

THERAPEUTICAL OPTIONS IN POSTMENOPAUSAL OSTEOPOROSIS

C. Dumitrache, D. Grigorie

INTRODUCTION

Osteoporosis is a major health problem, with increasing prevalence and with considerable medical, social and financial implications.

Osteoporosis is a skeletal disorder characterized by compromised bone strength predisposing a person to an increased risk of fracture. Bone strength reflects the bone density and the bone quality. The only clinically applicable index of bone quality at present is a patient's history of a fragility fracture.

Although it is important to relieve pain and to limit the impact of deformities in established osteoporosis, the primary goal of treatment is to prevent fractures. Therefore, prevention and therapy should be considered together.

At present, it is recommended that all postmenopausal women and men over 50 years of age be assessed for the presence of risk factors for osteoporosis. Risk factors for osteoporotic fracture should not be considered to be independent from one another, they are additive. Four factors have been identified as predictors of fracture related to osteoporosis: low bone mineral density (BMD), prior fragility fracture, age and family history of osteoporosis. BMD measurement is recommended in the presence of one major or two minor risk factor of osteoporosis.

Because osteoporosis is a multifactorial condition, its management includes non-pharmacological and pharmacological interventions.

NON-PHARMACOLOGICAL INTERVENTIONS

Nutrition

Calcium and vitamin D are essentials adjuncts in the treatment of osteoporosis.

The optimal calcium daily intake recommended varies between 1-2g/day:

- Children and adolescents: 800-1200 mg/day;
- Premenopausal women: 1000 mg/day;
- Postmenopausal women: 1500 mg/ day;
- Men < 50 years: 1000 mg/day;
- Men > 50 years: 1500 mg/day;
- Pregnant or lactating women: 1000 mg/day.¹

Several nutritional factors influence the calcium requirement, such as sodium, protein, caffeine, fiber, and vitamin D status. Several studies show that the effect of caffeine and fiber is small, whereas sodium intake (more than 2100mg/day) increases urinary excretion of calcium.²

Optimal vitamin D daily intake is:³

- Men and women < 50 years: 200-400UI (5-10mg)/day;
- men and women > 50 years: 400-800UI (10-20mg)/day.

We can use other forms of vitamin D such calcidiol (25[OH]D), calcitriol (1,25[OH]₂D).⁴

Exercise, lifestyle and falls prevention

The beneficial effect of exercise on bone mass and bone strength in normal and osteoporotic individuals is still unclear. On the basis of limited data, half hour of weight-bearing exercise per day is recommended for the patients who can tolerate it. After a vertebral fracture, a supervised exercise program to maintain strength and flexibility of the thoracic and lumbar spine is recommended in the

elderly. Patients should avoid weight lifting and learn how to bend to avoid exercise strain on their spine. All lifestyle factors that might be deleterious to bone metabolism should be corrected.

PHARMACOLOGICAL INTERVENTION

The goal of therapy is to prevent fragility fractures, and drugs for osteoporosis should demonstrated their ability to significantly decrease the incidence of fractures. (Table 1)

Table 1. Drugs used in osteoporosis

Agents	Vertebral fractures	Hip fractures
HRT	+	+
Etidronate	+	0
Alendronate	++	+
Raloxifene	++	0
Calcitonin	+	0
Fluoride	+/-	-
Vitamin D derivatives	+/-	0

HRT

The benefits and risks of HRT have to be explained to patients. The duration of HRT to control the menopausal symptoms is far shorter (1-2 years) than the duration of treatment required to reduce the risk of fragility fractures (over 5 years). Women who have undergone hysterectomy can be given estrogen alone and those with an intact uterus should be given both estrogen and progestin to prevent the risk of endometrial carcinoma. Several controlled trials have shown that estrogens stop bone loss in early and late postmenopausal women by inhibiting bone resorption and that it results in a small increment in BMD (5-10% over a period of 1-3 years). Studies show that estrogen decreases the risk of hip fractures by about 30 % and the risk of spine fractures by about 50 %.⁵ Estrogens have a dose-dependent effect and this effect disappears when HRT is stopped. HRT is the first line preventive therapy in postmenopausal women with low bone density and for the women who experience menopause before age of 45. In current users, HRT taken for more than 5 years after menopause increases risk of breast cancer by 26 %, the risk of coronary heart disease by 29% and the risk of stroke by 41 %.⁶ HRT is a second line treatment for the postmenopausal women with osteoporosis.⁷

Biphosphonates

Biphosphonates are stable analogues of pyrophosphate characterized by two P-C-P bonds. Biphosphonates have a strong affinity for bone apatite and are potent inhibitors of bone resorption. They

produce their effect by reducing the recruitment and activity of osteoclasts and increasing their apoptosis. Oral bioavailability is low, between 1 and 3 % of the dose ingested, and their half-life in the bone is very prolonged.

Etidronate, given in an intermittent regimen (400 mg/day 2 weeks for 3 months) has led to an increase of about 3.5% in spine BMD after 2 years, with a reduction in a vertebral fracture rate.⁸ Etidronate does not appear to be effective in preventing bone loss at the hip and in reducing nonvertebral fractures.

When administered continuously for long periods, etidronate can cause impaired mineralisation on bone.

Alendronate given in a continuous regimen (70 mg once weekly or 10 mg/day) increase BMD at the lumbar spine and at the hip (8.8% after 3 years of treatment). This treatment reduces the incidence of new vertebral, wrist and hip fractures by half and prevented height loss.⁹

Biphosphonates can also be used in secondary osteoporosis such as corticosteroid – induced osteoporosis.⁷

Risedronate is generally well tolerated. After 3 years of treatment at 5 mg/day, risedronate reduced the incidence of vertebral fractures by 41-49 % and nonvertebral fractures by 33-39 % and reduced hip fractures rate by 40 %.^{10,11}

Biphosphonates are first-line treatment for postmenopausal women with osteoporosis, especially those with pre-existing vertebral fractures.⁷

Selective Estrogen Receptor Modulators (SERM)

This compounds act as estrogen agonist or antagonist, depending on target tissue.

Raloxifene inhibit the action of estrogen in the breast and in the endometrium and also act as an estrogen agonist of bone and lipid metabolism. In a large 2 year randomized controlled study, raloxifene increase lumbar spine BMD and total hip BMD with 2.4 %.¹² Results of MORE study show that the incidence of breast cancer is reduced by half in postmenopausal women.¹³

Raloxifene is efficacious in preventing vertebral fractures in postmenopausal women with osteoporosis but has not yet been shown to be effective in preventing nonvertebral fractures.⁷

Calcitonin

Calcitonin, a peptide produce by thyroid C-cells, reduce bone resorption by inhibiting osteoclast activity. The role of nasal calcitonin in the management of

postmenopausal osteoporosis is not yet clearly documented. In a 3-year randomized trial, nasal calcitonin 200 ui/day significantly reduced the rate of vertebral, but not peripheral fractures.¹⁴

Calcitonin has some analgesic properties and may be particularly useful in patients with recent painful vertebral fractures.

VitaminD analogues

The effect of vitamin D analogues on BMD appears to be small and limited to the spine. Alfacalcidol and calcitriol are used in some countries for the treatment of osteoporosis.

Parathyroid hormone (PTH)

PTH given intermittently produces a significant increase of BMD (especially trabecular bone mass) and reduces the incidence of fracture.

PTH stimulates bone formation and is effective in preventing both vertebral and nonvertebral fractures in postmenopausal women with severe osteoporosis.⁷ PTH increases BMD at all skeletal sites with the exception of the radius.¹⁵

Strontium ranelate

Strontium ranelate is a new therapeutically agent. It acts by increasing bone formation and reducing bone resorption. A recent study 36-months with 2 g/day show an increase of lumbar spine BMD with 14.4 % and hip BMD with 8.3 % and a reduce of fracture risk with 49% after one year of treatment.¹⁵

The decision making process should be based on an analysis of the patient's risk of fracture and the efficacy and tolerance of the drugs likely to be prescribed. This decision should be take into account age, existing risk factors, magnitude of bone loss, presence or absence of previous fragility fractures.

REFERENCES

1. NIH Consensus Conference: Optimal calcium intake. *JAMA* 1994; 272:1942-8.
2. Devine A, Criddle EA, Dick EM, et al. A longitudinal study of the effect of sodium and calcium intakes on bone density in postmenopausal women, *Am J Clin Nutr* 1995;62:740-5.
3. Kiel DP, Felson DT, Hannan MT, et al. Caffeine and the risk of hip fracture: the Framingham study, *Am J Epidemiology* 1990;132:675-84.
4. Dawson Huges B, Dallal GE, Krall EA et al. Effects of vitamin D supplementation on overall bone loss in healthy postmenopausal women, *Ann Intern Med* 1991;115:505-12.
5. Lufkin EG, Wahner HV, et al. treatment of postmenopausal osteoporosis with transdermal estrogen, *Ann Intern Med* 1992; 117:1-9.
6. Writing group for the Women's Health Initiative investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women; principal results from the WHI Randomised Controlled Trial, *JAMA* 2002;288:321-33.
7. Jacques P Brown. 2002 Clinical practice guidelines for the diagnosis and management of osteoporosis in Canada. *CMAJ* 2002;167.
8. Watts NB et al. Intermittent cyclical etidronate treatment of postmenopausal osteoporosis, *N Engl J Med* 1990;323:73-9.
9. Black DM, Cummings SR et al. randomized trial of effect of alendronate on risk of fracture in women with existing fractures. *Lancet* 1996;348:1535-41.
10. Harris ST, Watts NB et al. Effects of Risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomised controlled trial. Vertebral efficacy with risedronate Therapy (VERT) Study Group. *JAMA* 1999;282:1344-52.
11. Reginster JY, Minne HV et al. randomized trial of the effects of Risedronate on vertebral fractures in women with established postmenopausal osteoporosis, *Osteoporos Int* 2000;11:83-91.
12. Delmas PD, Bjarnason NH, et al. Effect of raloxifene on bone mineral density, serum cholesterol concentration and uterine endometrium in postmenopausal women, *N Engl J Med* 1997; 337:1641-7.
13. Cummings SR, Ekert S et al. The effect of raloxifene on risk of breast cancer in postmenopausal women: results from the MORE randomized trial, *JAMA* 1999;28:2189-97.
14. Silverman SR, Chesnut C et al. Salmon calcitonin nasal spray reduces risk of vertebral fractures in established osteoporosis - PROOF study, *Bone* 1998;23:174.
15. Neer RM, Arnaud CD 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.
16. Meunier JP, Roux C et al. The effects of strontium ranelate on the risk of vertebral fractures in women with postmenopausal osteoporosis. *N Engl J Med* 2004;350:459-68.