



**CURRENTS IN PRACTICE**

# Osteoporosis

## PART 1

*Exciting new options for advanced disease*

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osteoporosis affects one in four women and one in eight men. This debilitating disease results in an increased risk of fractures, the most common of which are vertebral fractures followed by breaks in the hip and wrist. Hip fractures are associated with approximately 20% mortality one year after the fracture, while vertebral fractures have a similar mortality rate after only five years. Vertebral fractures are also linked to the development of dorsal kyphosis and a restrictive lung defect. About half of all patients who sustain a hip fracture won't regain independence and nearly 30% will require long-term hospitalization or care. Traditional treatment options include the essential antiresorptive therapies, however, the newer anabolic agents represent an exciting option to manage patients with advanced disease.

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# How is a clinical diagnosis made?

**Osteoporosis is** diagnosed in the presence of a fragility fracture. Fragility fractures are defined as breaks that occur from a fall within standing height. The most common tend to affect the spine, hip

and forearm. Osteoporosis can also be diagnosed prior to the onset of a fracture by bone densitometry. The World Health Organization defines osteoporosis as a bone density T score of less than or equal to -2.5 standard deviation below the mean bone mineral density of the young adult population. Severe osteoporosis is characterized as a T score of less than or equal to -2.5, but in the presence of a fragility fracture. If a patient has suffered a fragility fracture, a diagnosis of osteoporosis can be made even if the bone density is higher than a T score of -2.5.

Approximately one-third of postmenopausal women have osteoporosis due to a secondary cause; two-thirds of these women will have osteoporosis purely because of estrogen deficiency. In men diagnosed with osteoporosis, about 50% of cases result from another medical condition.

Because of the significant number of individuals who have secondary osteoporosis, it's necessary and essential to complete a history and physical, and carry out additional lab tests prior to confirming a diagnosis of idiopathic osteoporosis.

A proper and detailed history and physical examination should guide the physician as to the extent and need of any additional workup. Important investigations that shouldn't be missed include a complete blood count,

serum calcium — which must be corrected for albumin (see sidebar) — phosphate, alkaline phosphatase, serum creatinine and serum protein electrophoresis, as well thyroid function.

## FORMULA FOR CORRECTING CALCIUM FOR ALBUMIN

$$\text{calcium corrected} = \text{calcium} + (40 - \text{albumin}) \times 0.02$$

**TABLE 1. WHO CRITERIA FOR DIAGNOSING OSTEOPOROSIS**

T score	Classification
greater than or equal to -1	normal
-2.5 to -1	osteopenia
less than or equal to -2.5	osteoporosis
less than or equal to -2.5 in the presence of a fragility fracture	severe osteoporosis

# Who's at risk for osteoporosis?

**The Osteoporosis Society** of Canada recently published evidence-based guidelines that identify major and minor risk factors for fracture. Postmenopausal women and men over age 50 with at least

one major or two minor risk factors should be considered candidates for bone densitometry. The following table outlines both major and minor risk factors for osteoporosis.

## CURRENTS IN PRACTICE *update*

**TABLE 2. RISK FACTORS FOR OSTEOPOROSIS**

**Major risk factors**

over age 65	malabsorption syndrome
vertebral compression fractures	primary hyperparathyroidism
fragility fracture after age 40	propensity to falls
family history of osteoporotic fracture (especially maternal hip fracture)	appearance of osteopenia on radiograph
systemic glucocorticoid therapy use of at least three months	hypogonadism
	early menopause (before age 45)

**Minor risk factors**

rheumatoid arthritis	smoking
history of clinical hyperthyroidism	excess alcohol use
long-term anticonvulsant therapy	excess caffeine consumption
weight loss of more than 10% of weight by age 25	low dietary calcium intake
weight of less than 57 kg	long-term heparin therapy

# Who needs to be treated?

**When evaluating** fracture risk, the bone density results should be considered with other clinical risk

factors for fractures. Important independent risk factors include low body weight, history of postmenopausal fracture, a family history of fracture and poor neuromuscular function. When to intervene is determined by the possibility of fracture and by combining the results of the bone density exam with the patient's age and other significant risk factors for fracture.

The Osteoporosis Society of Canada recently recommended that postmenopausal women with a T score of less than -2.5 or less than -1.5 in the presence of one major or two minor osteoporosis risk factors need to be treated. Men who are over age 50 and have a T score of less than -2.5 are also candidates for therapy, as well as those who've had fragility fractures.

Individuals who've been on long-term glucocorticoid therapy (e.g. prednisone) of more than 7.5 mg a day for more than three months must also be tested and treated with antiresorptive therapy if bone loss is present. Steroid therapy results in decreased calcium absorption from the bowel. It also decreases bone formation and increases bone resorption, resulting in bone loss. These effects can be seen with even small doses of steroid therapy (prednisone 2.5 mg daily). It's important, therefore, to consider bone density testing in those who've been on long-term steroid therapy (i.e. more than 3 months) to ensure that bone health isn't compromised. Finally, if an individual has had a fragility

### SECONDARY CAUSES OF OSTEOPOROSIS

#### Conditions and disorders

- hyperthyroidism
- hypogonadism
- hyperparathyroidism
- hypercortisolism
- hypercalciuria
- malabsorption (celiac disease, inflammatory bowel disease, postgastrectomy)
- liver/renal disease
- malignancy
- myeloproliferative disorders
- connective tissue diseases

#### Medications and other drugs

- corticosteroids
- heparin
- gonadotropin-releasing hormone agonists
- medroxyprogesterone acetate
- anticonvulsants
- cytotoxic chemotherapy

fracture despite a normal bone density result or a relatively well-maintained bone density, further investigation and treatment is also warranted.

## Where does treatment start?

**Any discussion** about managing patients with osteoporosis should first begin with a conversation about lifestyle and diet modification. The average North American diet contains approximately 500 mg

of calcium a day — far below the recommendations of the Osteoporosis Society of Canada of 1,500 mg of daily elemental calcium. If patients are taking calcium supplements, they should be in the form of calcium carbonate or calcium citrate as these have the greatest percentage of elemental calcium. Vitamin D supplementation is also recommended in doses of 400 international units (IU) a day for individuals younger than age 50 and 800 IU daily for those older than age 50.

Moreover, patients should be advised to stop smoking and limit their consumption of alcohol and coffee. As an alternative, you may suggest they switch to drinking tea. Other lifestyle changes that can impact on the risk and progression of osteoporosis include regular weight bearing exercise — which can't be stressed enough — and hip protector pads, which are valuable in preventing hip fractures, especially among the elderly.

## What are the first-line therapies?

**First-line agents** for managing patients with osteoporosis include the amino bisphosphonates (alendronate and risedronate), as well as the selective estrogen receptor modulator, raloxifene. The bis-

phosphonates are effective in preventing vertebral and non-vertebral fractures, lowering the rate of these fractures by approximately half. Raloxifene has also been shown to reduce the incidence of vertebral fractures by about 50%. Currently there is no data that confirms a reduction in non-vertebral fractures with raloxifene. The Multiple Outcomes of Raloxifene Evaluation (MORE) trial, which studied raloxifene's effect on fracture wasn't powered to evaluate non-vertebral fractures. In fact, few hip fractures were seen in the raloxifene trial. The number of hip fractures in the placebo arm of the raloxifene study was 0.7% compared to 2.2 % in the alendronate Fracture Intervention Trial

**CURRENTS IN PRACTICE** *update*

(FIT) and 3.9% in the risedronate Hip Intervention Program (HIP). Thus, there were insufficient numbers of hip fractures to detect a statistically significant impact on hip fracture.

Because of these factors, it's difficult to draw conclusions regarding the efficacy of drug therapy to prevent a fracture in the absence of head-to-head data. Raloxifene does have additional and impressive extra-skeletal benefits, including a lower risk of breast cancer, reduced LDL cholesterol, in addition to reductions in fibrinogen, lipoprotein A and homocysteine levels.

Another valuable antiresorptive agent is calcitonin, which is effective in improving the management of bone pain following a vertebral fracture. In the Prevent Recurrence of Osteoporosis Fractures (PROOF) study, there were modest reductions in vertebral fractures with this agent; however, a dose response wasn't evident and a significant number of patients dropped out of the calcitonin trial, thereby reducing the strength of the study.

## Is hormone therapy still useful?

**Hormone replacement** therapy (HRT) in the Women's Health Initiative (WHI) has been shown to reduce vertebral and non-vertebral fractures by approximately 34%.

On the flipside, however, HRT was linked to a 29% increased incidence of cardiac events, a 41% higher rate of stroke and a two-fold rise in the risk of thromboembolic disease. An increased risk of breast cancer by 26% and a lower likelihood of colorectal cancer were also noted.

Overall, the risks associated with HRT far outweigh the benefits with five years or more of treatment. The results from the WHI led to the modification of the Osteoporosis Society of Canada's recommendations for the use of HRT and the management of postmenopausal osteoporosis. As a result, HRT is no longer considered a first-line treatment option.

## Are the anabolic agents effective?

**Anabolic agents** increase osteoblastic function. They also boost the production of bone matrix by osteoblasts, as well as increase the actual number of osteoblasts. A number of anabolic agents have been

evaluated and, currently, the Health Protection Branch has approved teriparatide as the first anabolic agent for the treatment of osteoporosis.

Teriparatide is a fragment of human parathyroid hormone (PTH). It was approved in Canada in June 2004 for the treatment of postmenopausal osteoporosis and for improvement in bone density in men. Intermittent PTH administration has been shown to result in bone formation. This explains why PTH results in major improvements in bone mineral density (BMD) and reduces fractures, and why individuals with primary hyperparathyroidism who have continuously elevated PTH levels experience bone loss and fractures. Teriparatide is given as a 20- $\mu$ g subcutaneous daily dose for 18 months and its effects are greatest during the first 4-6 hours post injection.

Teriparatide results in increases in the lumbar spine BMD by 9% compared to placebo. It improves bone strength and reduces the risk of fractures. Femoral and whole body BMD is also improved. In a trial of women being treated with teriparatide, a reduction in vertebral fracture was noted in 65% vs placebo. Non-vertebral fragility fractures were reduced by 53% compared to placebo.

Teriparatide is generally well tolerated. Side effects are minor and include nausea and headaches. Mild hypercalcemia may be noted on a transient basis. In rat studies, an increased risk of osteosarcoma was evident among the rats that received lifelong teriparatide in doses equivalent to more than 10 times the usual human dose. Osteosarcoma has not been seen in rat studies using lower doses of teriparatide for shorter time periods. There have been no cases of osteosarcoma in humans or in monkey studies. It's also worth noting that primary hyperparathyroid patients don't have an increased risk of osteosarcoma.

## What about strontium?

**Strontium ranelate** consists of two atoms of strontium and organic ranelic acid. Because of its chemical and physical similarities to calcium, strontium has the ability to incorporate into the bone at the same rate as calcium and, likewise, can accumulate in the skeleton. Strontium is present in soil and water and, in small amounts, occurs naturally in blood, bone and soft tissue. Strontium is actively absorbed in the bowel and its absorption is vitamin D dependent. Strontium absorption decreases with age and in the presence of a high dietary calcium intake.

Recent evidence has shown that strontium ranelate has the ability to stimulate new bone formation and is effective in reducing bone loss. In clinical trials evaluating strontium, increases in BMD have been seen which persist even after BMD is adjusted for the presence of strontium.

**CURRENTS IN PRACTICE** *update*

Phase III clinical trials have confirmed that strontium ranelate reduces vertebral fractures. In a study of 1,649 postmenopausal women with osteoporosis, investigators looked at the effects of 2 g of strontium per day vs placebo (Meunier, PJ et al. *NEJM* 2004 350:459-68). After one year, there was a risk reduction of 49% in new vertebral fractures among women in the strontium group and 41% after three years. The results of the effects of strontium ranelate on the risk of non-vertebral fractures were published last month (*J Clin Endocrinol Metab* 2005; 90:2816-22). The results showed that high-risk women had a 36% reduction in the risk of hip fractures. Strontium was well tolerated with a safety profile comparable to placebo, and no negative effect on bone mineralization was noted.

## What's the final word? **As our population** continues to age, osteoporosis will remain an important health issue for years to

come. The good news is that we're making major strides in improving the treatment options for this common condition. Anabolic agents are now available to complement existing antiresorptive medications and further the management of patients with postmenopausal osteoporosis. With these and other interventional strategies, we can significantly improve bone structure and reduce the risk of future fracture. **PE**

Next month, Osteoporosis – part 2: Managing osteoporosis in men and premenopausal women

## References:

Brown JP, Josse RG. Scientific Advisory Council of the Osteoporosis Society of Canada. 2002 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada. *CMAJ* 2002;167(suppl 10):S1-S34.

Khan AA, Brown J et al. Standards and guidelines for performing central dual x-ray densitometry from the Canadian Panel of International Society for Clinical Densitometry. *J Clin Densitom* 2002;5:435-45.

Khan AA, Brown JP et al. The 2002 Canadian bone densitometry recommendations: take-home messages. *CMAJ* 2002;167:1141-5.

Khan AA, Bachrach L et al. Standards and guidelines for performing central dual x-ray absorptiometry in premenopausal women, men and children. *J Clin Densitom* 2004;7:51-64.

Meunier PJ, Roux C et al. The effects of strontium ranelate on the risk of vertebral fracture in women with postmenopausal osteoporosis. *NEJM* 2004;350:459-68.

Neer RM, Arnaud CD et al. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. *NEJM* 2001;344:1434-41.

Reginster JY, Seeman E et al. Strontium ranelate reduces the risk of nonvertebral fractures in postmenopausal women with osteoporosis: Treatment of Peripheral Osteoporosis (TROPOS) study. *J Clin Endocrinol Metab* 2005;90: 2816-22.

**deeper pockets  
for fast food?**  
page 32