leur utilisation. *Annales de Biologie Clinique.* 2000; 58(6):683–704. [PubMed: 11098165]
72. Writing Group for the Women’s Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women’s Health Initiative Randomized Controlled Trial. *J Am Med Assoc.* 2002; 288:321–33.
73. Writing Group for the Women’s Health Initiative Investigators. *J Am Med Assoc.* 2004; 291:1701–12.
74. Blake JM, Collins JA, Reid RL, Fedorkow DM, Lalonde AB. The SOGC statement on the WHI report on estrogen and progestin use in postmenopausal women. *J Obstet Gynaecol Can.* 2002; 24:783–90. [PubMed: 12399806]
75. NAMS Board of Trustees. Recommendations for estrogen and progestogen use in peri- and postmenopausal women: October 2004 position statement of The North American Menopause Society. *Menopause.* 2004; 11:589–600. [PubMed: 15545786]
76. Bhavnani BR, Strickler RC. Menopausal hormone therapy. *J Obstet Gynaecol Can.* 2005; 27:137–62. [PubMed: 15937590]
77. Ettinger B, Genant HK, Cann CE. Long-term estrogen replacement therapy prevents bone loss and fractures. *Ann Intern Med.* 1985; 102:319–24. [PubMed: 2982302]
78. Nachtigall LE, Nachtigall RH, Nachtigall RD, Beckman EM. Estrogen replacement therapy I: a 10-year prospective study in the relationship to osteoporosis. *Obstet Gynecol.* 1979; 53:277–81. [PubMed: 218151]
79. Lufkin EG, Wahner HW, O’Fallon WM, Hodgson SF, Kotowica MA, Lane AW, et al. Treatment of postmenopausal osteoporosis with transdermal estrogen. *Ann Intern Med.* 1992; 117:1–9. [PubMed: 1534476]
80. Genant HK, Lucas J, Weiss S, Akin M, Emkey R, McNaney-Flint H, et al. Low-dose esterified estrogen therapy: effects on bone, plasma estradiol concentrations, endometrium, and lipid levels. *Estratab/Osteoporosis Study Group. Arch Intern Med.* 1997; 157:2609–15. [PubMed: 9531230]
81. Ettinger B, Ensrud KE, Wallace R, Johnson KC, Cummings SR, Yankov V, et al. Effects of ultralow-dose transdermal estradiol on bone mineral density: a randomized clinical trial. *Obstet Gynecol.* 2004; 104:443–51. [PubMed: 15339752]
82. Ettinger B, Black DM, Mitlak BH, Knickerbocker RK, Nickelsen T, Genant HK, et al. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. *Multiple Outcomes of Raloxifene Evaluation (MORE) Investigators. J Am Med Assoc.* 1999; 282:637–45.
83. Lufkin EG, Wong M, Deal C. The role of selective estrogen receptor modulators in the prevention and treatment of osteoporosis. *Rheum Dis Clin North Am.* 2001; 27:163–85. vii. [PubMed: 11285993]
84. Delmas PD, Ensrud KE, Adachi JD, Harper KD, Sarkar S, Gennari C, et al. Efficacy of raloxifene on vertebral fracture risk reduction in postmenopausal women with osteoporosis: four-year results from a randomized clinical trial. *J Clin Endocrinol Metab.* 2002; 87(8):3609–17. [PubMed: 12161484]
85. Maricic M, Adachi JD, Sarkar S, Wu W, Wong M, Harper KD. Early effects of raloxifene on clinical vertebral fractures at 12 months in postmenopausal women with osteoporosis. *Arch Intern Med.* 2002; 162(10):1140–3. [PubMed: 12020184]
86. Delmas PD, Genant HK, Crans GG, Stock JL, Wong M, Siris E, et al. Severity of prevalent vertebral fractures and the risk of subsequent vertebral and nonvertebral fractures: results from the MORE trial. *Bone.* 2003; 33(4):522–32. [PubMed: 14555255]
87. Kanis JA, Johnell O, Black DM, Downs RW, Sarkar S, Fuerst T, et al. Effect of raloxifene on the risk of new vertebral fracture in postmenopausal women with osteopenia or osteoporosis: a reanalysis of the Multiple Outcomes of Raloxifene Evaluation trial. *Bone.* 2003; 33(3):293–300. [PubMed: 13678769]

88. Cranney A, Guyatt G, Griffith L, Wells G, Tugwell P, Rosen C. Osteoporosis Methodology Group and The Osteoporosis Research Advisory Group. Meta-analyses of therapies for postmenopausal osteoporosis. IX: summary of meta-analyses of therapies for postmenopausal osteoporosis. *Endocr Rev.* 2002; 23:570–8. [PubMed: 12202472]
89. Jolly EE, Bjarnason NH, Neven P, Plouffe L Jr, Johnston CC Jr, Watts SD, et al. Prevention of osteoporosis and uterine effects in postmenopausal women taking raloxifene for 5 years. *Menopause.* 2003; 10(4):337–44. [PubMed: 12851517]
90. Cauley JA, Norton L, Lippman ME, Eckert S, Krueger KA, Purdie DW, et al. Continued breast cancer risk reduction in postmenopausal women treated with raloxifene: 4-year results from the MORE trial. Multiple outcomes of raloxifene evaluation. *Breast Cancer Res Treat.* 2001; 65(2): 125–34. [PubMed: 11261828]
91. Martino S, Cauley JA, Barrett-Connor E, Powles TJ, Mershon J, Disch D. Continuing outcomes relevant to Evista: breast cancer incidence in postmenopausal osteoporotic women in a randomized trial of raloxifene. *J Natl Cancer Inst.* 2004; 96:1751–61. [PubMed: 15572757]
92. Barrett-Connor E, Grady D, Sashegyi A, Anderson PW, Cox DA, Hosszowski K, et al. for the MORE Investigators. Raloxifene and cardiovascular events in osteoporotic postmenopausal women: 4-year results from the MORE–Multiple Outcomes of Raloxifene Evaluation) Randomized Trial. *J Am Med Assoc.* 2002; 287:847–57.
93. Grady D, Wenger NK, Herrington D, Khan S, Furberg C, Hunninghake D, et al. Postmenopausal hormone therapy increases risk for venous thromboembolic disease: the heart and estrogen/progestin replacement study. *Ann Int Med.* 2000; 132(9):689–96. [PubMed: 10787361]
94. Fisher B, Costantino JP, Wickherham DL, Redmond CK, Kavanah M, Cronin WM. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. *J Natl Cancer Inst.* 1998; 90:1371–88. [PubMed: 9747868]
95. Mathoo JM, Cranney A, Papaioannou A, Adachi JD. Rational use of oral bisphosphonates for the treatment of osteoporosis. *Curr Osteoporos Rep.* 2004; 2:17–23. [PubMed: 16036078]
96. Cranney A, Guyatt G, Krolicki N, Welch V, Griffith L, Adachi JD, et al. Osteoporosis Research Advisory Group–ORAG. A meta-analysis of etidronate for the treatment of postmenopausal osteoporosis. *Osteoporos Int.* 2001; 12:140–51. [PubMed: 11303715]
97. Cranney A, Wells G, Willan A, Griffith L, Zytaruk N, Robinson V, et al. Meta-analyses of therapies for postmenopausal osteoporosis. II. meta-analysis of alendronate for the treatment of postmenopausal women. *Endocr Rev.* 2002; 23:508–16. [PubMed: 12202465]
98. Black DM, Cummings SR, Karpf DB, Cauley JA, Thompson DE, Nevitt MC, et al. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. *Lancet.* 1996; (348–9041):1535–41. [PubMed: 8950879]
99. Black DM, Thompson DE, Bauer DC, Ensrud K, Musliner T, Hochberg MC. Fracture risk reduction with alendronate in women with osteoporosis: the Fracture Intervention Trial–FIT) Research Group. *J Clin Endocrinol Metab.* 2000; 85:4118–24. [PubMed: 11095442]
100. Quandt SA, Thompson DE, Schneider DL, Nevitt MC, Black DM. Fracture Intervention Trial Research Group. Effect of alendronate on vertebral fracture risk in women with bone mineral density T scores of –1.6 to –2. 5 at the femoral neck: the Fracture Intervention Trial. *Mayo Clin Proc.* 2005; 80:343–9. [PubMed: 15757015]
101. Tonino RP, Meunier PJ, Emkey R, Rodriguez-Portales JA, Menkes CJ, Wasnich RD, et al. Skeletal benefits of alendronate: 7-year treatment of postmenopausal osteoporotic women. Phase III Osteoporosis Treatment Study Group. *J Clin Endocrinol Metab.* 2000; 85:3109–15. [PubMed: 10999794]
102. Cranney A, Tugwell P, Adachi J, Weaver B, Zytaruk N, Papaioannou A, et al. Meta-analyses of therapies for postmenopausal osteoporosis. III. meta-analysis of risedronate for the treatment of postmenopausal osteoporosis. *Endocr Rev.* 2002; 23:517–23. [PubMed: 12202466]
103. Harris ST, Watts NB, Genant HK, McKeever CD, Hangartner T, Keller M, et al. Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. Vertebral Efficacy with Risedronate Therapy–VERT) Study Group. *J Am Med Assoc.* 1999; (282–14):1344–52.

104. Reginster J-Y, Minne HW, Sorensen OH, Hooper M, Roux C, Brandi ML, et al. Randomized trial of the effects of risedronate on vertebral fractures in women with established postmenopausal osteoporosis. Vertebral Efficacy with Risedronate Therapy (VERT) Study Group. *Osteoporos Int.* 2000; 11(1):83–91. [PubMed: 10663363]
105. Heaney RP, Zizic TM, Fogelman I, Olszynski WP, Geusens P, Kasibhatla C, et al. Risedronate reduces the risk of first vertebral fracture in osteoporotic women. *Osteoporos Int.* 2002; 13:501–5. [PubMed: 12107665]
106. Harrington JT, Ste-Marie LG, Brandi ML, Civitelli R, Fardellone P, Grauer A, et al. Risedronate rapidly reduces the risk for nonvertebral fractures in women with postmenopausal osteoporosis. *Calcif Tissue Int.* 2004; 74:129–35. Epub 2003 Dec 5. [PubMed: 14648009]
107. Roux C, Seeman E, Eastell R, Adachi J, Jackson RD, Felsenberg D, et al. Efficacy of risedronate on clinical vertebral fractures within six months. *Curr Med Res Opin.* 2004; 20(4):433–9. [PubMed: 15119979]
108. Sorensen OH, Crawford GM, Mulder H, Hosking DJ, Gennari C, Mellstrom D, et al. Long-term efficacy of risedronate: a 5-year placebo-controlled clinical experience. *Bone.* 2003; 32(2):120–6. [PubMed: 12633783]
109. Mellstrom DD, Sorensen OH, Goemaere S, Roux C, Johnson TD, Chines AA. Seven years of treatment with risedronate in women with postmenopausal osteoporosis. *Calcif Tissue Int.* 2004; 75:462–8. Epub 2004 Oct 7. [PubMed: 15455188]
110. McClung MR, Geusens P, Miller PD, Zippel H, Bensen WG, Roux C, et al. Effect of risedronate on the risk of hip fracture in elderly women. *N Engl J Med.* 2001; 344:333–40. [PubMed: 11172164]
111. Bauer DC, Black D, Ensrud K, Thompson D, Hochberg M, Nevitt M, et al. Upper gastrointestinal tract safety profile of alendronate: the fracture intervention trial. *Arch Intern Med.* 2000; 160:517–25. [PubMed: 10695692]
112. Taggart H, Bolognese MA, Lindsay R, Ettinger MP, Mulder H, Josse RG, et al. Upper gastrointestinal tract safety of risedronate: a pooled analysis of 9 clinical trials. *Mayo Clin Proc.* 2002; 77:262–70. [PubMed: 11888030]
113. Schnitzer T, Bone HG, Crepaldi G, Adami S, McClung M, Kiel D, et al. Therapeutic equivalence of alendronate 70 mg once-weekly and alendronate 10 mg daily in the treatment of osteoporosis. Alendronate Once-Weekly Study Group. *Aging–Milano.* 2000; 12:1–12. [PubMed: 10746426]
114. Rizzoli R, Greenspan SL, Bone G 3rd, Schnitzer TJ, Watts NB, Adami S, et al. Two-year results of once-weekly administration of alendronate 70 mg for the treatment of postmenopausal osteoporosis. *J Bone Miner Res.* 2002; 17:1988–96. [PubMed: 12412806]
115. Brown JP, Kendler DL, McClung MR, Emkey RD, Adachi JD, Bolognese MA, et al. The efficacy and tolerability of risedronate once a week for the treatment of postmenopausal osteoporosis. *Calcif Tissue Int.* 2002; 71:103–11. Epub 2002 Jun 27. [PubMed: 12085156]
116. Papaioannou A, Ioannidis G, Adachi JD, Sebaldt RJ, Ferko N, Puglia M, et al. Adherence to bisphosphonates and hormone replacement therapy in a tertiary care setting of patients in the CANDOO database. *Osteoporos Int.* 2003; 14:808–13. Epub 2003 Sep 11. [PubMed: 14523610]
117. Neer RM, Arnaud CD, Zanchetta JR, Prince R, Gaich GA, Reginster JY, et al. Effect of parathyroid hormone –1–34 on fractures and bone mineral density in postmenopausal women with osteoporosis. *N Engl J Med.* 2001; 344:1434–41. [PubMed: 11346808]
118. Jiang Y, Zhao JJ, Mitlak BH, Wang O, Genant HK, Eriksen EF. Recombinant human parathyroid hormone –1–34 [teriparatide] improves both cortical and cancellous bone structure. *J Bone Miner Res.* 2003; 18:1932–41. [PubMed: 14606504]
119. Borah B, Dufresne TE, Chmielewski PA, Johnson TD, Chines A, Manhart MD. Risedronate preserves bone architecture in postmenopausal women with osteoporosis as measured by three-dimensional microcomputed tomography. *Bone.* 2004; 34:736–46. [PubMed: 15050906]
120. Vahle JL, Sato M, Long GG, Young JK, Francis PC, Engelhardt JA, et al. Skeletal changes in rats given daily subcutaneous injections of recombinant human parathyroid hormone –1–34 for 2 years and relevance to human safety. *Toxicol Pathol.* 2002; 30:312–21. [PubMed: 12051548]

121. Lindsay R, Cosman F, Lobo RA, Walsh BW, Harris ST, Reagan JE. Addition of alendronate to ongoing hormone replacement therapy in the treatment of osteoporosis: a randomized, controlled clinical trial. *J Clin Endocrinol Metab.* 1999; 84:3076–81. [PubMed: 10487668]
122. Wimalawansa SJ. Combined therapy with estrogen and etidronate has an additive effect on bone mineral density in the hip and vertebrae: four-year randomized study. *Am J Med.* 1995; 99:36–42. [PubMed: 7598140]
123. Delmas PD, Vergnaud P, Arlot ME, Pastoureau P, Meunier PJ, Nilssen MHL. The anabolic effect of human PTH –1–34) on bone formation is blunted when bone resorption is inhibited by the bisphosphonate tiludronate – is activated resorption a prerequisite for the in vivo effect of PTH on formation in a remodelling system? *Bone.* 1995; 16:603–10. [PubMed: 7669436]
124. Rittmaster RS, Bolognese M, Ettinger MP, Hanley DA, Hodsman AB, Kendler DL, et al. Enhancement of bone mass in osteoporotic women with parathyroid hormone followed by alendronate. *J Clin Endocrinol Metab.* 2000; 85:2129–34. [PubMed: 10852440]
125. Cosman F, Nieves J, Woelfert L, Formica C, Gordon S, Shen V, et al. Parathyroid hormone added to established hormone therapy: effects on vertebral fracture and maintenance of bone mass after parathyroid hormone withdrawal. *J Bone Miner Res.* 2001; 16:925–31. [PubMed: 11341338]
126. Reeve J, Bradbeer JN, Arlot M, Davies UM, Green JR, Hampton L, et al. hPTH 1–34 treatment of osteoporosis with added hormone replacement therapy: biochemical, kinetic and histological responses. *Osteoporosis Int.* 1991; 1:162–70.
127. Ettinger B, San Martin JA, Crans GG, Pavo I. Differential effects of Teriparatide after treatment with raloxifene or alendronate. *J Bone Miner Res.* 2004; 19:745–51. [PubMed: 15068497]
128. Roe EB, Sanchez SD, Cann CE, del Puerto GA, Pierini E, Arnaud CD. PTH-induced increases in bone density are preserved with estrogen: results from a follow-up year in postmenopausal osteoporosis [abstract]. *J Bone Miner Res.* 2000; 15:S193.
129. Chesnut CH 3rd, Silverman S, Andriano K, Genant G, Gimona A, Harris S, et al. A randomized trial of nasal spray salmon calcitonin in post-menopausal women with established osteoporosis: the prevent recurrence of osteoporotic fractures study. PROOF Study Group. *Am J Med.* 2000; 109:267–76. [PubMed: 10996576]
130. Faulkner KG. The tale of the T-score: review and perspective. *Osteoporosis Int.* 2005; 16:347–52. [PubMed: 15565352]
131. Siris ES, Chen Y-T, Abbott TA, Barrett-Connor, Miller PD, Wehren LE, Berger ML. Bone mineral density thresholds for pharmacological intervention to prevent fractures. *Arch Intern Med.* 2004; 164:1108–12. [PubMed: 15159268]
132. Kanis JA, Johnell O, Oden A, Dawson A, De Laet C, Jonsson B. Ten year probabilities of osteoporotic fractures according to BMD and diagnostic thresholds. *Osteoporosis Int.* 2001; 12:989–95. [PubMed: 11846333]
133. Ste-Marie L, Sod E, Johnson T, Chines A. Five years of treatment with risedronate and its effects on bone safety in women with postmenopausal osteoporosis. *Calcif Tissue Int.* 2004; 75:469–76. [PubMed: 15478000]
134. Bone HG, Hosking D, Devogelaer JP, Tucci JR, Emkey RD, Tonino RP, et al. Ten years–experience with alendronate for osteoporosis in postmenopausal women. *N Engl J Med.* 2004; 350(12):1189–99. [PubMed: 15028823]
135. Yates J, Barrett-Connor E, Barlas S, Chen YT, Miller PD, Siris ES. Rapid loss of hip fracture after estrogen cessation: evidence from the National Osteoporosis Risk Assessment. *Obstet Gynecol.* 2004; 103(3):440–6. [PubMed: 14990403]

RECOMMENDATIONS

- 1 The goals of osteoporosis management should be fracture risk assessment and prevention of fracture (IB). Bone mineral density should not be viewed as the only indicator for management success because therapy may or may not be associated with significant increases in BMD. (IA)
- 2 Physicians should be aware that a prevalent vertebral or non-vertebral fragility fracture markedly increases the risk of future fracture. (IA)
- 3 Fragility fracture after the age of 40, over 65 years of age without fragility fracture, low BMD, and family history of osteoporotic fracture (especially maternal hip fracture) should be recognized as the key risk factors for fragility fractures. Systemic glucocorticoid use of more than 3 months duration should be considered as another major risk factor. (IA)
- 4 Evaluation of osteoporosis in postmenopausal women should include the assessment of clinical risk factors for low BMD and BMD testing. (IB)
- 5 Central (hip and spine) measurements by dual energy X-ray absorptiometry (DXA) should be used for both risk assessment (IA) and follow-up (IB), as they provide the most accurate and precise measurements of BMD.
- 6 Further evidence should be collected to determine the role of peripheral BMD measurements (e.g., ultrasound or DXA measurements in the radius, phalanx, or heel) in clinical practice. (II-2D)
- 7 Postmenopausal women with historical height loss greater than 6 cm, prospective height loss greater than 2 cm, kyphosis, or acute incapacitating back pain syndrome should be sent for spine radiographs with a specific request to rule out vertebral fractures. (IA)
- 8 Until more data becomes available on other clinical applications, bone turnover markers can be used to rapidly assess adherence and effectiveness of pharmacological interventions. (IB)

Calcium and Vitamin D

- 9 Although it might not be sufficient as the sole therapy for osteoporosis, routine supplementation with calcium (1000 mg/d) and vitamin D3 (800 IU/d) is still recommended as mandatory adjunct therapy to the main pharmacological interventions (antiresorptive and anabolic drugs). (IB)

Hormone Therapy

- 10 Hormone therapy (HT) should be prescribed to symptomatic postmenopausal women as the most effective therapy for symptom relief (IA) and a reasonable choice for the prevention of bone loss and fracture (IA). The risks should be weighted against the benefits if estrogen therapy is being used solely for fracture prevention. (ID)

Bisphosphonates

11 Treatment with alendronate or risedronate should be considered to decrease vertebral, non-vertebral, and hip fractures. (IA)

12 Treatment with etidronate can be considered to decrease vertebral fractures. (IB)

Selective Estrogen Receptor Modulators

13 Treatment with raloxifene should be considered to decrease vertebral fractures. (IA)

Calcitonin

14 Treatment with calcitonin can be considered to decrease vertebral fractures and to reduce pain associated with acute vertebral fractures. (IB)

Parathyroid Hormone

15 Treatment with teriparatide should be considered to decrease vertebral and non-vertebral fractures in postmenopausal women with severe osteoporosis. (IA)

Combination Therapy

16 Although combination of antiresorptive therapies may be synergistic in increasing bone mineral density, the anti-fracture effectiveness has not been proven; therefore, it is not recommended. (ID)

Table 11.1Recommended Calcium and Vitamin D Intake From All Sources^{39*}

Calcium	
Children (4–8)	800 mg
Adolescents (9–18)	1300 mg
Premenopausal women	1000 mg
Men < 50	1000 mg
Menopausal women	1500 mg
Men > 50	1500 mg
Pregnant or lactating women	1000 mg
Vitamin D	
< age 50	400 IU
> age 50	800 IU

*“All sources” means total diet and supplement.

“2002 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada” — Reprinted from, *CMAJ* 12-Nov-02; 167(10 Suppl), Page(s) pages S1–S34 by permission of the publisher. © 2003 CMA Media Inc

Table 11.2**WHO Diagnostic Categories for BMD in Postmenopausal Caucasian Women³⁷**

1	Normal: BMD or BMC not more than 1 SD below the peak bone mass or young adult mean (T-score above -1).
2	Osteopenic: BMD or BMC between 1 and 2.5 SD below the young adult mean (T-score between -1 and -2.5).
3	Osteoporosis: BMD or BMC 2.5 SD or more below the young adult mean (T-score at or below -2.5).
4	Severe osteoporosis (established osteoporosis): BMD or BMC 2.5 SD or more below the young adult mean (T-score at or below -2.5) and the presence of one or more fragility fractures.

WHO: World Health Organization; BMD: bone mineral density; BMC: bone mineral content; SD: standard deviation.

Table 11.3**Risk Factors That Identify who Should be Assessed for Osteoporosis³⁹**

Major Risk Factors	Minor Risk Factors
Age 65 years	Rheumatoid arthritis
Vertebral compression fracture	Past history of clinical hyperthyroidism
Fragility fracture after age 40	Chronic anticonvulsant therapy
Family history of osteoporotic fracture	Low dietary calcium intake
Systemic glucocorticoid therapy 3 months	Smoker
Malabsorption syndrome	Excessive alcohol intake
Primary hyperparathyroidism	Excessive caffeine intake
Propensity to fall	Weight 57 kg
Osteopenia apparent on X-ray film	Weight loss 10% of weight at age 25
Hypogonadism	Chronic heparin therapy
Early menopause (before age 45)	

Osteoporosis Canada has taken the position that “BMD testing is appropriate for targeted case-finding among women under the age of 65 and for all women age 65 and older because of the high risk of osteoporosis and fracture after that age.”³⁹

“2002 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada” — Reprinted from, *CMAJ* 12-Nov-02; 167(10 Suppl), Page(s) pages S1–S34 by permission of the publisher. © 2003 CMA Media Inc.

Table 11.4

Common side effects and contraindications of drugs used in osteoporosis

Drug (trade name)	Common side effects	Contraindications and precautions
Alendronate (Fosamax)	<ul style="list-style-type: none"> Abdominal pain Nausea Diarrhea 	<ul style="list-style-type: none"> Abnormalities of the esophagus Inability to sit/stand upright for 30 minutes Hypersensitivity to the drug Women of childbearing potential Renal insufficiency (# mL/min)
Cyclical etidronate (Didrocal)	<ul style="list-style-type: none"> Diarrhea Nausea Flatulence 	<ul style="list-style-type: none"> Clinically overt osteomalacia Hypersensitivity to the drug Women of childbearing potential Renal insufficiency (mL/min)
Nasal calcitonin (Miacalcin NS)	<ul style="list-style-type: none"> Rhinitis Nasal dryness Epistaxis Abdominal pain 	<ul style="list-style-type: none"> Hypersensitivity to the drug Women of childbearing potential
Raloxifene (Evista)	<ul style="list-style-type: none"> Vasodilatation (flushing) Leg cramps 	<ul style="list-style-type: none"> History of venous thromboembolic events Hypersensitivity to the drug Women of childbearing potential
Risedronate (Actonel)	<ul style="list-style-type: none"> Abdominal pain Hypertension Joint problems 	<ul style="list-style-type: none"> Abnormalities of the esophagus Inability to sit/stand upright for 30 minutes Hypersensitivity to the drug Women of childbearing potential Renal insufficiency (mL/min)
Teriparatide (Forteo)	<ul style="list-style-type: none"> Nausea Dizziness Leg cramps 	<ul style="list-style-type: none"> Hypersensitivity to the drug Pre-existing hypercalcemia Severe renal insufficiency Bone metastases or history of bone cancer Patients at increased risk of developing osteosarcoma that should not be treated with teriparatide: <ul style="list-style-type: none"> Paget's Disease Unexplained elevations of alkaline phosphatase History of internal or external radiotherapy of the skeleton

Table 11.5

Non-hormonal osteoporosis medications

Treatment	Regimen
Alendronate (Fosamax)	10 mg daily 70 mg once weekly
Cyclical etidronate* (Didrocal)	400 mg daily for 2 weeks followed by 500 mg calcium daily for 76 days in a 3-month kit (Didrocal)
Nasal calcitonin (Miacalcin NS)	200 IU daily, intranasally via alternating nostrils
Parathyroid hormone	20 µg subcutaneously daily
Raloxifene (Evista)	60 mg daily
Risedronate (Actonel)	5 mg daily 35 mg once weekly
Prevention	Regimen
Alendronate (Fosamax)	5 mg daily
Cyclical etidronate* (Didrocal)	400 mg daily for 2 weeks followed by 500 mg calcium daily for 76 days in a 3-month kit (Didrocal)
Raloxifene (Evista)	60 mg daily
Risedronate (Actonel)	5 mg daily

* Etidronate alone (Didronel) is only available as a 200 mg tablet.

Table 11.6Ten-year fracture risk for women⁴⁰

Age (years)	Low risk <10%	Moderate risk 10%–20%	High risk >20%
Lowest T-Score			
Lumbar spine, total hip, femoral neck, trochanter			
50	> -2.3	-2.3 to -3.9	< -3.9
55	> -1.9	-1.9 to -3.4	< -3.4
60	> -1.4	-1.4 to -3.0	< -3.0
65	> -1.0	-1.0 to -2.6	< -2.6
70	> -0.8	-0.8 to -2.2	< -2.2
75	> -0.7	-0.7 to -2.1	< -2.1
80	> -0.6	-0.6 to -2.0	< -2.0
85	> -0.7	-0.7 to -2.2	< -2.2