

## OSTEOPOROSIS MANAGEMENT AND INVESTIGATION

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There is a huge care gap in the management of osteoporosis in this country. As yet unpublished findings from the Canadian Multicentre Osteoporosis Study (CaMOS) would suggest that approximately 80% of women, and nearly 100% of men who suffer a fragility fracture do not get assessed or treated for osteoporosis.

### **RISK ASSESSMENT AND INVESTIGATIONS:**

#### HISTORY:

- height loss
- back pain; development of dorsal kyphosis.
- menstrual history, use of postmenopausal ovarian hormone therapy.
- In males, hypogonadism and alcoholism are important causes of osteoporosis.
- diet: calcium intake, use of calcium or vitamin D supplements, lactose intolerance.
- lifestyle issues: alcohol intake, inactivity or prolonged periods of bed rest, smoking history, excessive caffeine intake, weight less than 57 kg. or weight loss after age 25.
- medications: glucocorticoids, heparin therapy, anticonvulsants, sedatives (cause falling).
- past medical history: previous fractures; increased propensity to fall.
- endocrine diseases: hyperthyroidism, hyperparathyroidism, hypogonadism, Cushing's Syndrome; gastrointestinal disease; anorexia nervosa.
- family history of osteoporotic fracture (particularly maternal hip fracture).

#### PHYSICAL EXAMINATION:

Kyphosis, muscle weakness (inability to rise from a chair), impaired visual acuity, other disabilities causing a tendency to fall.

#### LABORATORY INVESTIGATIONS:

- all should be normal: complete blood count, serum calcium, alkaline phosphatase (may be elevated in acute recovery from fracture), creatinine, serum protein electrophoresis.
- Serum 25-OH Vitamin D if there is a question about the patient's Vitamin D nutrition.
- other more specific markers of calcium or bone metabolism may be helpful in assessing apparent failure to respond to therapy.

#### DIAGNOSTIC IMAGING:

- X-rays should only be used for identifying fractures.
- a bone scan can identify fracture activity.

#### BONE DENSITY MEASUREMENTS:

- bone density of the spine and hip by Dual Energy X-ray Absorptiometry (DEXA) is currently the preferred method of assessing bone mass and fracture risk, as well as following response to therapy (1). Other methods, eg. heel ultrasound, are acceptable for assessing fracture risk if DEXA is not available, but probably lack the precision necessary for following response to therapy (2).
- in the postmenopausal female osteoporosis has been defined as a lumbar spine or femoral neck DEXA more than 2.5 standard deviations below the mean value for a same sex young adult ("T-score" of -2.5 or lower). Osteopenia (thin bones) is defined as a bone density between 1.0 and 2.5 standard deviations below the young adult mean (3). This definition is being used by many clinicians as a guide to management decisions. However, it should not be used as the sole criterion for defining osteoporosis in men and premenopausal women.
- bone density measurement (BMD) is only indicated if it will affect clinical management decisions.

Osteoporosis experts suggest it is of use in the following clinical situations (1,2,4):

1. To diagnose osteopenia at menopause in selected individuals. The U.S. National Osteoporosis Foundation recommends BMD measurements for postmenopausal women aged 50-65 with one of the following risk factors: **(i) smoker; (ii) history of fracture after age 40; (iii) family history of osteoporotic fracture after age 50; (iv) body weight < 57 kg.)** (3).

2. To confirm or deny the diagnosis of osteoporosis in patients with radiologic abnormalities consistent with osteoporosis, eg. radiologic diagnosis of osteopenia or vertebral fractures.
3. Patients with medical problems known to cause rapid bone loss, such as primary hyperparathyroidism or high dose prolonged (greater than three months) glucocorticoid therapy, in order to recommend treatment options (parathyroid surgery or bone-sparing pharmacologic therapy, respectively).
4. To monitor the response to osteoporosis therapy. However, it should be noted that changes in bone density may not reflect therapeutic benefit of a drug. Small increases in bone mass may result in significant fracture prevention benefits, as the strength of bone appears to be proportional to the square of the density.

## **PREVENTION AND TREATMENT**

### NONPHARMACOLOGIC APPROACHES

- reduce risk of falling.
- adequate dietary calcium.
- stop smoking, reduce alcohol and caffeine intake.

### PHARMACOLOGIC APPROACHES

Therapies for osteoporosis can be classified as those which prevent bone resorption (anti-resorptive) and those which stimulate bone formation. At present, all of the drugs approved by the Government of Canada Therapeutics Products Directorate for osteoporosis therapy (estrogen, alendronate, cyclical etidronate, risedronate, raloxifene, and salmon calcitonin) would be categorized as anti-resorptive in their action. Because of the coupled nature of bone turnover (bone formation always follows resorption), treatment with anti-resorptive agents results in a general slowing down of bone formation and the overall rate of bone remodeling, while the mandatory coupled bone formation proceeds normally. These agents therefore cause an initial increase in bone mass, which eventually plateaus, as the overall rate of bone turnover is markedly reduced.

### **ANTI-RESORPTIVE AGENTS:**

#### **1. Estrogen (+/-) Progesterone (references 5,6)**

Estrogen, with progesterone (if the patient has not had a hysterectomy), is considered the front-line choice for prevention of osteoporosis in the early postmenopause. Earlier reviews by osteoporosis expert organizations have made estrogen the first choice treatment of established osteoporosis (definition by BMD +/- fractures) in older postmenopausal women (1,4). **However, most clinicians would now rank the bisphosphonates and raloxifene ahead of estrogen for older postmenopausal women with established osteoporosis, because of the superior clinical trial evidence in preventing fractures.**

#### **2. Bisphosphonates (references 7-13)**

Etidronate (Didronel, Didrocal), alendronate (Fosamax) and risedronate (Actonel) are approved for prevention and treatment of osteoporosis and also Paget's Disease of bone. Risedronate appears to be similar to alendronate in anti-fracture efficacy. Other available bisphosphonates such as clodronate (Bonefos, Ostac), pamidronate (Aredia) and zoledronate (Zometa) are presently used in the management of malignancy-associated osteolysis, hypercalcemia, and Paget's Disease, but have also been used in the treatment of osteoporosis in small clinical trials of short duration. Cyclical etidronate risedronate and alendronate are also approved for the prevention and treatment of glucocorticoid-induced osteoporosis in Canada. Alendronate has also shown to be effective in the treatment of osteoporosis in men.

### **3. Selective Estrogen Receptor Modulators: Raloxifene (References 14-16)**

Raloxifene (Evista) has now been approved for both prevention of postmenopausal bone loss and the treatment of established osteoporosis. There is clear clinical trial evidence of prevention of vertebral fractures. Raloxifene is an estrogen antagonist in breast and uterine tissue, and appears to reduce the incidence of breast cancer. It has estrogen-like activity on bone and lipid metabolism. Large clinical trials are currently in progress to assess raloxifene's ability to prevent heart disease and breast cancer.

For the person at risk for osteoporosis in the first 5-15 years postmenopause, raloxifene is considered an appropriate first-line choice and alternative to estrogen because, like estrogen, it has beneficial effects on biochemical risk factors for cardiovascular disease (eg. lipid metabolism). Like estrogen, there is a modest increased risk of deep vein thrombosis and pulmonary embolism in postmenopausal women using raloxifene. Raloxifene does not treat menopause symptoms of estrogen deficiency, and will aggravate the vasomotor symptoms (hot flushes) if given too early in menopause. Patients should be warned of this.

### **4. Calcitonin (Reference 17)**

A nasal spray of salmon CT (Miacalcin), 200 units once daily, has been shown to prevent vertebral fractures, and has recently been granted HPB approval for treatment of established osteoporosis with vertebral fractures.

### **5. Combination Therapy? (References 18-20)**

Combining a bisphosphonate with estrogen or raloxifene is the subject of several recent or on-going clinical trials. Estrogen or raloxifene plus a bisphosphonate has additive or synergistic effects on BMD, but no fracture benefit has yet been demonstrated. If a patient continues to lose BMD while taking estrogen, I may add a bisphosphonate without stopping estrogen, but it is not my practice to initiate therapy with the combination.

### **6. Glucocorticoid Osteoporosis (Reference 21)**

A Canadian group has recently published a review of this problem and proposed a treatment algorithm.

### **Vertebral Fractures are important! (references 22-26)**

The **major risk factors for osteoporosis are age, bone density, and previous osteoporotic fracture.**

With respect to the latter, the importance of vertebral fractures as predictors of future problems cannot be over-emphasized. It is now clear that the presence of a vertebral fracture places a patient at high risk for another vertebral fracture within a year of suffering the first fracture, and vertebral fractures have been clearly associated with high risk of other fractures including hip fractures, morbidity, and even mortality.

### **CONCLUSION**

Most clinicians working in this field hold the position that postmenopausal ovarian hormone therapy remains the first choice for prevention of osteoporosis for women in the first 5-10 years after menopause. Raloxifene is approved for the prevention of postmenopausal bone loss and should be considered a solid alternative to estrogen. Raloxifene also has better randomized controlled clinical trial evidence for fracture prevention than estrogen.

After age 60-65, the majority view would be bisphosphonate therapy should be chosen over ovarian hormone therapy for the treatment of osteoporosis (a fragility fracture and/or bone density in the "osteoporosis" range), because of better patient acceptability and far superior randomized placebo controlled clinical trial evidence for fracture prevention. Raloxifene and calcitonin are well tolerated alternatives to bisphosphonate therapy in the treatment of established osteoporosis.

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