Volume 1 • Issue 2 • 2016

Review Article

Orthopaedic Surgery and Traumatology

ISSN: 2573-4962

Preventing fractures in postmenopausal women with osteoporosis

Ramji Lal Sahu[1]* and Pratiksha Gupta[2]

[1]Professor, Department of Orthopaedics, SMS&R, Sharda University Greater Noida UP India

[2]Professor, Department of Gynaecology and Obstetrics, Post Graduate Institute of Medical Sciences and research, ESIC, Basaidarapur, New Delhi, India

***Corresponding Author:** Ramji Lal Sahu, MS, Professor, Department of Orthopaedics, SMS & R, Sharda University Greater Noida UP India.

Received: October 23, 2016; **Published:** October 26, 2016

Abstract

Several medications have shown their ability to reduce fractures in patients with osteoporosis. Since patients who have experienced a previous fracture are at high risk for subsequent vertebral or hip fracture, it is of prime importance to treat such patients with medications that have demonstrated their ability to reduce fracture rates in patients with prevalent fractures. Results obtained with calcium and vitamins D, in this particular population, are not fully satisfactory and these medications are probably better used in conjunction with other therapeutic regimens. Bisphosphonates have shown their ability to reduce vertebral (alendronate, risedronate, ibandronate) and non-vertebral (alendronate, risedronate) fractures in patients with established osteoporosis. Raloxifene has also shown similar properties, notwithstanding its effect on non-vertebral fractures. This compound also has interesting non-skeletal benefits, including effects on the breast and heart. Teriparatide, a bone-forming agent, promptly reduces the rate of vertebral and all non-vertebral fractures, without significant adverse effects. Strontium ranelate, the first agent shown to concomitantly decrease bone resorption and stimulate bone formation, has also shown its ability to reduce rates of vertebral and non-vertebral fractures in patients with established osteoporosis. It significantly reduces hip fractures in elderly individuals at high risk for such events. Its safety profile is also excellent.

Volume 1 Issue 2 October 2016

Introduction

Osteoporosis affects almost 44 million people over the age of 50 in the United States, approximately 80% of whom are postmenopausal women. Both conditions increase susceptibility to fracture. [1–4] Approximately 700,000 osteoporosis related vertebral fractures occur each year in the United States. [1] Although fracture rates are highest in women with osteoporosis defined by bone density (T score –2.5 or below), the National Osteoporosis Risk Assessment (NORA) study [5] found that most fractures (82%) occur in women with peripheral bone mineral density T scores greater than –2.5. Osteoporotic fractures are associated with increased morbidity and mortality, a compromised quality of life, [6–9] and an estimated $17 billion in direct medical expenditures annually. [10] Too often, postmenopausal osteoporosis remains undiagnosed until a fragility fracture occurs. At this point, women are likely to sustain more fractures, and morbidity and mortality rates climb.

Who should be screened for Osteoporosis?

Risk factors help in assessing whether a patient may have low bone mass or be at risk for fracture and in deciding if he or she should be screened for osteoporosis (Table1). [11] The National Osteoporosis Foundation recommends bone mass measurements for: Postmenopausal women younger than 65 years with at least one risk factor for osteoporosis or with a fracture. (Table 2) All women age 65 and older regardless of their risk profile. [11] By and large, screening is best done with tabletop measurements of bone density in both the hip and spine by dual-energy x-ray absorptiometry (DXA). Another screening tool, ie, ultrasonography of the heel, can be used for mass screening if DXA is not available. Although a low reading by ultrasonography and DXA of the finger or wrist is predictive of future fractures, the correlation is less precise than with DXA of the hip and spine. Our patient presents with vertebral fractures and several other risk factors: advanced age, height loss, a recent fracture, family history of osteoporosis, estrogen deficiency, white race, low body weight, low level of physical activity, and vitamin D deficiency. [12] She is also at higher risk for falling because of instability exacerbated by her medications. [12,13] However, nothing in her medical history suggests secondary osteoporosis, eg, due to glucocorticoid therapy, and her normal parathyroid hormone level rules out secondary hypoparathyroidism.

Nonmodifiable

White race
Female sex
Family history of osteoporosis
Previous atraumatic fracture
Advanced age

Potentially modifiable

Estrogen deficiency
Low calcium intake (lifelong)
Current cigarette smoking
Low body weight (< about 127 pounds)
Excessive alcohol intake
Inadequate physical activity
Poor health Frailty

Medications

Glucocorticoids Anticonvulsants Excess thyroid hormone Heparin

Diseases

Rheumatoid arthritis
Hyperthyroidism Hyperparathyroidism
Cushing disease
Lymphoma or leukemia
Myeloma
Sarcoidosis
Malabsorption,
gastrectomy, or malnutrition

Table 1: *Risk factors for low bone mass.*

Classification	T Score*
Normal	> –1
Osteopenia	–1 to –2.499
Osteoporosis	≤ –2.5
Severe osteoporosis fractures	≤ 2.5 with fragility

*Standard deviations below the mean values for a healthy young adult.

Table 2: *World Health Organization criteria for diagnosis of osteoporosis.*

Bone Density Measurements

Bone density measurements can be taken of the spine, hip, or wrist; when values are available for more than one site, risk is determined by the lowest value. Fracture risk approximately doubles for each standard deviation below the mean. [14,15] (Table 2). Furthermore, once a patient sustains a fracture, she is five times more likely to sustain another fracture within a year than is a woman without a fracture [16] In addition to previous fracture and low bone mineral density, the NORA study found that poor health status and mobility also contribute to fracture risk. [17] Patient with low bone density, combined with multiple (more than five) risk factors for fracture, make her risk of hip fracture 10 times higher than for a woman with low bone mineral density but with no more than two risk factors. [18] Her life expectancy is also shortened—the odds for survival decrease with more vertebral or hip fractures. [19] Therefore, she has a clear and urgent need for treatment to prevent additional fractures.

Nonpharmacologic Treatments

Supplemental calcium and vitamin D This patient's housebound lifestyle may limit her sun exposure, an important factor in vitamin D metabolism. Calcium and vitamin D supplementation is recommended to bring intake levels to the following: • Elemental calcium 1,500 mg/day • Vitamin D 400–1,000 IU/day. If the parathyroid hormone level is elevated, a higher dose of vitamin D might be warranted (50,000 IU once or twice a week for 3–6 months with careful monitoring of serum calcium levels and a repeat testing of vitamin D and parathyroid levels at 3–6 months). In women with symptomatic osteoporosis, calcium and vitamin D supplementation alone do not reduce the risk of vertebral fractures, but they do increase the efficacy of osteoporosis medications. Other measures Encourage exercise. Weight-bearing exercise for 30 to 60 minutes at least 3 times a week improves muscle strength and balance, reducing the risk of falling. [20] Manage depression. This patient's depression should be managed with counseling, antidepressants, or both. This may help increase appetite and physical activity. Remove hazards at home, such as throw rugs, which are easily slipped on. Adjust current medications if necessary. This patient's antihypertensive and sedative medications should be changed or the dosages adjusted to help avoid dizziness and postural hypotension. Consider hip protectors to reduce the impact of a fall. [21]

Pharmacologic Treatments

Patients with vertebral fractures and low bone density in the hips and spine require medication. (In general, patients with a T score of less than –2.0, or less than –1.5 with risk factors, should be considered for management with medication.) Several medications are available in the United States for treating postmenopausal osteoporosis (Table 3). Which one to prescribe depends on how effective it is, how quickly benefits are realized, and how well the patient tolerates it. Patients must comply with treatment over the long term to benefit. The most clinically relevant measure of a medication's efficacy is how well it reduces fracture risk. Although bone density is a good predictor of fracture risk and can determine the need for osteoporosis treatment, the increases in density that are associated with medications do not completely explain how they protect against fractures. [22–24] (Table 4) compares the efficacy of different medications in clinical trials.

Medication	Dose
Bisphosphonates	
Alendronate	10 mg/day or 70 mg/week
Risedronate	5 mg/day or 35 mg/week
Ibandronate*	2.5 mg/day
Selective estrogen receptor modulator	
Raloxifene	60 mg/day
Calcitonin (salmon)	
Nasal spray	200 IU/day
Injection	100 IU/day
Parathyroid hormone	
Teriparatide	20 µg/day

*Recently approved by the US Food and Drug Administration but not yet available for clinical use. T

Table 3: *Treatments for osteoporosis available in the United States.*

Study Fractures	No.	Duration	Reduction in	
Nonvertebral	**Vertebral**			
Risedronate				
Harris., *et al*. 27	2,458	3 years	41%*	39%*
Reginster., *et al*. 28	1,226	3 years	49%*	33%
McClung., *et al*. 44,	66 ,331	3 years	55%*	20%*
Alendronate				
Black., *et al*. 26	2,027	3 years	47%*	20%
Cummings., *et al*. 42	4,432	4 years	44%*	12%
Liberman., *et al*. 29	994	3 years	48%*	21%
Raloxifene				
Ettinger., *et al*. 53	7,705	3 years	30%*	10%
Salmon calcitonin nasal spray				
Chestnut., *et al*. 57	1,255	5 years	33%*	12%
Teriparatide				
Neer., *et al*. 58	1,637	21 months	65%*	35%*

*Statistically significant difference compared with placebo group (P < .05)

Table 4: *Efficacy of treatments for osteoporosis in long-term placebo-controlled trials.*

Bisphosphonates

The bisphosphonates currently available are alendronate and risedronate. A third agent, ibandronate, was recently approved by the US Food and Drug Administration for the treatment and prevention of postmenopausal osteoporosis. Its early trial data are promising, [25] but it is not yet available for clinical use. Bisphosphonates prevent vertebral fractures Alendronate and risedronate reduce the incidence of new vertebral fractures by 40% to 50% after 3 years of treatment in postmenopausal women with osteoporosis, including those with radiographically verified vertebral fractures at baseline. [26–29] Short-term benefit. The benefit becomes apparent early

on, which is especially important to patients who already have vertebral fractures, in view of their high risk for subsequent fractures. A post hoc analysis found a lower relative risk of clinical vertebral fractures after 1 year of alendronate therapy (59%, P < .001) in patients with at least one vertebral fracture or a T score of less than –2.5. [30] In two prospective studies in postmenopausal women with osteoporosis who had at least one vertebral fracture at baseline, risedronate reduced the risk of morphometric vertebral fractures at 1 year by 65%27 and 61%. [28]

Pooled data from risedronate trials demonstrated a reduction (P < .01) in clinical vertebral fracture risk as early as 6 months after start of treatment. [31] Among women with two or more radiographically determined vertebral fractures at baseline, a 68% (P < .001) risk reduction in new vertebral fractures was observed after 1 year of treatment with risedronate. [32] Long-term benefit. Patients had 63% fewer symptomatic vertebral fractures on alendronate vs placebo during a 4-year period in the Fracture Intervention Trial (FIT) (P < .001). [33] Skeletal benefits have been reported for up to 10 years, with bone density increased slightly in the spine and maintained in the hip during treatment years 4 to 10 (fracture risk reduction was not calculated because the extension of the trial was not placebo-controlled). [34, 35]

A placebo-controlled 2-year extension of the Vertebral Efficacy with Risedronate Therapy-Multinational (VERT-MN) study of 265 patients showed that morphometric vertebral fracture risk was reduced by 59% (P = .01) during years 4 and 5 with daily risedronate vs placebo. [36] An open-label 2- year extension showed a sustained effect with a nearly constant incidence of vertebral fractures throughout treatment (4.7% for years 0–3, 5.2% for years 4–5, and 3.8% for years 6–7). [37] Once-a-week pills Risedronate and alendronate are available as once-weekly formulations, which have demonstrated similar benefits in lumbar spine and hip bone density and in bone turnover markers compared with their once-a-day counterparts. [38–40] The incidence of clinical vertebral fractures was also similar for both formulations of alendronate after 1 and 2 years of therapy. [38, 40] A post hoc analysis found that the 1-year risk of morphometric vertebral fractures was reduced by 77% (P = .018) for patients on once-weekly risedronate vs a historical placebo control group. [41] Less effect on no vertebral fracture risk There is conflicting evidence about whether alendronate reduces the risk of nonvertebral fractures. The FIT authors found no significant risk reduction. [26,42] However, the Fosamax International Trial (FOSIT) found that it reduced the risk over 1 year by 47% (P = .021) in postmenopausal women with low bone mass (T score –2 or below). [43] Another post hoc analysis also showed that nonvertebral fracture risk declined after 2 years (26%, P = .011). [30] Risedronate reduced nonvertebral fracture risk by up to 39% in long-term prospective clinical trials. [27,28,44]

Pooled results from four major trials indicate that risk is reduced by 74% (P = .001) at 1 year and that risk reduction is evident as early as 6 months. [45] Hip fracture risk. FIT found that in 2,027 women with at least one existing vertebral fracture, alendronate reduced hip fracture risk by 51% (P = .047). [26] However, risk was not reduced in subjects with low bone density in the femoral neck or in subjects who had no vertebral fractures at baseline. [42] In a prospective, double-blind, placebocontrolled trial, [44] risedronate reduced the incidence of hip fracture by 40% (P = .009) in 5,445 women with confirmed osteoporosis (mean T scores about –2.7 to –2.9) and by 60% (P = .003) in 1,703 women who had vertebral fractures at baseline. However, it did not significantly reduce hip fractures in a group of women over age 80 without confirmed osteoporosis. These data underscore that hip fractures and falls pose a serious risk to older women, who should be screened with DXA to establish the diagnosis of osteoporosis. The data also underscore the need to prevent falls in this population. Upper GI side effects of bisphosphonates to reduce the risk of esophageal irritation, patients should be advised not to lie down for 30 minutes after they have taken their dose. [46,47]

After alendronate was introduced in 1995, there were numerous reports of upper gastrointestinal (GI) problems, including ulcerative or erosive esophagitis and esophageal stricture. These occurred more often and more severely than was predicted from clinical trials, [48] in which the reported rates of upper GI adverse events for patients taking either alendronate or risedronate were similar to those of placebo. [26–29,42,44] However, a newer review indicates that reports of esophagitis have declined, possibly because physicians have become more aware of the problem and are advising their patients about how to take these medications. [49] Is risedronate better tolerated than alendronate? It is possible that subjects in the clinical trials of risedronate were more likely than those in the alendronate trials to have had a history of GI problems at baseline. Risedronate trials did not exclude patients with acute GI disorders or

those taking acid-suppressive therapy or nonsteroidal anti-inflammatory drugs (including aspirin), [27,28,44] while some of the alendronate trials did exclude women with active peptic ulcer disease [26,29,42] or dyspepsia. [26,42] A retrospective analysis of a claims database of nearly 4,000 men and women older than 65 years found that once-daily risedronate was associated with significantly fewer GI adverse events and medical costs related to these events than once-daily and once-weekly alendronate. [50,51]

Moreover, risedronate recipients in these analyses were more likely to have had GI problems before treatment than were the alendronate recipients. However, pooled data from 10,068 patients (> 98% postmenopausal women) treated with risedronate or placebo for up to 3 years showed no significant difference in the incidence of upper GI adverse events overall or after stratification for upper GI disease or use of nonsteroidal anti-inflammatory drugs, H2-blockers, or proton pump inhibitors. [52] It is difficult to be certain whether risedronate is more tolerable than alendronate without head-to-head clinical studies. Regardless, now that once-weekly formulations of both medications are available, patients may find it easier to comply with instructions and minimize potential GI problems.

Raloxifene

In a large clinical trial of 7,705 subjects (about one third with an existing vertebral fracture at baseline), daily raloxifene for 3 years significantly reduced the incidence of vertebral fractures by 30% overall (risk was reduced 30% for those with a vertebral fracture at baseline and 50% for those without, both $P < .05$). [53] A post hoc analysis of data from this study showed daily raloxifene reduced the risk of clinical vertebral fractures at 1 year by 68% ($P < .05$) in the overall population and 66% ($P < .05$) in women with a baseline vertebral fracture. [54] The incidence of nonvertebral fractures was similar with raloxifene or placebo in the overall study group. However, in a post hoc analysis, those with a severe vertebral fracture at baseline (> 40% decrease in vertebral height) had a 47% reduction ($P = .046$) in overall nonvertebral fracture risk after 3 years of daily raloxifene. [55] Adverse effects of raloxifene Daily raloxifene is associated with an increased incidence of influenza syndrome, hot flashes leg cramps, and peripheral edema compared with placebo. [53] It is also associated with a higher risk of thromboembolic events, with rates similar to those reported for postmenopausal women receiving estrogen therapy. [56]

Salmon Calcitonin

Salmon calcitonin nasal spray reduced the 5- year risk of new vertebral fractures by 33% ($P = .03$) in postmenopausal women with vertebral fractures at baseline at the approved daily dose of 200 IU (but not at 100 IU or 400 IU) vs placebo. [57] It did not reduce the risk of nonvertebral fractures, including hip fractures. The dropout rate was 59% over 5 years and was similar in all treatment groups. Salmon calcitonin nasal spray was generally well tolerated, but a slight increase in rhinitis was reported in treated patient's vs placebo.

Teriparatide

Teriparatide, a formulation of recombinant human parathyroid hormone (1-34), induces bone formation. In contrast, the other agents inhibit bone resorption. In a study in 1,637 postmenopausal women with at least one vertebral fracture, teriparatide (20 μg subcutaneously once a day) reduced the risk of new morphometric vertebral fractures by 65% ($P < .001$) and of nonvertebral fractures by 35% ($P = .04$) over a median follow-up of 21 months. [58] The risk of nonvertebral fractures considered to be fragility fractures was reduced by 53% ($P = .02$). Dizziness and leg cramps were reported in significantly more patients with teriparatide treatment than with placebo. [58] The US Food and Drug Administration recommends the use of teriparatide for no more than 2 years, as clinical data are available for only 21 months. [59]

Hormone Therapy

The Women's Health Initiative trial found that hormone therapy reduced the risk of hip and spine fractures. [60] However, risks associated with hormone therapy may be greater than previously thought, [61] and it should be used only as long as is necessary to treat menopausal symptoms.

Combination Therapy

In theory, it is possible that combinations of different medications may confer additive or synergistic benefits. However, recent data indicate that alendronate blunts the effects of teriparatide, [62,63] so these two agents should not be used simultaneously. [64] More studies are needed to determine whether different combinations of medications are beneficial. [65]

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