Osteoporosis: Hard Facts About Bones

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ABSTRACT

As a consequence of the aging process, osteoporosis affects all men and women. Age-related loss of bone mass leads to skeletal fragility and increases the risk of fracture. Bone densitometry provides a reasonable estimate of fracture risk, but factors independent of bone density also contribute to fracture risk. Fracture after age 50, either symptomatic or asymptomatic, substantially increases the risk of future fractures. However, data from recent studies suggest high-risk patients frequently do not receive evaluations or treatment for osteoporosis. All currently available agents for prevention and treatment of osteoporosis have proven efficacy for increasing bone density. An accumulation of clinical data show that relatively small increases in bone density are associated with reductions in fracture risk that are substantially greater than would be expected from the observed improvement in bone mass.

Postmenopausal osteoporosis is a systemic skeletal disease characterized by low bone mass, microarchitectural deterioration of bone tissue, and increased bone fragility and susceptibility to fracture. Bone mineral density (BMD) decreases, and fracture risk increases with aging. If left untreated or treated ineffectively, osteoporosis can cause irreversible deterioration of bone strength, leading to increased fracture risk. Osteoporosis can have major adverse effects on physical, emotional, and social well-being. The management of osteoporosis encompasses both prevention and treatment. An effective clinical strategy should reflect a multidisciplinary approach that addresses issues such as environmental modification to reduce the risk of falling, and lifestyle modifications, including smoking cessation and abstinence or moderation of alcohol consumption. Several available medical therapies can reduce the risk of fracture, including the bisphosphonates, which specifically affect bone mass, and raloxifene and estrogen, which offer multiple potential benefits. Numerous studies have documented that even small increases in BMD are associated with disproportionately large reductions in fracture risk.

Osteoporosis: Evolution and Effects

In women, BMD decreases and fracture risk increases with aging. Both men and women can develop osteoporosis, however, as well as individuals of any race. Osteoporosis-related fractures in women may lead to acute and chronic back pain, height loss, kyphosis, abdominal discomfort, rib and pelvic discomfort, sleep disorders, and loss of self-esteem.
The risks and impact of fractures should not be underestimated. For example, in the Multiple Outcomes of Raloxifene Evaluation (MORE) study, vertebral fracture occurred twice as often as any other major clinical event in placebo-treated patients who had no history of fracture before entry into the study.

Since 1994, BMD scanning has been the standard for diagnosing osteoporosis. BMD values more than 2.5 standard deviations below the mean for normal young adults (ie, T scores below -2.5) have been defined as osteoporotic. Declining BMD poses a continuum of risk for fracture that does not appear to plateau. However, a low BMD is not the only risk factor for fracture. Older age, poor health, poor eyesight, lack of exercise, maternal fracture history, any fracture after age 50, and several other factors are independent predictors of hip fracture.

Of particular interest, any fracture after age 50, whether asymptomatic or clinical, greatly increases the risk for subsequent fracture. The observation is noteworthy because approximately two thirds of spinal compression fractures are asymptomatic, meaning that only one third of vertebral compression fractures are associated with back pain.

BMD remains an important predictor of osteoporosis and fracture risk, but since the mid 1990s, the clinical perception of osteoporosis has changed in a subtle but important way. Increasingly, osteoporosis has come to be viewed as a risk factor for fracture, rather than the more conventional clinical view of osteoporosis as the fracture after the fact. This shift in perspective places osteoporosis in a clinical context similar to that of hypercholesterolemia as a risk factor for heart disease or hypertension as a risk factor for cardiovascular disease.

Somewhat disappointing and even disturbing, a classic osteoporotic fracture often does not result in the diagnosis or treatment of the underlying osteoporosis. In fact, as many as three fourths of all osteoporotic fractures may not be linked to the underlying disease or prompt specific therapy to prevent recurrent fractures.

Current clinical practices suggest a need for increased clinical suspicion and diligence in identifying and treating osteoporosis. Physicians and their patients can then consider a variety of therapies with proven efficacy for minimizing the hazards of osteoporosis.

**TREATMENT GOALS AND OPTIONS**

Clinical objectives differ for the management of established osteoporosis versus prevention. In patients with osteoporosis, the goals are to prevent further fractures, maximally increase bone density, relieve pain, and improve functional capabilities. Prevention strategies center on preventing bone loss and preventing an increase in fracture risk. Of the available therapies, some are better suited for prevention, whereas others are better suited for the treatment of established osteoporosis.

**NONPHARMACOLOGIC APPROACHES**

Some of the nonpharmacologic interventions for osteoporosis are fairly intuitive. Environmental modification and related strategies are obvious ways to prevent falls. Abstention or moderation of alcohol consumption can decrease the risk of falling and, thus, fractures. Because smoking increases the risk of osteoporosis, smoking cessation becomes an obvious clinical strategy.

As previously noted, physical inactivity is associated with an increased fracture risk. Regular exercise improves strength and balance and may induce subtle, but important, increases in bone density.

Women who are at risk for hip fracture due to frailty and falling can benefit from wearing hip protectors. The efficacy of hip protectors has been demonstrated in at least 2 large, randomized clinical trials.

Nutrition-based strategies include calcium and vitamin D supplementation. Older patients should consume 1200 mg to 1500 mg of calcium daily; 1000 mg of calcium daily is reasonable for younger patients. Total calcium intake can come from any combination of diet, fortified foods, and supplementation.

Vitamin D supplementation plays an important role in managing osteoporosis risk. For most people, the principal sources of vitamin D are sunlight and fortified dairy products such as milk. An older person who mainly stays indoors and rarely consumes milk or other dairy products has a significant risk of vitamin D deficiency. The routine measurement of vitamin D metabolites may not be necessary in clinical practice, but a daily vitamin D supplement may warrant recommendation. A reasonable goal is 800 IU daily for older patients and about one half of that dose for younger patients. Calcium and vitamin
Vitamin D supplementation should be given concomitantly with most pharmacologic therapies for osteoporosis.

**Pharmacologic Strategies**

Normal BMD reflects a balance between bone resorption and bone formation, whereas osteoporosis often reflects an imbalance in these 2 key components of bone metabolism, with resorption occurring at a greater rate than formation. Pharmacologic therapies for osteoporosis attempt to restore balance to bone metabolism. All "antiresorptive" therapies decrease bone resorption, but also decrease bone formation as a consequence of the normal coupling of these 2 physiologic processes. However, the decrease in bone resorption occurs at a faster rate than the decrease in bone formation, resulting in an overall increase in BMD. The greatest improvement in BMD occurs during the first year of antiresorptive therapy; smaller increases in density occur in subsequent years, with the density eventually reaching a plateau.

Results from several clinical studies of antiresorptive therapies have shown that even small increases in BMD result in disproportionately large reductions in fracture risk. The observation emphasizes that change in bone density does not reflect the entire benefit of therapy. The other factors that contribute to reduced fracture risk have yet to be elucidated, but improvement in "bone quality" has emerged as a recurrent theme in studies of osteoporosis therapies.

Osteoporosis literature on estrogen replacement therapy (ERT) is similar to the cardiovascular literature. Epidemiologic data show that women who use ERT have fewer fractures; however, no large-scale, randomized clinical trial has been conducted on this subject.

ERT also reflects the clinical dichotomy that exists among current osteoporosis therapies. Some agents are bone-specific; the benefits from ERT, however, go beyond preservation of bone mineral density. In addition to increasing BMD, ERT addresses symptoms of estrogen deficiency and may confer other extraskeletal benefits. On the other hand, ERT may also increase the risk of breast cancer, and the effect on fracture risk has yet to be demonstrated in a controlled trial.

Intranasal calcitonin has antiresorptive and analgesic effects. The agent offers the advantage of flexible timing of administration, has no known drug-drug interactions, and is well tolerated. Calcitonin treatment demonstrated antifracture efficacy in the Prevent Recurrence of Osteoporotic Fractures (PROOF) trial, which initially involved 1255 elderly women with a history of osteoporotic fractures. Spinal BMD increased by less than 1%, but the vertebral fracture rate decreased by 36% in women randomized to calcitonin, again emphasizing the concept of improved bone quality. The PROOF study showed no evidence of a reduction in nonvertebral fractures in women treated with calcitonin, although the study had very limited statistical power to do so.

Raloxifene, the first of the selective estrogen receptor modulators (SERMs), demonstrated its ability to improve BMD and reduce fracture risk in the M ORE (Multiple Outcomes of Raloxifene Evaluation) trial, which involved 7705 postmenopausal women. All patients had prevalent vertebral fractures or BMD T-score values of 2.5 or less.

The patients were randomized to placebo or to 1 of 2 doses of raloxifene (60 mg or 120 mg daily). Over 4 years of therapy, patients in the raloxifene groups had BMD increases of 1% to 3% in the hip and spine, primarily during the first year. Those modest changes in BMD translated into a 34% reduction in new vertebral fractures in patients with a history of fracture, and a 49% reduction in fracture risk in patients without prevalent vertebral fractures. The benefits of raloxifene therapy emerged during the first year of therapy, when patients on active treatment had a 68% overall reduction in fracture risk compared with the placebo group. During the 4 years of therapy, however, raloxifene therapy did not decrease the risk of nonvertebral fractures. Results of the M ORE trial also highlighted another key observation about raloxifene therapy: regardless of the degree of improvement in BMD, patients receiving raloxifene plus calcium and vitamin D had a reduced fracture risk compared with patients receiving calcium, vitamin D, and a placebo.
Like estrogen, raloxifene's benefits may extend beyond the skeletal system. The potential of SERMs for preventing breast cancer is being evaluated in the Study of Tamoxifen and Raloxifene (STAR), and their potential cardiovascular benefits are under investigation in the Raloxifene Use for The Heart (RUTH) study.

The bisphosphonates comprise almost a dozen different agents; only 2—alendronate and risedronate—are approved in the United States for osteoporosis prevention and treatment. In contrast to estrogen and raloxifene, the bisphosphonates have a single function, and the benefits are bone-specific. The relative merits of using bone-specific therapies versus those that have multiple effects are the subject of ongoing debate.

Alendronate increases hip, spine, and total body BMD, and clinical trials have documented that the drug reduces vertebral and nonvertebral fracture risk. Results with risedronate are fairly comparable with those achieved with alendronate. In clinical trials, rates of vertebral and nonvertebral fracture have been reduced by approximately 40%. One study showed that 1 hip fracture could be prevented for every 29 elderly women with low BMD and prevalent vertebral fractures who were treated with risedronate for 3 years.

As a class, the bisphosphonates are long-acting compounds, a trait that has given rise to investigation of intermittent dosing. Both alendronate and risedronate have demonstrated efficacy with weekly dosing that is similar to the efficacy observed with daily administration.

The availability of multiple pharmacologic options has sparked interest in combination therapy for osteoporosis, with data just beginning to emerge for some of the potential combinations. Initial findings suggest that the combination of alendronate and hormone replacement may improve BMD to a greater degree than either agent alone. Similar data have come from evaluations of hormone replacement and risedronate, and of raloxifene and alendronate combined. However, no long-term data are available to determine whether greater improvement in BMD with combination therapy translates into improved fracture prevention compared with results achieved with individual agents.

**Summary**

Bone mineral density decreases with age, with a concomitant increase in fracture risk. Available data suggest that the diagnosis and treatment of osteoporosis remain suboptimal, because the vast majority of at-risk patients go unrecognized or untreated. Multiple therapeutic options now exist for the prevention and treatment of osteoporosis. Antiresorptive drugs achieve similar reductions in vertebral fracture risk, but not all agents have demonstrated protection against nonvertebral fractures. Reductions in hip fracture risk have not been demonstrated in every trial of antiresorptive therapy, but some trials lacked sufficient statistical power. Some antiresorptive agents have nonbone effects, whereas others are bone-specific. The appropriate treatment for a given patient may depend on the nonbone advantages offered by a particular therapy as well as the therapy's ability to prevent both vertebral and nonvertebral fractures.

**REFERENCES**


