Advances in osteoporosis therapy

2003 update of practical guidelines

Aliya Khan, MD, FRCPC, FACP

ABSTRACT

OBJECTIVE To review evidence for current therapies for postmenopausal osteoporosis and to establish practical guidelines for management of osteoporosis by family physicians.

QUALITY OF EVIDENCE MEDLINE was searched from January 1990 to January 2003. Articles retrieved were graded by level of evidence (I to III). Recommendations for diagnosis and therapy were based on evidence from randomized controlled trials and meta-analyses.

MAIN MESSAGE Osteoporosis is treatable. Early diagnosis and intervention is recommended. After excluding secondary causes of osteoporosis, physicians should advise patients to take appropriate calcium and vitamin D supplementation. Those with osteopenia at risk of fractures and those with established osteoporosis need additional therapy.

CONCLUSION Approved pharmacologic therapies include alendronate, risedronate, raloxifene, calcitonin, cyclical etidronate, and hormone replacement therapy. Family physicians can help with early diagnosis and intervention and should discuss lifestyle modification with patients.

RÉSUMÉ

OBJECTIF Passer en revue les données scientifiques sur le traitement actuel de l'ostéoporose postménopausique et formuler des directives pratiques pour le médecin de famille confronté à ce problème.

QUALITÉ DES PREUVES Une recension a été effectuée dans MEDLINE entre janvier 1990 et janvier 2003. Les articles retenus ont été classés d'après le niveau des preuves (de I à III). Les données sur lesquelles sont fondées les recommandations sur le diagnostic et le traitement provenaient d'essais randomisés et de méta-analyses.

PRINCIPAL MESSAGE On peut traiter l'ostéoporose, mais on recommande un diagnostic et un traitement précoces. Une fois exclues les causes secondaires d'ostéoporose, on doit prescrire des suppléments adéquats de calcium et de vitamine D. Les cas d'ostéopénie avec risque de fracture ou d'ostéoporose bien installée nécessitent d'autres traitements.

CONCLUSION Les médications approuvées incluent l'alendronate, le risédronate, le raloxifène, la calcitonine, l'étidronate cyclique et l'hormonothérapie substitutive. Le médecin de famille peut contribuer au diagnostic et au traitement précoces et il doit discuter avec le patient des changements du mode de vie.

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Osteoporosis is a common condition that affects about one in four women and one in eight men.[1] It is associated with an increased risk of fractures; vertebral fractures are the most common and account for about 40% of all osteoporotic fractures.[2] Fractures of the hip and wrist and other nonvertebral fractures are the next most common. Hip fractures are associated with 20% mortality 1 year after fracture. About half of all patients sustaining hip fractures will not regain independence, and one third will require institutionalization.[2] Unfortunately, most patients with osteoporosis, including those presenting with fragility fractures, are not diagnosed, evaluated, or treated.[3]

This paper focuses on postmenopausal osteoporosis and reviews advances in diagnosis and therapy. Osteoporosis management is of great importance to family physicians because of the high prevalence of the condition and its associated morbidity and mortality.

Quality of evidence

An advanced MEDLINE search was used to identify all randomized controlled trials (RCTs) evaluating therapies for postmenopausal osteoporosis. The search was limited to English-language articles published from January 1990 to January 2003. The term "postmenopausal osteoporosis" was cross-matched with the MeSH headings "therapy" and "prevention." Appropriate articles were appraised. Those reporting on RCTs with level I or II evidence were selected.

Diagnosis

Osteoporosis is clinically diagnosed by fragility fractures or development of dorsal kyphosis secondary to vertebral fracture. The World Health Organization defines osteoporosis as a progressive systemic disease characterized by low bone density and microarchitectural deterioration in bone that predisposes patients to increased bone fragility and fracture.[2] Fragility fractures are fractures caused by trauma that would not cause a normal bone to fracture or by a fall from standing.[4] Before fragility fractures occur, osteoporosis can be diagnosed on the basis of decreased bone mineral density (BMD) (**Table 1**).

A single standard deviation reduction represents about a 10% decrease in BMD from the mean value. For each standard deviation decrease in BMD, risk of fracture approximately doubles.[5] Standards of practice for bone densitometry defining the minimum level of acceptable performance were developed recently for Canada.[5]

Dr Khan *is an Associate Clinical Professor of Medicine at McMaster University in Hamilton, Ont, Chair of the Canadian Panel of the International Society of Clinical Densitometry and member of the Scientific Advisory Council of the Osteoporosis Society of Canada.*

Table 1. World Health Organization criteria for diagnosis of osteoporosis: *T score represents the number of standard deviations a patient is above or below the mean bone mineral density of a young adult population.*

T SCORE	CLASSIFICATION
≥ -1	Normal
-2.5 to -1	Osteopenia
≤ -2.5	Osteoporosis
≤ -2.5 and fracture	Severe osteoporosis

Clinical evaluation

Following assessment of risk of fracture, clinical evaluation should exclude secondary causes of osteoporosis. Clinical assessment includes a complete history and physical examination and appropriate laboratory tests (**Table 2**).[6] History and physical examination will guide physicians as to need for additional investigation. Other investigations helpful in evaluating and excluding secondary causes of osteoporosis include measuring thyroid-stimulating hormone, 24-hour urine calcium, serum parathyroid hormone concentration, and vitamin D concentration (**Table 3**).

Table 2. Tests to exclude secondary causes of osteoporosis

Complete blood count
Serum calcium (correct for albumin)
Serum phosphate
Total alkaline phosphatase
Serum creatinine
Serum protein electrophoresis

Intervention

It is important to discuss lifestyle modification with patients. The average North American diet contains only about 500 mg of calcium: current recommendations for postmenopausal women suggest 1500 mg of elemental calcium each day.[6] Calcium carbonate or calcium citrate are recommended supplements, as is vitamin D in doses of 400 IU/d for those younger than age 50 and 800 IU/d for those older than 50.[6]

The importance of stopping smoking, avoiding or limiting alcohol intake, and doing regular weight-bearing exercises should be stressed.[7] Use of hip-protector

pads has been shown to significantly reduce the likelihood of hip fractures in elderly people.[8]

Table 3. Secondary causes of osteoporosis: *Osteoporosis is secondary to another condition in about 30% of postmenopausal women.*

Drugs
• Steroids
• Heparin
• Gonadotropin–releasing hormone agonists
• Medroxyprogesterone acetate (eg, Depo-Provera)
• Anticonvulsants
• Cytotoxic chemotherapy
Hyperthyroidism
Hypogonadism: premature menopause or amenorrhea lasting longer than 6 months
Hyperparathyroidism
Hypercortisolism
Hypercalciuria
Malabsorption: celiac disease, inflammatory bowel disease, after gastrectomy
Liver disease (for example, primary biliary cirrhosis)
Renal disease
Malignancies and myeloproliferative disorders
Connective tissue disorders
Inherited disorders (osteogenesis imperfecta, Ehlers-Danlos syndrome, Marfan syndrome)

Pharmacotherapy

Currently available therapies are all antiresorptive agents that decrease bone turnover (**Table 4**[9-15]).

Bisphosphonates. Bisphosphonates are compounds that specifically bind to the hydroxyapatite crystals on bone surfaces and inhibit osteoclast function.[16] The first bisphosphonate available for prevention and treatment of osteoporosis was etidronate. It was shown to be effective in decreasing vertebral fractures among postmenopausal women who were at high risk of such fractures.[10,17] No evidence indicates etidronate has a beneficial effect on risk of hip or nonvertebral fractures.

Because etidronate can impair bone mineralization in the same doses as it inhibits bone resorption, it must be given cyclically with drug-free intervals every 3 months. Given continuously, etidronate can impair bone mineralization and allow osteomalacia to develop. Evidence on the efficacy of etidronate for preventing fractures is weak (level II), so it is a second-line drug for osteoporosis. It is, however, cheap and covered by most provinces' drug benefit plans.

More potent bisphosphonates (alendronate and risedronate) that selectively inhibit bone resorption have been developed. High doses are required to inhibit bone mineralization. Alendronate is effective at preventing vertebral, hip, and nonvertebral fractures (level I evidence).[11,18] The incidence of multiple

Table 4. Results of studies on therapies approved for postmenopausal osteoporosis

THERAPY	LEVEL OF EVIDENCE	DURATION OF STUDY (Y)	NO. OF PATIENTS	REDUCTION IN RELATIVE RISK OF NEW VERTEBRAL FRACTURES VS PLACEBO (%)	REDUCTION IN RELATIVE RISK OF HIP FRACTURE (%)
Alendronate[11]	I	3	2027	47	51
Risedronate[12]	I	3	2458	41	Not significant
Risedronate[13]	I	3	9331	Not applicable	30*
Etidronate[10]	II	3	423	18	Not significant
Raloxifene[14]	I	3	7705	30 (patients with pre-existing fractures)	Not significant
				50 (patients with no pre-existing fractures)	Not significant
Calcitonin[15]	II	5	1255	33 (with 200-IU/d dose)	Not significant
Hormone replacement therapy[9]	I	5.2	16 608	34	34

**Subgroup analyses: age 70-79 with T <-3, 40%; similar patients with previous vertebral fractures, 60%; age ≥ 80 with risk factors, not significant.*

new vertebral fractures in patients taking alendronate was lower by 90% in comparison with patients taking placebo ($P < .001$).[11] In a prespecified analysis among women with osteoporosis taking alendronate, incidence of new hip fractures was reduced by 63% within 18 months and new symptomatic vertebral fractures by 59% within 12 months in comparison with placebo.[19]

Alendronate has a rapid antifracture effect. Meta-analyses of trials evaluating alendronate have demonstrated impressive and consistent reductions in vertebral and nonvertebral fractures among women with postmenopausal osteoporosis.[20-22]

Alendronate is generally safe and well tolerated; adverse events are not significantly more frequent than with placebo.[11,18] It is important for patients to take alendronate and other bisphosphonates in a fasting state because a very small amount of the drug is actually absorbed. It is also important to stay upright for about 30 minutes after taking the medication. In patients with gastroesophageal reflux, alendronate, like other aminobisphosphonates, can inhibit the ability of the esophageal epithelial cells to repair acid-induced injury.[19,23] Alendronate taken once weekly at a dose of 70 mg is convenient for patients.[24] It is more expensive than etidronate, however, and is not fully covered on all provinces' drug benefit plans.

Risedronate, an aminobisphosphonate, has also been shown to prevent vertebral and nonvertebral fractures effectively.[12,13,25] Following 12 months' therapy with risedronate, vertebral fractures were reduced by 61% to 65% in comparison with placebo in two trials (level I evidence).[12,25] The drug had a rapid antifracture effect.

The effect of risedronate on risk of hip fracture in elderly women was specifically evaluated in the Hip Intervention Program.[13] Significant reductions in hip fractures, defined by BMD criteria, were noted in women with osteoporosis. No reduction in risk of hip fractures was seen in women who enrolled on the basis of clinical risk factors for fractures.

Once-weekly therapy with risedronate (35 mg) has comparable effects to once-daily risedronate (5 mg) with respect to BMD changes in spine and hip.[26] Risedronate in once-weekly doses is available in Canada; it is also safe and well tolerated. It is more expensive than etidronate and not covered on all provincial drug-benefit plans.

Selective estrogen-receptor modulators. Raloxifene is a valuable treatment for both preventing and treating postmenopausal osteoporosis.[27] Raloxifene reduces incidence of new vertebral fractures by 55% after 3 years' therapy (60 mg/d) (level I evidence).[14,28] Raloxifene has a rapid antifracture effect with a 68% reduction in clinical vertebral fractures after 12 months' therapy.[29]

Reduction in nonvertebral fractures has not reached statistical significance in comparisons of placebo with raloxifene. The Multiple Outcomes of Raloxifene Evaluation (MORE) study,[30] however, was not designed to evaluate effect on risk of nonvertebral fractures. Participants were younger and had less severe osteoporosis than patients in other trials. Women were withdrawn from the MORE trial if they had excessive bone loss or if two or more new vertebral fractures developed. This might have contributed to the very few hip fractures seen in this study. Because of differences in study population, it is difficult to compare drugs and draw conclusions about their efficacy for preventing fractures; a head-to-head trial of the various agents is needed.

Raloxifene has additional benefits. Reductions in total and low-density lipoprotein cholesterol, fibrinogen, lipoprotein A, and homocystine levels have been seen with raloxifene,[31] but no effect has been seen on triglycerides or serum high-density lipoprotein levels.[31] In the MORE trial, cardiac events were reduced by 40% in women at increased risk of cardiovascular disease.[30] Impressive reductions in risk of breast cancer have been documented, with an 84% reduction in estrogen–receptor–positive breast cancers in comparison with placebo.[32] Incidence of thromboembolic disease increases with raloxifene therapy as it can with hormone replacement therapy (HRT); history of thromboembolic events is a contraindication to therapy.

Raloxifene offers additional extraskeletal benefits. It is particularly beneficial for people at risk for vertebral fracture if they are also at increased risk of coronary artery disease or breast cancer. Raloxifene can also be used in combination with aminobisphosphonates for patients at risk of hip fractures.

Calcitonin. Salmon calcitonin is effective at preventing osteoclast-mediated bone resorption.[15,33] The Prevent Recurrence of Osteoporotic Fractures (PROOF) study evaluated calcitonin nasal spray in varying doses.[15] Risk of vertebral fracture was significantly reduced with the 200-IU/d dose,[15] but not with the 100-IU/d or 400-IU/d doses. Unfortunately, the PROOF trial had a high drop-out rate because the study was being completed at the same time as approvals for calcitonin and alendronate were

received. Patients chose to withdraw from the double-blind trial and proceed with open-label drug therapy. Drop-out rates were similar in the therapy and placebo arms of the study. The high drop-out rates might have contributed to the lack of effect seen with the 100-IU/d and 400-IU/d doses.

Salmon calcitonin reduced risk of new vertebral fractures by 62% in comparison with placebo in osteoporotic women older than 75[34] (level II evidence) and was very well tolerated. Adverse effects were limited to minor rhinitis. Calcitonin has no negative effects on bone mineralization and is thus safe for patients with osteomalacia or renal or liver disease. For this patient population, calcitonin is preferred over bisphosphonates. It also benefits patients who have gastrointestinal symptoms and are unable to tolerate oral bisphosphonates. Calcitonin can be used in certain circumstances for premenopausal women, and in combination with other antiresorptive agents. Calcitonin also significantly decreased bone pain associated with vertebral fractures due to its specific and potent analgesic effects (level I evidence).[35]

Hormone replacement therapy. Hormone replacement therapy has been shown in the recent Women's Health Initiative trial to reduce risk of fractures in postmenopausal women.[9] A total of 16 608 postmenopausal women aged 50 to 79 years received 0.625 mg of conjugated equine estrogen with 2.5 mg of medroxyprogesterone acetate or placebo daily. At 5.2 years, relative risk of clinical, vertebral, and hip fractures was reduced by 34% (level I evidence).[9] In comparison with placebo, however, HRT was associated with a 29% increased incidence of cardiac events, a 41% increased risk of stroke, a doubling of thromboembolic events, and a 26% increased risk of breast cancer. Benefits included a reduction in osteoporotic fractures and a 37% reduction in colorectal cancer. The overall risks associated with HRT outweighed the benefits with 5 years or more of treatment.[9]

Hormone replacement therapy is recommended primarily for menopausal and vasomotor symptoms. Patients at increased risk of breast cancer, heart disease, stroke, or thromboembolic events should be cautioned against use of HRT. For prevention and treatment of osteoporosis, many alternatives that are not associated with this adverse-effect profile are currently available.

Future therapy

Large trials have shown that parathyroid hormone therapy (PTH) can stimulate new bone

Editor's key points

- Osteoporosis is a silent but growing epidemic among seniors that can be prevented by ensuring they get adequate amounts of calcium, vitamin D, and exercise; stop smoking; and limit alcohol.
- Once osteoporosis is established and secondary causes are ruled out, usual treatment starts with bisphosphonates. Etidronate, which has the least evidence supporting it, is covered by drug plans; alendronate and risedronate have stronger evidence, but are more expensive and are often not covered.
- Raloxifene helps reduce vertebral fractures as well as breast cancer and cardiovascular disease. It can slightly increase risk of thromboembolism. It can be used in combination with bisphosphonates.
- Nasal calcitonin has been shown to reduce fractures effectively with minor side effects and to reduce bone pain in vertebral fractures.
- On the horizon is parathyroid therapy. It stimulates production of new bone and has been shown to reduce fractures.

Points de repère du rédacteur

- L'ostéoporose, une épidémie silencieuse qui affecte un nombre croissant de personnes âgées, peut être enrayée par des suppléments adéquats de calcium et de vitamine D ainsi que par l'activité physique, l'arrêt du tabac et la restriction de l'alcool.
- Quand l'ostéoporose est déjà installée et que les causes secondaires ont été exclues, on commence habituellement par administrer des biphosphonates. L'étidronate, pour lequel les données sont les moins solides, est couvert par les programmes d'assurance médicaments; l'alendronate et le risedronate, mieux étayés scientifiquement, sont toutefois plus chers et souvent non couverts.
- Le raloxifène aide à prévenir les fractures vertébrales, mais aussi le cancer du sein et les maladies cardiovasculaires. Il peut toutefois augmenter légèrement le risque de thromboembolie. On peut le combiner aux biphosphonates.
- La calcitonine nasale réduit efficacement les fractures, sans effets secondaires importants; elle diminue également les douleurs osseuses dans les fractures vertébrales.•
- Les hormones parathyroïdiennes constituent le traitement d'avenir. Elles stimulent la néoformation osseuse et réduisent efficacement les fractures.

formation.[36,37] Significant increases (7% to 10% per year) in bone density have been seen with PTH. Histomorphometric studies have shown that PTH can improve the microarchitecture in osteoporotic bone and reverse the deterioration that was once thought to be irreversible.

The N-terminal fragment of PTH, known as teriparatide, has been evaluated in doses of 20 and 40 μg in an RCT.[36] In this 21-month study, PTH reduced risk of vertebral fractures by 65% and 69%, and risk of nonvertebral fractures by 53% and 54%, using the 20-μg/d and 40-μg/d doses, respectively, in comparison with placebo (level I evidence). Side effects included nausea and headache. Persistent hypercalcemia in about 3% of patients required dose modification. The recommended dose for teriparatide is 20 μg/d. Increases in men's BMD have also been seen with PTH.[37] Parathyroid hormone (1-34) therapy has been approved by the United States' Food and Drug Administration. Studies of PTH in combination with antiresorptive therapy indicate that these combinations are safe and effective for clinical use.[38,39]

Conclusion

Osteoporosis is an important health care issue that needs to be addressed. Better diagnosis and management of osteoporosis will lower health care costs and reduce the morbidity and mortality associated with it. Patients at risk of osteoporosis should be evaluated for risk factors for fracture. After excluding secondary causes of osteoporosis, physicians should counsel for lifestyle modification and introduce pharmacotherapy for prevention and treatment of osteoporosis. With appropriate intervention, fractures can be significantly reduced.

Competing interests

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Correspondence to: *Dr A. Khan, 209-331 Sheddon Ave, Oakville, ON L6J 1X8; telephone (905) 844-5677; fax (905) 844-8966; e-mail* avkhan@aol.com

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