MANAGEMENT OF OSTEOPOROSIS IN ELDERLY WOMEN

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Osteoporosis is characterized by low bone mineral density (BMD) and poor bone quality, resulting in reduced bone strength and increased risk of fracture. Osteoporotic fractures are associated with increased mortality and morbidity, particularly in the elderly, as well as high healthcare costs. The risk of fragility fractures increases with aging, independently of BMD. Many therapeutic agents are available for the treatment of osteoporosis, yet there are limited data on their efficacy and safety in the elderly. Post-hoc analyses of data from prospective, randomized, placebo-controlled clinical trials evaluating drugs for the treatment of postmenopausal osteoporosis have shown a similar response in elderly postmenopausal women as compared with younger postmenopausal women. This article reviews the evidence regarding the treatment of osteoporosis in elderly women and provides suggestions for long-term management in clinical practice. (Annals of Long-Term Care: Clinical Care and Aging 2009;17[10]:35-39)

Introduction
Osteoporosis is a systemic skeletal disease that affects millions of people worldwide. Approximately 30% of elderly women have osteoporosis in the United States, and at least 40% of these women will sustain one or more fractures in their remaining lifetime, with the incidence of fractures increasing with advancing age. Osteoporosis is diagnosed by measuring a patient's bone mineral density (BMD) by dual-energy x-ray absorptiometry (DXA) and applying criteria established by the World Health Organization (WHO). A patient with a BMD value at least 2.5 standard deviations below the mean BMD of a young-adult reference population (T-score ≤ -2.5) at the femoral neck, total hip, lumbar spine, or 33% (one-third) radius, if measured, is classified as having osteoporosis. A diagnosis of osteoporosis may also be made in a patient with a fragility fracture independently of BMD, assuming that other causes of fracture have been considered and found not to be present.

Risk factors for fracture that are independent of BMD include age, previous fracture, parent with hip fracture, current smoking, glucocorticoid therapy, rheumatoid arthritis, and excess alcohol ingestion. The incidence of osteoporotic fractures increases with advancing age and is associated with healthcare expenditures over $17 billion per year in the United States. Unfortunately, few studies of drug therapy for osteoporosis have included data in postmenopausal females age 75 years or older to guide the management of these high-risk patients. This article reviews the evidence for the treatment of osteoporosis in elderly postmenopausal women, focusing on the bisphosphonates (the drug class most often used to treat osteoporosis) and teriparatide (a bone anabolic agent for patients at high risk of fracture).

Nonpharmacological Therapy
Universal recommendations from the National Osteoporosis Foundation (NOF) for all adults over age 50, regardless of fracture risk, include: (1) at least 1200 mg elemental calcium per day; (2) vitamin D3 800-1000 IU per day; (3) regular weight-bearing and muscle-strengthening exercise; (4) avoidance of cigarette smoking and excessive alcohol intake; and (5) prevention of falls.

Frailty in the elderly, defined by a constellation of signs and symptoms (eg, unintentional weight loss, muscle weakness, reduced energy and endurance, slowness of gait, low physical activity), is associated with increased risk of falls, disability, loss of independence, and mortality. Falls are a particular concern in the elderly, and are a common cause for fragility fractures. In the Study of Osteoporotic Fractures, which included 6724 women age 69 years and older, frail women had an increased risk of falls, fractures, and death as compared with women with robust health, but the correlation between frailty and these outcomes persists in women age 80 years and older. Frailty is a dynamic state, not entirely an inevitable consequence of advancing age.9suggesting that appropriate interventions may reduce frailty and the risk of its consequences.

Falls and fall-related injuries are common in the elderly, with the risk increasing with advancing age.10 Many types of interventions to reduce fall risk have been evaluated, including gait and balance training, physical exercise, assistive devices, and environmental modifications. Systematic reviews have shown that multifactorial programs and programs to improve muscle strength and balance can significantly reduce the risk of falls,11,12 although less is known about effectiveness in reducing fall-related injuries. The elderly are at high risk for vitamin D deficiency,13 with vitamin D deficiency being associated with muscle weakness, poor balance, and falls. A meta-analysis of double-blind studies reported that vitamin D supplementation in sufficiently high doses (700-800 IU per day) may reduce the risk of hip fractures and other nonvertebral fractures in elderly ambulatory and institutionalized patients.15

Pharmacological Therapy
The NOF recommends pharmacological therapy for patients at high risk for fracture according to any one of the following: (1) previous hip or vertebral fracture; (2) T-score of -2.5 or below at the femoral neck or lumbar spine, or Z-score in the osteopenia range (between -1.0 and -2.5) at any examination site; or (3) parent with history of hip fracture. Other causes of fracture may also be considered for patients at high risk of fracture. Strategies for osteoporosis management that include both pharmacological and nonpharmacological therapies can help to prevent fractures and other complications of osteoporosis.
vitamin D 15

Once a decision has been made to treat with a pharmacological agent, the most appropriate drug must be selected. Factors to consider in drug selection include comorbidities, patient preferences and previous drug experiences, and the expected efficacy and safety of a drug for a particular patient. Following is a review of the results from randomized, controlled clinical trials of bisphosphonates and teriparatide, the two most effective treatments of osteoporosis in the elderly. Raloxifene and salmon calcitonin are not discussed due to lack of proven efficacy in the reduction of nonvertebral fractures, a major concern in the elderly; raloxifene has additional drawbacks in the elderly due to increased risk of venous thromboembolic events and fatal stroke in patients at high risk for coronary artery disease.

Bisphosphonates

As a class, bisphosphonates are highly effective antiresorptive agents that stabilize or increase BMD, halt the deterioration of bone microarchitecture, and reduce fracture risk. Bisphosphonates effective include alendronate, ibandronate, and zoledronic acid. Potential safety concerns with bisphosphonate therapy for osteoporosis include gastrointestinal intolerance, acute-phase reactions, hypercalcemia, osteonecrosis of the jaw, musculoskeletal pain, impaired renal function, and low-trauma subtrochanteric femur fractures. Recent reviews suggest that in patients appropriately selected for treatment, these risks are very small in proportion to the expected benefit of fracture risk reduction18,19.

Alendronate. The Fraction Intervention Trial (FIT)20,21 showed that alendronate reduced the risk of fractures in women with postmenopausal osteoporosis (PMO). A post-hoc analysis of data from 3568 women enrolled in FIT (age 55-80 yr at baseline and 60-85 yr at the close of the study) showed that alendronate reduced the risk of symptomatic fractures across a spectrum of ages22 (Figure). The overall clinical fracture rate increased steadily as age increased during the study. As compared with placebo, alendronate treatment was associated with fewer fractures at the hip, spine, wrist, or composite (hip, spine, wrist), regardless of age. Alendronate was equally effective in reducing the risk of symptomatic fractures in women age 75 and 85 years as compared with women younger than age 65 years. The raw data suggested a relative risk reduction of hip fracture of about 60% for women over age 80 years. In this analysis, for each fracture endpoint, the number of patient-years at risk (PYR) was calculated for each age group (55 to < 65, 65 to < 70, 70 to < 75, and 75-85 years). Patients could contribute to more than one age group; for example, a woman entering the study at age 72 and leaving at age 77 would have contributed 3 PYR to the age group 70 to < 75 years and 2 PYR to the age group 75-85 years. Patients age 70 years and older during the study constituted about 8% of the PYR: 455 for alendronate and 456 for placebo. The number of fractures (composite endpoint – spine, hip, and wrist fractures) for patients age 70-80 years was 9 in the alendronate group and 22 in the placebo group in the overall analysis. The risk reduction for the composite event for alendronate versus placebo was 65, 80, 111, and 161 women with fractures per 10,000 PYR for the 55 to < 65, 65 to < 70, 70 to < 75, and 75-85 year age groups, respectively (Figure). It was concluded that alendronate is effective at reducing the risk of symptomatic osteoporotic fracture in women regardless of age.

Risedronate. The efficacy and safety of risedronate in reducing the risk of vertebral and nonvertebral fractures in osteoporotic postmenopausal women, including those older than age 75 years, was studied in three randomized, double-blind, controlled 3-year trials: Hip Intervention Program (HIP),23 Vertebral Efficacy in Osteoporotic Therapy-Multinational (VERT-MN),24 and VERT-North America (VERT-NA).25 VERT-MN and VERT-NA enrolled postmenopausal women up to age 85 years, while HIP enrolled women stratified by age 70-79 years with documented osteopenia, and age 80 and older primarily selected due to the presence of at least one nonvertebral risk factor for osteoporosis. VERT-MN reported a significant reduction in vertebral fractures and VERT-NA reported a significant reduction in vertebral and nonvertebral fractures with risedronate as compared with placebo. In HIP, risedronate treatment was associated with a reduction of hip fracture risk in women age 70-79 years with confirmed osteoporosis (n = 5445), but not in those age 80 years and older selected primarily on the basis of clinical risk factors for fracture (n = 3888). In a subgroup of 941 older women known to have osteoporosis (T-score < –2.5 or < –2.0), the incidence of hip fracture was 7.2% in those assigned to risedronate and 9.7% in those assigned to placebo (P = 0.37). A post-hoc pooled analysis of data from HIP, VERT-NA, and VERT-MN has evaluated the safety and efficacy of risedronate in 1392 women age 80 years and older with and without osteoporosis.26 After 1 year of treatment, the incidence of new vertebral fractures was 81% lower in the risedronate group as compared with placebo (P = 0.01), and after 3 years of treatment, the incidence was 64% lower with risedronate as compared with placebo (P = 0.003). Risedronate was well tolerated and had a safety profile comparable to that of placebo. It was concluded that risedronate is efficacious and safe in elderly patients with osteoporosis, as well as in younger patients.

Ibandronate. A significant reduction in the risk of vertebral fracture was shown in a 3-year study of ibandronate as compared to placebo in 2966 women age 55-80 years with PMO.27 A double-blind randomized, double-blind, controlled trial showed no effect of age on tolerability in the daily ibandronate group, intermittent ibandronate group, or placebo group. Patients age 70 years and older were not included in the data set. In gastrointestional events with oral ibandronate as compared with younger patients or those receiving placebo. The eValuation of IBandronate Efficacy (VIBE)28 retrospective cohort study compared fracture risk in 745 patients taking monthly ibandronate with 56,837 patients taking a weekly bisphosphonate. The primary analysis showed no significant difference in the risk of hip, nonvertebral, and any clinical fracture between age groups, and a reduced risk of vertebral fractures in the ibandronate group. These findings were similar in a sensitivity analysis for the subgroup of patients age 65 and older, suggesting equivalent fracture risk reduction with ibandronate in this age group as compared with previous studies.

Zoledronic acid. The Health Outcomes and Reduced Incidence with Zoledronic acid Office yearly (HORIZON)-Pivotal Fracture Trial (PFT)29 evaluated the safety and efficacy of zoledronic acid given as an annual intravenous injection for 5 years in patients age 65-89 years with PMO. Treatment with zoledronic acid reduced fracture risk as compared with placebo, with a generally good safety profile.29,30 The HORIZON-Recurrent Fracture Trial (HORIZON-RFT)31 demonstrated a reduction in fracture risk in patients age 55 years and older who were started on treatment with zoledronic acid shortly after surgery for a hip fracture. A post-hoc subgroup analysis of HORIZON-PFT data by age showed that hip BMD response was similar in all age categories (< 70, 70-79, and >80 yr).31 In HORIZON-RFT, a post-hoc subgroup analysis showed a robust increase in BMD at the hip in all age categories, including those age 85 years and older.32

Teriparatide

The FIT assessed the safety and efficacy of teriparatide (recombinant human parathyroid hormone [1-34]) as compared with placebo in 1637 women age 42-86 years,33 showing a significant increase in vertebral and nonvertebral fracture risk with teriparatide. In a post-hoc analysis comparing treatment effect in subgroups defined by age (< 70, 70-79, and >79 yr), there was no age-related difference in bone turnover markers, femoral neck BMD, vertebral fractures, new nonvertebral fragility fractures, height loss, hypercalcemia, and hyperparathyroidism.34 These findings were also consistent in treatment-emergent adverse events by age. An 18-month multicenter, double-blind, controlled trial compared teriparatide with alendronate in 428 women and men with glucocorticoid-induced osteoporosis.35 This study, which included subjects ranging in age from 22-89 years, found that BMD increased more in patients receiving teriparatide as compared with placebo in all age categories, with a significant difference between age groups. VERT-MN reported a significant reduction in vertebral fractures and VERT-NA reported a significant reduction in vertebral and nonvertebral fractures with risedronate as compared with placebo.
Strategies for Long-Term Management of Osteoporosis in the Elderly

All patients, regardless of age and fracture risk, should be advised on the importance of healthy lifestyle and good nutrition for maintaining optimal skeletal health. For those at high risk of falling, interventions to improve muscle strength and balance, making the living environment safer, use of assistive devices appropriately, and minimizing exposure to medications that may be sedating, cause hypotension, or impair balance should be considered. The management of osteoporosis begins with an assessment of fracture risk, usually with BMD testing combined with clinical risk factors.

When fracture risk is high, as suggested by low BMD, previous fracture, or high estimation of 10-year probability of fracture using FRAX, pharmacological therapy may be indicated. The selection of a drug should be based on individual patient considerations, including comorbidities, concomitant medications, financial resources, competing healthcare priorities, life expectancy, preferences, and anticipated compliance and persistence with therapy. Common concerns in the elderly that might lead to avoidance of oral bisphosphonates include esophageal disorders, malabsorption, and inability to remain upright for 30-60 minutes after dosing.

For effective use of oral bisphosphonates, the patient must understand and adhere to dosing procedures and be reliable in taking the medication at the appropriate time intervals. The optimal duration of time for continuing therapy is unknown, but long-term data with alendronate show that it appears to be effective and safe for at least 10 years. The FIT Long-term Extension (FLEX) study evaluated the effects of continuing or stopping alendronate after 5 years of treatment. It was found that those who stopped treatment had a moderate decrease in BMD, gradual rise in markers of bone turnover, and an increased risk of clinical vertebral fractures compared with those who continued, while the risk of nonvertebral fractures and morphometric vertebral fractures was similar in both groups. Transiliac bone biopsies in FLEX subjects treated for 10 years did not show any qualitative abnormalities, with double tetracycline labelling seen in all specimens. A subgroup analysis of FLEX data showed that nonvertebral fracture risk was increased in women in the discontinuation group when BMD was in the osteoporotic range after 5 years of alendronate therapy.40 Hip fracture rates, evaluated in another study of administrative claims databases, were increased among women compliant with bisphosphonate therapy for 2 years who subsequently discontinued therapy, suggesting that discontinuation is not advisable under these circumstances.

Teriparatide should be considered for patients at very high risk for fracture (eg, those with very low T-score or previous fracture). Teriparatide should not be given to patients with previous external beam or implant radiation to the skeleton, Paget’s disease of bone, skeletal malignancy (primary, metastatic, or unexplained elevation of serum alkaline phosphatase), or metabolic bone disease other than osteoporosis, any of which are potential concerns in the elderly. The approved duration of therapy with teriparatide is no more than 24 months. A course of therapy with teriparatide should be followed by an antiresorptive agent, usually a bisphosphonate, since it is likely that the benefit achieved with teriparatide will otherwise be lost.

Efforts to improve long-term compliance and persistence to therapy should include education of the patient and family on the goals of therapy, and the benefits and potential risks of medication. Since adverse effects, perceived adverse effects, and fear of adverse effects are common reasons for discontinuation of treatment, patients must be followed regularly to address concerns that develop and change the treatment plan when necessary.

Summary

The incidence of osteoporotic fractures increases with advancing age, independently of BMD. Most clinical trials of interventions to reduce fracture risk in women with PMO have included a wide age range of patients; most of the data on efficacy and safety in the elderly have been from post-hoc subgroup analyses. The bulk of the evidence suggests that nonpharmacological and pharmacological therapies that are effective and safe in elderly postmenopausal women are similarly safe and effective in elderly postmenopausal men. Special issues of concern for the long-term management of osteoporosis in the elderly include concomitant medications with potential drug-drug interactions and effects that may impair balance and fall risk. Long-term prospective clinical trials of nonpharmacological and pharmacological interventions in the elderly are needed to provide a better understanding of the pathogenesis of fractures in this population and identify optimal strategies for therapy.

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References


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