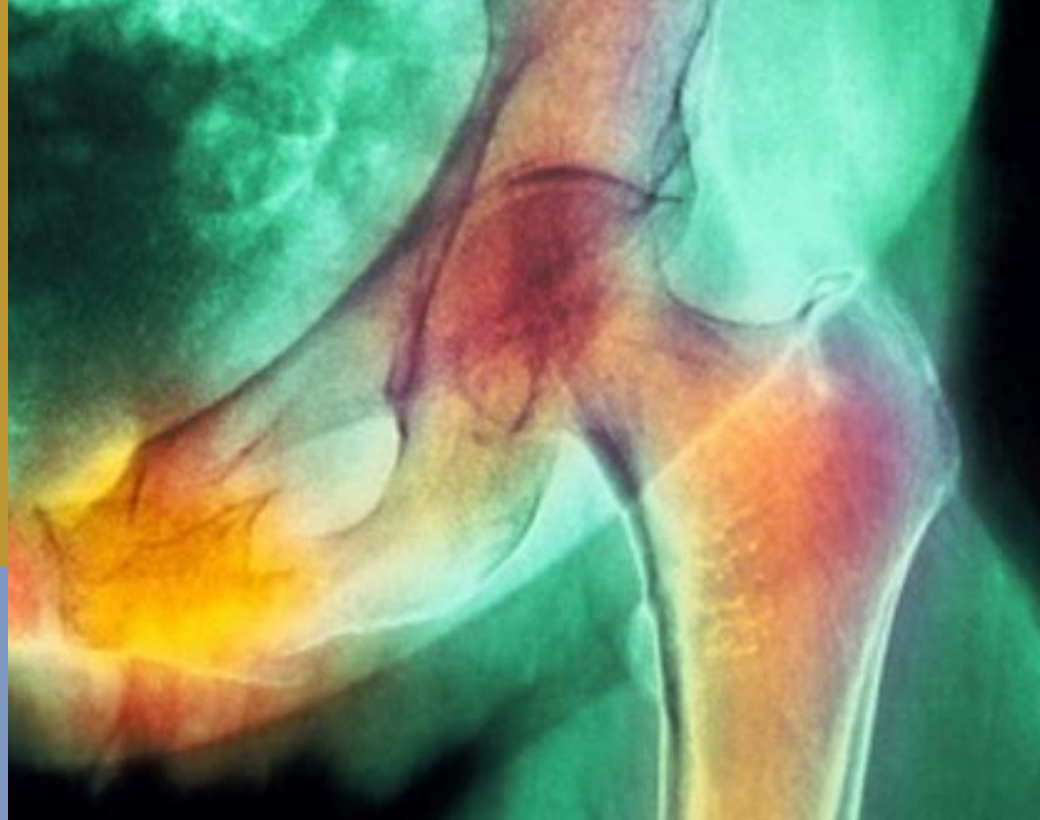


REDUCING OSTEOPOROTIC FRACTURES:

What Family Doctors Need to Know



About 1.4 million Canadians suffer from osteoporosis. Among women over 50, one in four has the disease, while one in eight men over 50 suffers from osteoporosis. An age-related decline in bone mass begins around age 35 and accelerates in women after menopause, with decreases in circulating estrogen. This results in decreased bone density and bone quality and is associated with an increased number of fractures in postmenopausal women. Most osteoporotic fractures occur in the hip, spine and wrist. Because the loss of bone in osteoporosis generally occurs without symptoms, the disease is sometimes called “the silent thief.”

The latest national osteoporosis recommendations issued by Osteoporosis Canada for men were developed by Dr. Aliya Khan and other experts outlining the current management of the disease in Canada.¹

DIAGNOSIS

Osteoporosis has no clinical manifestations until a fracture occurs – most commonly, a vertebral fracture. In adults over 40, any fracture that occurs with minimal trauma should be further evaluated as it signals impaired bone strength, says Dr. Khan. “Such fractures should lead to diagnostic testing and pharmacologic intervention.”

Osteoporosis is diagnosed by bone densitometry, which evaluates bone mineral density (BMD). The World Health Organization defines osteopenia (low bone mass) as a BMD between 1 and 2.5 standard deviations below the mean range, and osteoporosis as a BMD more than or equal to 2.5 standard deviations below this mean.

It is important to note that low BMD is not necessarily pathological. “In premenopausal women or young men, low BMD could simply be a reflection of low peak bone mass and

may not require pharmacologic therapy as these individuals may not be at increased risk of fracture,” says Dr. Khan, noting that “about 15% of healthy young adults, including premenopausal women and men under 50, have a BMD T-score of less than -1.” Of course, “it is necessary to exclude secondary causes of low bone mass in such individuals.”

TREATMENT: GOALS AND GAPS

Once a patient has been identified to be at risk of fracture, the most important therapeutic goal is to reduce this risk as quickly as possible. Thankfully, current therapies can slow or even reverse the progression of osteoporosis.² That said, the majority of patients with hip, forearm or vertebral fractures do not receive evaluation and treatment for underlying osteoporosis, indicating a significant treatment gap.

In this regard, a Canadian literature review reported in *BMC Musculoskeletal Disorders* in 2004 determined that the proportion of adults over 40 with a fragility fracture who received a diagnostic test for, or physician diagnosis of, osteoporosis ranged from 1.7% to 50%.³ Similarly, pharmacologic therapy was prescribed to just 5.2% to 37.5% of patients. The reviewers concluded that, “many Canadians who experience fragility fracture are not receiving osteoporosis management for the prevention of future fractures.”

DRUG THERAPY

A) Selective estrogen receptor modulators (SERMs)

SERMs, which bind to estrogen receptors, have estrogen-like effects on the skeleton, decreasing the activity of the osteoclasts (which remove bone) and enhancing the activity of the osteoblasts (cells that build new bone). In so doing, they normalize bone turnover, improve

bone quality and create a milieu that approaches the premenopausal state.

The SERM raloxifene is a valuable agent in the prevention and treatment of osteoporosis, especially in people at elevated risk of breast cancer. In the Multiple Outcomes of Raloxifene Evaluation (MORE) study, patients treated with raloxifene over four years showed significant reductions in vertebral fracture risk. No significant effect on the risk of nonvertebral fractures was noted. As raloxifene has been associated with increases in the incidence of thromboembolic events (similar to the rates seen with hormone replacement therapy), it is contraindicated in people at increased risk for such events.

B) Aminobisphosphonates

The aminobisphosphonates, alendronate and risedronate, have consistently been shown to be effective in preventing both vertebral and nonvertebral fractures. They decrease osteoclast function and normalize bone turnover to premenopausal states leading to improvements in overall bone strength.

Hierarchy of evidence

“When evaluating effectiveness of drug therapy, it is important to remember that the randomized control trial evaluates cause and effect and is able to objectively assess the impact of therapy. The randomized control trial is the golden standard for evaluating response to treatment.” Explained Dr. Khan, “systematic reviews are a higher level of evidence than single studies, as they can demonstrate consistency of effect. Systematic reviews can also have a meta-analysis component, which is a pooled average across different studies. A meta-analysis collects all the studies that have been published and averages the effect of treatment. The systematic review is the highest level of evidence and is of great value in assessing drug efficacy.”

Lower levels of evidence include observational studies and can be prospective, retrospective, case control or cross-sectional surveys. Observational studies provide a lower level of evidence than randomized control trials. As the intervention is not controlled, it is not possible to prove that the cause resulted in the effect noted, as contributing factors to fracture are not controlled for. Both alendronate and risedronate have shown consistent efficacy in the

prevention and treatment of osteoporosis effectively reducing morphometric vertebral fractures, clinical vertebral fractures as early as a year after intervention and also effectively reducing hip and nonvertebral fractures.

It should be noted that, “there are no data on the use of bisphosphonates in premenopausal women or young men not on steroid therapy,” says Dr. Khan. Thus, “these agents are not suitable for young people under the age of 50 unless there is a history of prednisone use, primary hyperparathyroidism or other skeletal disorder resulting in increases in bone turnover or increased rates of bone loss.” Dr. Khan explained that bisphosphonate therapy should not be used in people with low peak bone mass and normal bone turnover such as in estrogen-replete premenopausal woman because, “we all need a healthy amount of bone turnover to allow repair of microdamage that accumulates with normal skeletal wear and tear.” Khan and colleagues published guidelines regarding the diagnosis of osteoporosis in premenopausal women and men in conjunction with the ISCD.⁴

Observational Data

A large retrospective observational study (REAL study) recently evaluated risedronate and alendronate to confirm the results of the randomized control trials in the real world.⁵ Using health claims data in the United States, study investigators created two cohorts of women 65 years and older: those who received risedronate (n=12,215) and those who received alendronate (n=21,615). All candidates for the study supposedly took the medication once a week and adherence was measured as a function of the gaps between prescription refills. The risedronate cohort was followed for an average of 226 days on therapy and the alendronate cohort was followed for 238 days. The two arms were generally comparable; however, the risedronate cohort was slightly older, used more concomitant medications, had a greater history of glucocorticoid use and had more patients with rheumatoid arthritis. These factors may increase fracture risk. The primary outcome measures were the six- and 12-month rates of nonvertebral fractures and hip fractures. There were 507 nonvertebral fractures and 109 hip fractures. Through one year of therapy, the incidence of nonvertebral fractures



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in the risedronate group was 18% lower than in the alendronate group. The incidence of hip fracture in the risedronate group was 43% lower than the alendronate group.

Dr. Khan explained, “as with other retrospective observational studies, this study has a number of limitations, including the fact that vitamin D intake was not evaluated. As the data is from health claims, it is not possible to assess which patients were receiving vitamin D supplementation. Vitamin D has a major effect on the risk of falls and would impact the incidence of nonvertebral fractures.” In fact, a recent study by Bischoff and colleagues demonstrated that the risk of falls can decrease by 49% with vitamin D 800 i.u. daily supplementation over a 12-week period.⁶ Thus, not controlling for vitamin D intake constitutes a limitation in this one-year study specifically evaluating hip fractures and nonvertebral fractures. Compliance also needs to be further addressed as data suggests that compliance rates are about 50% at best. In observational studies, compliance is assumed instead of closely evaluated as in randomized control trials. Lastly, it is not clear how many patients were receiving medications from other sources such as samples or purchased drugs from outside the U.S., i.e., Canada or Mexico. It has been estimated that 5% to 10% of patients obtain their drugs from outside the U.S. due to the difference in price and this has not been taken into consideration in this study. Such limitations are common in retrospective observational studies; thus, conclusions regarding drug efficacy are more appropriately made on the basis of randomized control trials.

Randomized Control Trial Data

“The safety and tolerability profiles of alendronate and risedronate have been found to be virtually identical. Both drugs have been shown to be effective in preventing vertebral and nonvertebral fracture and reducing height loss.” In the VERT trial, risedronate in doses of 5 mg a day reduced the incidence of new fractures within six months of therapy and lowered the risk of new vertebral fractures within one year. Maintaining this risk reduction has been noted for up to seven years of treatment. Risedronate has also been shown to effectively reduce the risk of nonvertebral fractures after three years of treatment in the HIP study, as published by McClung and colleagues. “Other studies have confirmed that risedronate prevents bone loss and preserves trabecular structure and reductions in vertebral fracture risk have been independent of increases in BMD.”

In the FIT trial, alendronate has been demonstrated to reduce the risk of vertebral fractures in postmenopausal women with and without baseline vertebral fractures. Several trials have shown that alendronate increases bone mineral density. In the head-to-head randomized control trial (FACTS), alendronate resulted in larger increases in BMD in comparison to risedronate over two years. In the fracture intervention trial long-term extension study,

increases in BMD were noted at the spine and at the hip through 10 years of treatment with reductions in fracture risk. “Bone biopsies performed in patients following 10 years of alendronate treatment revealed normal bone with no evidence of ‘frozen bone’ or microfracture accumulation.

“Randomized control trials have consistently shown both alendronate and risedronate to be effective in the prevention of both vertebral and nonvertebral fractures and to have particular value in the prevention of hip fracture, a serious fracture most costly in terms of dollars, as well as quality of life. Both agents were effective treatment options and should be offered to appropriate patients at risk of fragility fracture.”

Meta-analyses

Meta-analyses enable pooling of all data and have been conducted for the bisphosphonates. Only alendronate, risedronate and hormone replacement therapy have been shown to reduce the risk of hip fracture. Alendronate reduced the risk of nonvertebral and hip fracture by 49% and 55%, respectively. The reductions with risedronate were 27% and 26%, respectively.⁷

In late 2006, the Canadian Agency for Drugs and Technologies in Health issued a paper entitled, “Bisphosphonates and teriparatide for the prevention of osteoporotic fractures in postmenopausal women.”⁸ The paper reported on two systematic reviews of the clinical literature evaluating and pooling data from randomized controlled trials. The first review compared bisphosphonates with placebo while the second review compared teriparatide to bisphosphonates or placebo. The following conclusions were reached:

1. None of the bisphosphonates were effective for the primary prevention of nonvertebral fractures and teriparatide’s usefulness as a primary preventive agent could not be assessed.
2. Alendronate was effective in primary prevention of vertebral fractures.
3. Teriparatide and some bisphosphonates are effective in the secondary prevention of clinically important fractures. Specifically, teriparatide was shown to reduce the risk of nonvertebral fractures, while alendronate and risedronate reduced the risk of both nonvertebral fractures and hip fractures. Alendronate also reduced the risk of wrist fractures (see Table 1).

“The data from such systematic reviews and meta-analyses are very powerful,” says Dr. Khan. In combination with findings from randomized control trials, they can help guide clinical practice.”

Recently, zoledronic acid, an aminobisphosphonate, which can be given intravenously, was found to be a powerful inhibitor of bone resorption. It has been shown to be effective in preventing vertebral and nonvertebral fractures over three years of therapy and is a valuable addition to the treatment options in the management of postmenopausal osteoporosis. I.V. bisphosphonates are also of value in the management of skeletal complications in patients

with malignancy and are an important component of therapy in this patient population.

Recently, osteonecrosis of the jaw, an avascular bone necrosis, have been reported. The vast majority of these individuals have been on concomitant chemotherapy or radiotherapy both of which are risk factors for avascular bone necrosis. The condition has been reported in high-risk individuals most commonly following dental surgery such as dental extraction. The true incidence of this extremely rare condition is not known and is currently being evaluated in Canada and national guidelines are being developed.

C) Hormone replacement therapy (HRT)

Given the risks of long-term HRT in postmenopausal women over 50, this therapy is now considered appropriate (for limited time periods) for select patients with menopausal symptoms.

D) Anabolic agents – teriparatide

Daily therapy with teriparatide (a truncated form of parathyroid hormone) stimulates osteoblast activity and, as a result, “reverses the microarchitectural deterioration seen in osteoporosis and leads to increases in BMD and bone strength,” says Dr. Khan. “People with severe osteoporosis or fractures on bisphosphonates are suitable candidates

for teriparatide.” In appropriate patients, “the drug can produce remarkable improvements in bone structure,” she says.

E) Strontium ranelate

Strontium ranelate is a natural element that is incorporated into bone and accumulates in the skeleton due to its physical and chemical similarities to calcium. “Strontium ranelate stimulates replication of preosteoblasts and synthesis of bone matrix and prevents bone resorption by inhibiting osteoclasts. It has been shown to be effective in preventing vertebral and nonvertebral fractures.” This agent is well tolerated and side-effects have been limited to nausea and diarrhea. While not currently approved, the drug is expected to be available in Canada sometime over the next 12 months.

F) RANKL inhibitors

These agents block the action of RANKL, a cytokine necessary for the activation of osteoclasts. The RANKL inhibitor, denosumab, is a monoclonal antibody that binds to human RANKL, thus preventing osteoclast activation and decreasing bone resorption.

Denosumab is being evaluated in postmenopausal osteoporosis. While it is not currently available, it is also being evaluated in individuals with metastatic skeletal disease in oncology patients and it is expected to become a valuable addition in the management of these conditions. •

Table 1: RR of fractures when bisphosphonates or teriparatide are used for secondary prevention

| | Vertebral RR (95% CI) | Nonvertebral RR (95% CI) | Hip RR (95% CI) | Wrist RR (95% CI) |
|-----------------------|--------------------------|-----------------------------|----------------------|----------------------|
| Etidronate 400 mg | 0.53 (0.32; 0.87) | 1.07 (1.07; 1.60) | 1.20 (0.37; 3.88) | 0.87 (0.32; 2.36) |
| Alendronate 10 mg | 0.55 (0.43; 0.69) | 0.77 (0.64; 0.92) | 0.47 (0.26; 0.85) | 0.52 (0.36; 0.75) |
| Risedronate 5 mg | 0.61 (0.50; 0.76) | 0.80 (0.72; 0.90) | 0.74 (0.59; 0.94) | 0.67 (0.42; 1.07) |
| Teriparatide 20 µg | 0.35 (0.22; 0.55) | 0.65 (0.43; 0.98) | 0.50 (0.09; 2.73) | 0.54 (0.22; 1.35) |

*Etidronate, alendronate and risedronate data from G. Wells *et al.*, teriparatide data based on Neer *et al.* relative to placebo, statistical heterogeneity observed ($p=0.069$ mainly due to a study with relatively small number of subjects, weight=0.2% of all studies)—when random effects approach used, RR=0.52 (0.25; 1.08): “Bisphosphonates and Teriparatide for the Prevention of Osteoporotic Fractures in Postmenopausal Women” by the Canadian Agency for Drugs and Technologies in Health (October 2006 – Technology overview no 22).

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