Current approach to fracture prevention in postmenopausal osteoporosis

B. Kaplan, *M.D.*; **M. Hirsch,** *M.D.*

Department of Obstetrics and Gynecology, Rabin Medical Center, Petah Tikva, and Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv (Israel)

Summary

The prevention and management of osteoporosis are becoming increasingly prominent concerns as the number of postmenopausal women reaching old age continues to grow. Often the first sign of osteoporosis is a fractured bone. It is important that women with low bone density be identified as early as possible and measures taken to reverse the process. These include proper diet and exercise, supplements of calcium and vitamin D, and in cases with proven osteoporosis, antiresorptive or anabolic agents to improve bone strength. Women should also be cautioned to avoid falling as much as possible.

Introduction

Osteoporosis is the most common metabolic bone disease in the Western world, affecting every third postmenopausal woman. Average bone loss is 2% annually, and up to 5% annually in the first five to ten years after menopause. By age 70 years, approximately 50% of the individual bone mass is lost. The trabecular bone of the vertebrae and femoral neck is the most affected [1, 2].

Osteoporotic fractures, occurring mainly at the spine, hip, and distal forearm, represent a major health problem, and in the last few years, they have greatly increased overall health expenditures in most Western countries. The majority of these costs are attributable to the need for inpatient care; there are also indirect costs of lost wages and productivity of the patient or caregiver. The number of postmenopausal osteoporotic fractures is expected to grow with the predicted increase in life expectancy over the next years. Current means of prevention and treatment, besides lifestyle changes, include antiresorptive medications, which inhibit osteoclast recruitment or activity thereby increasing or stabilizing bone mineral density, and anabolic agents, which activate osteoblasts and stimulate the formation of new bone [3].

Risk identification: Bone screening

Early identification of women at risk of postmenopausal osteoporosis is important for proper prevention and treatment. Bone mineral density (BMD) serves as a predictive factor of fracture risk. According to the World Health Organization criteria, osteopenia is defined as a T score of –1 to –2.49, and osteoporosis as a T score of ≤ -2.5. The combination of bone density score and age yields an estimate of absolute risk of fractures in postmenopausal women. It is well recognized that women with osteoporosis have a greater risk of fracture and derive greater benefit from preventive treatment than women without osteoporosis. Osteoporosis may have a rapidly progressive course once a first fracture occurs, further increasing the likelihood of subsequent fractures [4].

Nonpharmacological means of prevention

Diet and dietary supplements

The daily calcium requirement for postmenopausal women is 1500 mg [5]. This level cannot be reached by diet alone in most people. Furthermore, calcium alone, even in sufficient amounts by diet or supplements, usually fails to prevent early postmenopausal bone loss [6], although studies report a significant decrease in fracture risk in older women [7-9]. The effect of vitamin D alone on fracture risk is also uncertain. Combined vitamin D and calcium supplementation has been shown to prevent osteoporotic fractures in community-dwelling elderly people, especially in winter [10]. Most researchers recommend that calcium and vitamin D supplements should be administered along with other anti-osteoporotic medications, particularly in women aged 65 or more.

Revised manuscript accepted for publication July 16, 2004

Complementary medicine

As yet, none of the complementary or alternative therapies has been proven to play a significant role in the prevention of osteoporotic fractures. Isoflavone, the main natural ingredient in soybean products, is the best studied agent so far, but there are still no large, randomized, controlled studies conferring it with anti-osteoporotic properties.

Exercise

Weight-bearing exercise has a positive effect on bone mass [11, 12], mediated by increased osteoblastic activity [13]. However, the effect lasts only as long as the exercise continues, and it is usually insufficient to prevent bone loss in the early postmenopausal years [14]. It also remains unclear if exercise by itself can reduce fracture risk. Nevertheless, exercise improves muscle strength and coordination which, in turn, reduces falls, thereby contributing to the prevention of fractures [15]. Since most falls that cause hip fracture occur at home, women should be cautioned to look out for slippery rugs, poor lighting, lack of handrails, and other potential dangers.

Pharmacological treatments

Hormonal therapy

Estrogen might be one of the most effective agents for preventing postmenopausal osteoporosis. Many randomized controlled studies have shown a significant increase in BMD following oral or transdermal estrogen-progestin therapy (EPT) or estrogen monotherapy (ET), at both higher and lower doses, given either early or late in the postmenopausal period [16-20]. These findings were confirmed by the large Women's Health Initiative studies which reported a significant reduction in the occurrence of osteoporotic fractures of the hip and spine in women receiving EPT or ET [21, 22]. However, the concomitant increase in the risk of cardiovascular disease [21, 22] and breast cancer [21] associated with hormonal treatment prompted the FDA to limit the use of estrogen or estrogen-progestin to short-term relief of postmenopausal symptoms. Although long-term use of EPT/ET for the primary prevention of osteoporosis is not currently recommended, even limited hormonal therapy in the early postmenopausal years exerts long-lasting preventive effects against bone loss [23]. Furthermore, a recent international expert workshop suggested that EPT/ET should be the initial option for osteoporosis prevention and for fracture risk reduction in women at significant risk of fracture, regardless of the presence of menopausal symptoms [24].

Bisphosphonates

Alendronate and risedronate are the most common bisphosphonates in clinical use. They reduce bone resorption and bone loss by inhibiting osteoclast activity. Studies have shown an increase in BMD and a 30-50% reduced rate of spine and hip fractures in women with osteoporosis treated with alendronate and risedronate [25, 26]. They can be used to prevent bone loss or to treat established osteoporosis [27-32]. Alendronate appears to have sustained and well-tolerated effects over a 10-year period [33]. Because of their poor intestinal absorption, bisphosphonates may cause adverse upper gastrointestinal effects and are contraindicated in individuals with gastroesophageal reflux disease. They must always be taken on an empty stomach with plain water, and patients need to remain upright for at least 30 minutes thereafter, with no intake of food or drink during that time. As a result, most women find once-weekly dosing more convenient. This schedule also enhances compliance and thereby improves the effectiveness of therapy. Once-weekly dosing has been found to be equivalent to daily dosing with regard to efficacy and tolerability [34].

Zoledronic acid is a new heterocyclic nitrogen-containing bisphosphonate [35]. A one-year, double-blind, placebo-controlled trial of a single infusion of zoledronic acid in 351 postmenopausal women with low BMD, showed positive effects on bone turnover and bone density, equal to those achieved with daily oral dosing with other bisphosphonates and with proven efficacy against fractures [36]. These findings suggest that zoledronic acid might serve as a good alternative to the difficult-to administer oral bisphosphonates for the treatment of postmenopausal osteoporosis.

Raloxifene

Raloxifene is a selective estrogen receptor modulator (SERM) that inhibits the action of estrogen in the breast and endometrium and acts as an estrogen agonist on bone and lipid metabolism. One study found that three years of therapy with 60 mg/day of raloxifene increased lumbar spine BMD by 3% [37]. A recent post hoc analysis of the MORE trial showed that compared to placebo, raloxifene reduced the relative risk of new vertebral fractures by 69% for postmenopausal patients with osteoporosis, and by 47% for postmenopausal patients with osteopenia [38]. Thus, raloxifene is the first antiresorptive agent with a proven benefit for vertebral fracture risk in women with osteopenia diagnosed by total hip BMD. This advantage, together with raloxifene 72% risk reduction of invasive breast cancer [39] and 62% risk reduction of stroke in patients at high risk of cardiovascular disease [40], may make this agent the ideal alternative to EPT/ET. However, raloxifene does have one major downside: it can worsen vasomotor symptoms, the very effects EPT/ET so efficiently relieves.

Tibolone

Tibolone, a selective synthetic steroid, is indicated for the relief of climacteric complaints and the prevention of bone loss in postmenopausal women. Clinical trials have shown that tibolone prevents bone loss and increases BMD in early

and late postmenopause [41] in both osteopenic as well as osteoporotic women [42]. Its effects on BMD are mediated by the activation of the estrogen receptor in bone tissue. At present, there are several ongoing studies investigating tibolone anti fracture efficacy and breast tissue safety.

Calcitonin

Salmon or human calcitonin, which regulates plasma calcium by inhibiting bone resorption, may serve as an option in patients for whom other therapies are either contraindicated or inconvenient. Salmon calcitonin is usually given in the form of an intra-nasal spray at a daily dose of 200 IU (suppositories are weak and poorly tolerated). Researchers reported that calcitonin increases BMD and decreases the risk of vertebral fractures [43]. However, in addition to side-effects of nausea, flushing, diarrhea and nasal discomfort, some patients may show an immunologic reaction to the non-human form.

Parathyroid hormone (PTH)

Almost all existing agents for the prevention and treatment of osteoporosis reduce bone resorption by disabling or killing osteoclasts. A new generation of potential bone-building drugs is currently emerging. So far, the only successful agent available is teriparatide, a peptide fragment of human recombinant parathyroid hormone (PTH). Teriparatide, administered by daily subcutaneous injections, has been found to improve bone strength and quality, as reflected by an increase in trabecular thickness and connectivity, and an increase in cortical thickness [44, 45]. Compared to placebo, 21 months of treatment with teriparatide 20 mcg/day in postmenopausal women with severe osteoporosis was associated with a rapid and significant increase in spine and hip BMD (3% and 9%, respectively), in addition to a 65% risk reduction of new vertebral fractures, 53% risk reduction of non vertebral fractures, 90% risk reduction of new moderate or severe vertebral fractures, and a reduction in back pain and height loss [46]. The effect of the drug was maintained long after therapy was discontinued [44].

PTH should be used to restore weakened bone, heal fractures, and rebuild osteoporotic bone, but not to prevent postmenopausal bone loss. Its use is restricted by the FDA to a period of up to two years because of uncertainties relating to the risks of hyperparathyroidism and human osteosarcoma [47]. We suggest that in patients with the proper indications, clinicians should prescribe PTH for the short term and then revert to a protective antiresorptive agent.

Two other mini-PTHs, each with 31 amino acids, are being tested in clinical trials at present and an ongoing trial of full length human recombinant 84 amino acids PTH molecule with promising results [48].

Future directions

Strontium ranelate, given daily, is under investigation for use in the prevention of early postmenopausal bone loss. A 2-year, randomized, prospective placebo-controlled study reported a significant increase in BMD at the lumbar spine and hip in treated patients [49, 50].

According to observational studies, one of the by-products of Statins medications, prescribed for hyperlipidemia, is a lower risk for hip and vertebral fractures in postmenopausal women [51]. However, no controlled trial has as yet been designed to study the specific effect on statins on skeletal metabolism.

Evidence so far of the anti fracture efficacy of anabolic steroids, fluoride and active vitamin D metabolites is insufficient to justify their use.

Conclusion

Good lifestyle habits, while not shown to reduce fracture risk, may play a role in maintaining bone strength throughout life. To prevent and treat postmenopausal osteoporosis, women should be encouraged to perform weight-bearing exercise, avoid smoking, and optimize calcium and vitamin D intake through diet and supplements. Medications are indicated in the presence of a BMD of –1 to –2.5 SD with fracture or a BMD of less than –2.5 SD.

There is high-level evidence for the anti fracture efficacy of medical treatment in women with osteoporosis, particularly those with a prevalent fracture; the evidence is less compelling for women with osteopenia, with or without a fracture. The most rigorously investigated, FDA-approved drugs for the reduction of vertebral fractures are the bisphosphonates alendronate and risedronate and the selective estrogen-receptor modulator raloxifene. Other agents that hold promise are parathyroid hormone, strontium ranelate, and salmon calcitonin.

ET/EPT is not recommended for use for fracture prevention alone, but should be considered for women with menopausal symptoms. Tibolone may serve as an alternative. We suggest that if ET/EPT are indicated, they be followed by raloxifene, which also confers cardiac and breast protection. In later stages of life, treatment may be confined to risedronate or alendronate, which has demonstrated the most impressive fracture risk reduction in prospective clinical trials, especially in women over 75 years old, in whom the main concern is preventing hip fracture. PTH should be considered in patients with severe osteoporosis and fractures.

References

[1] Bowersox J., Wortman J.: "NIH Consensus Panel Addresses Osteoporosis Prevention". *Diagnosis and Therapy,* 2000, *17* (1).
[2] Finkelstein J.S.: "Osteoporosis". *Cecil Textbook of Medicine,* 1999, 258.
[3] Riggs B.L., Melton L.J.: "Involutional osteoporosis". *N. Engl. J. Med.,* 1986, *314*, 1676.
[4] Lindsay R., Silverman S.L., Cooper C., Hanley D.A., Barton I., Broy S.B. *et al.*: "Risk of new vertebral fracture in the year following a fracture". *JAMA,* 2001, *285*, 320.
[5] NIH Consence Statement, 1994, *12,* 1.
[6] Dawson-Hughes B., Dallal G.E., Krall E.A., Sadowski L., Sahyoun N., Tannenbaum S.: "A controlled trial of the effect of calcium supplementation on bone density in postmenopausal women". *N. Engl. J. Med.,* 1990, *323,* 878.
[7] Reid I.R., Ames R.W., Evans M.C. *et al.*: "Long-term effects of calcium supplementation on bone loss and fractures in postmenopausal women: A randomized controlled trail". *Am. J. Med.,* 1995, *98*, 331.
[8] Chevalley T., Rizzoli R., Nydegger V. *et al.*: " Effects of calcium supplements on femoral bone mineral density and vertebral fracture rate in vitamin D depleted elderly patients". *Osteoporosis Int.,* 1994, *4,* 245.
[9] Recker R., Hinders S., Davies K.M. *et al.*: "Correcting calcium nutritional deficiency prevents spine fractures in elderly women". *J. Bone Miner. Res.,* 1996, *11,* 1961.
[10] Larsen E.R., Mosekilde L., Foldspang A.J.: "Vitamin D and calcium supplementation prevents osteoporotic fractures in elderly community dwelling residents: a pragmatic population-based 3-year intervention study". *J. Bone Miner. Res.,* 2004, *19*, 370.
[11] Dalsky G.P., Stocke K.S., Ehsani A.A., Slatopolsky E., Lee W.C., Birge S.J. Jr.: "Weight-bearing exercise training and lumbar bone mineral content in postmenopausal women". *Ann. Intern. Med.,* 1988, *108,* 824.
[12] Welsh L., Rutherford O.M.: "Hip bone mineral density is improved by high-impact aerobic exercise in postmenopausal women and men over 50 years". *Eur. J. Appl. Physiol. Occup. Physiol.*, 1996, *74,* 511.
[13] Gutin B., Kasper M.J.: "Can vigorous Exercise play a role in osteoporosis prevention? A review". *Osteopors. Int.,* 1992, *2,* 55.
[14] Fiatarone M.A., Marks E.C., Ryan N.D., Meredith C.N., Lipsitz L.A., Evans W.J.: "High intensity strength training in nonagenarians: Effects on skeletal muscle". *JAMA*, 1990, *263*, 3029.
[15] NIH Consensus Development Panel on Osteoporosis Prevention, diagnosis and therapy. *JAMA*, 2001, *285,* 785.
[16] Lindsay R., Gallagher J.C., Kleerekoper M., Pickar J.H.: "Effect of lower doses of conjugated equine estrogens with and without medroxyprogesterone acetate on bone in early postmenopausal women". *JAMA,* 2002, *287,* 2668.
[17] Recker R.R., Davies K.M., Dowd R.M., Heaney R.P.: "The effect of low-dose continuous estrogen and progesterone therapy with calcium and vitamin D on bone in elderly women. A randomized, controlled trial". *Ann. Intern. Med.,* 1999, *130,* 897.
[18] Weiss S.R., Ellman H., Dolker M.: "A randomized controlled trial of four doses of transdermal estradiol for preventing postmenopausal bone loss. Transdermal Estradiol Investigator Group". *Obstet. Gynecol.,* 1999, *94,* 330.
[19] Schneider D.L., Barrett-Connor E.L., Morton D.J.: "Timing of postmenopausal estrogen for optimal bone mineral density. The Rancho Bernardo Study". *JAMA,* 1997, *277,* 543.
[20] Lindsay R., Tohme J.F.: "Estrogen treatment of patients with established postmenopausal osteoporosis". *Obstet. Gynecol.*, 1990, *76,* 290.
[21] Rossouw J.E., Anderson G.L., Prentice R.L., LaCroix A.Z., Kooperberg C., Stefanick M.L. *et al.*: "Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial". *JAMA*, 2002, *288,* 321.
[22] Effects of conjugated equine estrogen in postmenopausal women with hysterectomy. The Women's Health Initiative randomized controlled trial. *JAMA,* 2004, *291* (14), 1701.
[23] Bagger Y.Z., Tanko L.B., Alexandersen P., Hansen H.B., Mollgaard A., Ravn P., Qvist P., Kanis J.A., Christiansen C.: "Two to three years of hormone replacement treatment in healthy women have long-term preventive effects on bone mass and osteoporotic fractures: the PERF study". *Bone*, 2004, *34* (4), 728.
[24] Practical recommendations for hormone replacement therapy in the peri- and postmenopause. *Climacteric,* 2004, *7*, 210.
[25] Black D.M., Thompson D.E., Bauer D.C., Ensrud K., Musliner T., Hochberg M.C. *et al.*: "Fracture risk reduction with alendronate in women with osteoporosis: the Fracture Intervention Trial. FIT Research Group". *J. Clin. Endocrinol. Metab.,* 2000, *85*, 4118.
[26] McClung M.R., Geusens P., Miller P.D., Zippel H., Bensen W.G., Roux C. *et al.*: "Effect of risedronate on the risk of hip fracture in elderly women. Hip Intervention Program Study Group". *N. Engl. J. Med.*, 2001, *344*, 333.
[27] McClung M., Clemmesen B., Daifotis A., Gilchrist N.L., Eisman J., Weinstein R.S. *et al.*: "Alendronate prevents postmenopausal bone loss in women without osteoporosis. A double-blind, randomized, controlled trial. Alendronate Osteoporosis Prevention Study Group". *Ann. Intern. Med.*, 1998, *128*, 253.
[28] Ravn P., Bidstrup M., Wasnich R.D., Davis J.W., McClung M.R., Balske A. *et al.*: "Alendronate and estrogen-progestin in the long-term prevention of bone loss: four-year results from the early postmenopausal intervention cohort study. A randomized, controlled trial". *Ann. Intern. Med.,* 1999, *131,* 935.
[29] Mortensen L., Charles P., Bekker P.J., Digennaro J., Johnston C.C. Jr.: "Risedronate increases bone mass in an early postmenopausal population: two years of treatment plus one year of follow-up". *J. Clin. Endocrinol. Metab.*, 1998, *83,* 396.
[30] Tonino R.P., Meunier P.J., Emkey R., Rodriguez-Portales J.A., Menkes C.J., Wasnich R.D. *et al.*: "Skeletal benefits of alendronate: 7-year treatment of postmenopausal osteoporotic women. Phase III Osteoporosis Treatment Study Group". *J. Clin. Endocrinol. Metab.*, 2000, *85,* 3109.
[31] Reginster J., Minne H.W., Sorensen O.H., Hooper M., Roux C., Brandi M.L. *et al.*: "Randomized trial of the effects of risedronate on vertebral fractures in women with established postmenopausal osteoporosis. Vertebral Efficacy with Risedronate Therapy (VERT) Study Group". *Osteoporos. Int.,* 2000, *11,* 83.
[32] Harris S.T., Watts N.B., Genant H.K., McKeever C.D., Hangartner T., Keller M. *et al.*: "Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. Vertebral Efficacy With Risedronate Therapy (VERT) Study Group". *JAMA,* 1999, *282*, 1344.
[33] Strewler G.J.: "Decimal point-osteoporosis therapy at the 10-year mark". *N. Engl. J. Med.,* 2004, *350*, 1172.
[34] Rizzoli R., Greenspan S.L., Bone G. 3rd *et al.*: "The Alendronate Once-Weekly Study Group. Two year results of once weekly administration of alendronate 70 mg for the treatment of postmenopausal osteoporosis". *J. Bone Miner. Res.*, 2002, *17,* 1988.
[35] Green J.R., Muller K., Jaeggi K.A.: "Preclinical pharmacology of CGP 42'446, a new, potent, heterocyclic bisphosphonate compound". *J. Bone Miner. Res.*, 1994, *9*, 745.
[36] Reid I.R., Brown J.P., Burckhardt P., Horowitz Z., Richardson P., Trechsel U. *et al.*: "Intravenous zoledronic acid in postmenopausal women with low bone mineral density". *N. Engl. J. Med.*, 2002, *346,* 653.
[37] Ettinger B., Black D.M., Mitlak B.H. *et al.*: "Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. Multiple Outcomes of Raloxifene Evaluation (MORE) Investigators". *JAMA,* 1999, *282*, 637.

[38] Kanis J.A., Johnell O., Black D.M. *et al.*: "Effect of raloxifene on the risk of new vertebral fracture in postmenopausal women with osteopenia or osteoporosis: a reanalysis of the Multiple Outcomes of Raloxifene Evaluation trial". *Bone,* 2003, *33*, 293.
[39] Cauley J.A., Norton L., Lippman M.E. *et al.*: "Continued breast cancer risk reduction in postmenopausal women treated with raloxifene: 4-year results from the MORE trial. Multiple outcomes of raloxifene evaluation". *Breast Cancer Res. Treat.,* 2001, *65*, 125.
[40] Barrett-Connor E., Grady D., Sashegyi A. *et al.*: "Raloxifene and cardiovascular events in osteoporotic postmenopausal women: four-year results from the MORE (Multiple Outcomes of Raloxifene Evaluation) randomized trial". *JAMA,* 2002, *287*, 847.
[41] Moore R.A.: "Livial: a review of clinical studies". *Br. J. Obstet. Gynaecol.,* 1999, *106* (suppl. 19), 1.
[42] Gordana M. *et al.:* "The effect of Tibolone on bone mineral density in postmenopausal women with osteopenia or osteoporosis-8 year's follow-up". *Maturitas,* 2004, *47,* 229.
[43] Chesnut C. III, Silverman S., Andriano K. *et al.*: "A randomized trial of nasal spray salmon calcitonin in postmenopausal women with established osteoporosis: The Prevent Recurrence of Osteoporotic Fractures Study. PROOF Study Group". *Am. J. Med.*, 2000, *109,* 267.
[44] Jiang Y., Zhao J.J., Mitlak B.H. *et al.*: "Recombinant human parathyroid hormone (1-34) [teriparatide] improves both cortical and cancellous bone structure". *J. Bone Miner. Res.*, 2003, *18*, 1932.
[45] Zanchetta J.R., Bogado C.E., Ferretti J.L., Wang O., Wilson M.G., Sato M. *et al.*: "Effects of teriparatide [recombinant human parathyroid hormone (1-34)] on cortical bone in postmenopausal women with osteoporosis". *J. Bone Miner. Res.,* 2003, *18*, 539.
[46] Neer R.M., Arnaud C.D., Zanchetta J.R., Prince R., Gaich G.A., Reginster J.Y. *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.
[47] Betancourt M., Wirfel K.L., Raymond A.K. *et al.*: "Osteosarcoma of bone in a patient with primary hyperparathyroidism: A case report". *J. Bone Miner. Res.,* 2003, *18,* 163.
[48] Sorbera L.A., Leeson P.A.: "ALX1-11 Treatment of osteoporosis (rhPTH1-84) recombinant human parathyroid hormone". *Drugs of the Future*, 2000, *25,* 1007.
[49] Reginster J.T., Deroisy R., Dougados M. *et al.*: "Prevention of early postmenopausal bone loss by strontium ranelate: The randomized, two-year, double masked, dose ranging, placebo controlled PREVOS trial". *Osteoporos. Int.,* 2002, *13,* 925.
[50] Meunier P.J., Roux C., Seeman E., Ortolani S., Badurski J.E., Spector T.D. *et al.*: "The effects of strontium ranelate on the risk of vertebral fracture in women with postmenopausal osteoporosis". *N. Engl. J. Med.,* 2004, *350*, 459.
[51] Douglas C.B., Greg R.M.: "Use of statins and fracture results of 4 prospective studies and cumulative meta-analysis of observational studies and controlled trials". *Arch. Intern. Med.,* 2004, *164,* 146.

Address reprint requests to:
B. KAPLAN, M.D.
Department of Obstetrics & Gynecology
Rabin Medical Center
Beilinson Campus
49100 Petah-Tikva (Israel)