Osteoporosis and Skeletal Fractures

Michael J. Gardner, MD • Demetris Demetrakopoulos, BS • Michael K. Shindle, MD •
Matthew H. Griffith, MD • Joseph M. Lane, MD

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Abstract Osteoporosis affects millions of individuals worldwide, rendering them susceptible to fragility fractures of the spine, hip, and wrist and leading to significant morbidity, mortality, and economic cost. Given the substantial impact of osteoporosis on both patients and the medical community, it is imperative that physicians improve awareness and knowledge of osteoporosis in the setting of low-energy fractures. In this review, we provide information on effective means of preventing fragility fractures and introduce clinicians to issues pertinent to the patient who suffers an osteoporotic fracture. Prevention of fragility fractures centers around adequate mineral nutrition, including daily calcium and vitamin D supplementation, as well as prescription antiresorptive medications such as bisphosphonates or teriparatide therapy in severe cases, both of which have been shown to decrease future fracture risk. Balance and strength training also play important roles in the management of the osteoporotic patient, particularly following a low-energy fracture, and external hip protectors may be useful for certain patients. Kyphoplasty and vertebroplasty are two minimally invasive techniques that show great promise in the treatment of vertebral compression fractures, although questions regarding long-term biomechanical effects still exist. Traditionally, osteoporosis has been underdiagnosed and undertreated following a low-energy fracture in an elderly patient. Although treatment rates may be improving through public health initiatives, the majority of patients with osteoporosis remain inadequately treated. Perioperative intervention programs that focus on patient education about osteoporosis and treatment options lead to significant increases in intervention and treatment. Reducing the risk of skeletal fractures in patients susceptible to osteoporosis involves improved physician education on the risk factors and management of osteoporosis, as well as informing patients on the significance of dual-energy X-ray absorptiometry testing and medical treatment so that they may serve as their own healthcare advocates in this often-undertreated disease.

Introduction

With over 200 million individuals affected worldwide, osteoporosis is the most common metabolic bone disorder [1]. It is marked by reduced bone strength, decreased bone mass, and microarchitectural deterioration of bone tissue [2], ultimately resulting in increased susceptibility to fracture [3, 4]. According to the WHO, osteoporosis is defined as a bone mineral density (BMD) that is 2.5 standard deviations below the mean peak value in young adults of the same race and sex (T score of -2.5). BMD is a measurement of bone mass and a reflection of the amount of calcium in bone. Currently, the gold standard for measuring BMD is dual-energy X-ray absorptiometry (DEXA), which is the most accurate modality available [5], has excellent precision, and can measure central bone mass. Other modalities include computed tomography (CT) scanning, which utilizes more radiation and can be less precise, peripheral quantitative CT scanning, and ultrasound, which has not been shown to provide additional information about bone quality yet. Osteoporosis can be characterized as either high turnover or low turnover. In the high-turnover variety, osteoclastic activity is increased, and resorption lacunae are deeper and more numerous. In the low-turnover version, osteoblasts fail to form bone during normal bone turnover. The primary form of osteoporosis that occurs in perimenopausal women is a high-turnover osteoporosis [6].

There are over 1.5 million osteoporotic fractures annually in the USA alone [7], at a cost of approximately \$15 billion each year [2, 8–11]. The majority of these fractures occur in the spine, followed by the hip and wrist. Incidence varies according to age; vertebral fracture rates increase rapidly by the sixth decade of life, whereas the risk of hip fracture rises markedly by the eighth decade and beyond [8].

The clinical impact of fractures is substantial. Following a fragility fracture, significant pain, disability, and deformity can ensue. If fracture union is not achieved, the patient may suffer long-term disability. Degenerative joint disease distal to the fracture and reflex sympathetic dystrophy are other recognized complications [12]. Medical intervention is usually required, along with some form of physical or occupational therapy in order for the patient

M.J. Gardner, MD (✉) • D. Demetrakopoulos, BS • M.K. Shindle •
M.H. Griffith, MD • J.M. Lane, MD
Hospital for Special Surgery,
535 East 70th Street., New York, NY 10021, USA
e-mail: gardnerm@hss.edu

to return to a reasonable quality of life and level of functioning.

Hip fractures, while less common than vertebral fractures, account for the majority of the mortality, morbidity, and costs associated with osteoporosis [11]. Usually, surgical fixation or hip replacement is necessary if ambulatory capacity is to be restored. Hip fractures lead to a 15% increase in mortality within the first year, and more than 70% of survivors have profound decrease of function [3]. The high mortality associated with hip fractures in the elderly is a result of both the stress of the fracture as well as concurrent illness. Browner et al [13] found that women who suffer a fracture of the hip or pelvis have a 2.4-fold increase in mortality, although less than 15% of these deaths were directly attributed to the fracture. Hip fractures can lead to prolonged stays in rehabilitation hospitals or nursing homes following acute care and are the most common cause for admission to nursing homes [11].

Vertebral fractures are also associated with significant morbidity. Although sometimes asymptomatic initially, they can lead to height loss, kyphotic deformity, pain, and impaired ambulation and balance [14]. Patients with multiple vertebral fractures are at increased risk of pneumonia and death. Depression, anxiety, and withdrawal are also common [15].

A prior fracture increases the risk of future fractures, regardless of bone density [16]. In a retrospective analysis, Lindsay et al [17] reported that the presence of one or more vertebral fractures resulted in a five-fold increase in the risk for sustaining a subsequent vertebral fracture. Patients with hip fractures are several times more likely to have had at least one vertebral fracture and twice as likely to have sustained a distal radius fracture [9]. The lifetime risk of fractures of the hip, wrist, and spine is 40%. For a woman, the lifetime risk of hip fracture is 14%, and by 80 years of age, approximately 20% of women will have sustained a hip fracture, with the incidence rising to 50% of women by age 90 [1].

Compounding this problem, osteoporosis is underdiagnosed and too often undertreated. Patients who sustain a fragility fracture often do not receive adequate or appropriate medical treatment for the underlying osteoporosis. In a retrospective study of 1162 women who sustained distal radius fractures, only 24% had either diagnostic evaluation or treatment of fracture, 2.8% had a bone density scan, and 22.9% were treated with at least one antiosteoporotic medication [18]. In a prior study at our institution [19], we found that although rates of antiresorptive treatment rose significantly over the course of 4 years in postoperative hip fracture patients, still only 29% of fracture patients received treatment for osteoporosis.

Given the substantial impact of osteoporosis on both patients and the medical community, it is imperative that physicians improve awareness and knowledge of osteoporosis in the setting of low-energy fractures. In this review, we provide information on effective means of preventing fragility fractures and introduce clinicians to issues pertinent to the patient who suffers an osteoporotic fracture.

Prevention of fragility fractures

Adequate nutrition is critical as a universal prevention measure. Evidence indicates that the concomitant administration of calcium and vitamin D can prevent hip fractures and nonvertebral fractures in elderly women. Chapuy et al [20] reported that elderly, ambulatory women residing in nursing homes or apartment houses for the elderly, who had no serious medical conditions and who received 1200 mg of elemental calcium and 800 IU of vitamin D3 (cholecalciferol) daily for 18 months, sustained 43% fewer hip fractures and 32% fewer nonvertebral fractures, compared with the placebo group. These beneficial effects were confirmed in a follow-up study [21], which showed that calcium and cholecalciferol supplementation daily for 36 months resulted in a 29% decreased risk of hip fractures (combination of primary and recurrent) and a 24% decreased risk in all nonvertebral fractures (combination of primary and recurrent).

However, a number of studies have shown that calcium and vitamin D, while critical for improving bone mass, are inadequate for preventing future fractures in patients with established osteoporosis when taken alone [22–26]. In a recent, randomized, placebo-controlled trial [27], which examined the use of oral vitamin D3 and calcium for secondary prevention of fragility fractures in an elderly cohort, no differences were noted between subjects taking oral vitamin D3 or calcium alone or in combination vs. placebo. In a second randomized trial [28], supplementation with calcium and vitamin D3 was not found to reduce fracture risk in community-dwelling, elderly women with one or more risk factors for hip fracture.

Therefore, while beneficial for bone health, calcium and vitamin D, whether alone or in combination, should not be considered sufficient for fracture risk reduction in those with osteoporosis. For this purpose, bisphosphonates and other antiresorptive agents are necessary to treat osteoporosis following fragility fracture.

Medical treatment

Numerous agents have been developed to prevent and treat osteoporosis, including the following: alendronate (Fosamax), risedronate (Actonel), and raloxifene (Evista), which have been approved for the prevention and treatment of osteoporosis; teriparatide (Forteo) and nasal calcitonin spray (Miacalcin), which have been approved for treatment only; and estrogens or combinations of hormones (hormone replacement therapy), which have been approved for prevention only.

Bisphosphonates

Bisphosphonates are pyrophosphate analogs that inhibit osteoclast activity by strongly binding to the hydroxyapatite of bone [1]. They are considered potent pharmacologic agents in the prevention and treatment of osteoporosis. Currently, alendronate and risedronate are the most

commonly administered oral bisphosphonates used in the treatment of osteoporosis and fracture prevention of the spine and hip in the USA. Intravenous pamidronate and zoledronate have also been used as an alternative in patients who cannot tolerate the oral bisphosphonates or who are in assisted living situations.

Alendronate has been shown to increase BMD by DEXA scanning and decrease the risk of both vertebral and nonvertebral (hip) fractures in postmenopausal women [29, 30]. In a study of 2027 women with preexisting vertebral fractures, 5 mg of alendronate administered daily for 24 months, then increased to 10 mg daily, resulted in fewer secondary vertebral fractures in the treatment group and an increase in the lumbar spine, femoral neck, and trochanteric bone density [31]. Another long-term study of 3658 women with osteoporosis showed a significant decrease in the risk of fracture with alendronate treatment [32]. Pols et al [33] reported a 47% reduction in incidence of all nonvertebral fractures in postmenopausal women with low bone mass treated with alendronate.

Risedronate has shown a similar ability to increase BMD and reduce fracture risk. In a double-blind, placebo-controlled trial, Fogelman et al [34] observed increases in BMD after only 6 months of therapy with 5-mg oral daily dose of risedronate. In a triple-blind, three-arm placebo-controlled study of 2458 women receiving 5-mg oral daily dose of risedronate, BMD was significantly increased in the femoral neck, femoral trochanter, and lumbar spine at 3 years in the experimental group, with decreased new vertebral and nonvertebral fractures [35]. In the Hip Intervention Program study, risedronate treatment of women in their eighth decade with proven osteoporosis resulted in a reduction of hip fracture incidence of 40% [36].

Monthly intravenous pamidronate infusion has been used in the treatment of postmenopausal women with osteoporosis who are intolerant to oral bisphosphonates. One study demonstrated reduced bone turnover as measured by bone-GLA protein, alkaline phosphatase, and urinary hydroxyproline in 36 postmenopausal osteoporotic women after five courses of cyclical intravenous pamidronate therapy [37]. Another study showed that 30 mg of IV pamidronate for 3 months produced an increase in BMD of 6.2% in the lumbar spine and 4.7% in the hip [38]. Parenteral zoledronate is administered at intervals of 1 year. In a randomized, double-blind, placebo-controlled trial utilizing annual doses of zoledronate, the treatment group exhibited 4.3–5.1% higher BMD compared with the placebo group and suppressed biochemical markers of bone resorption [39]. Fracture data for parenteral pamidronate and zoledronate have not been reported in the literature to date.

There has been controversy regarding the effect of bisphosphonates on fracture healing. In rodent studies, long-term bisphosphonate administration has not been shown to delay healing *per se* but can lead to prolonged presence of callus and delay callus remodeling [40]. However, bisphosphonates can prevent disuse osteoporosis in the ipsilateral limb during fracture repair [41]. Thus, there are no strict guidelines on the administration of bisphosphonates during fracture healing. As newer more potent ana-

bolic agents, such as teriparatide, become less expensive, these will likely become the medications of choice in osteoporotic fractures.

Calcitonin

Nasal calcitonin is currently considered the most useful in the treatment of bony pain secondary to fracture [42]. In a 5-year, double-blind, randomized, placebo-controlled study of 1255 women with established osteoporosis, 200 IU of calcitonin was found to reduce the risk of new vertebral fractures by 33% compared with placebo. However, these benefits in fracture risk reduction do not extend to the hip [43, 44]. Because of the difficulty with administration in this elderly population as well as the lack of effect on hip fracture reduction, calcitonin is not considered a first line therapy for osteoporosis following fracture.

Teriparatide (recombinant human parathyroid hormone)

Parathyroid hormone (PTH) was recently approved by the US Food and Drug Administration as an anabolic osteoporosis medication. Intermittent administration preferentially increases bone formation over bone resorption, thereby increasing BMD and enhancing bone architecture and integrity [45, 46]. It can increase the connectivity density of bone [46], thicken trabeculae [47], increase cortical thickness, and inhibit osteocyte apoptosis [48], as well as reduce the risk of an osteoporotic fracture. Neer et al [49] demonstrated, in a double-blind, controlled trial involving 1637 postmenopausal women with vertebral fractures, that a 20- μ g subcutaneous daily dose of teriparatide [recombinant human PTH (1–34)] decreased the risk of new vertebral fractures by 65% and nonvertebral fractures by 54% after 10 months of use. Lumbar spine and hip BMDs were increased 10 and 2.8%, respectively. In a comparison of PTH vs. alendronate, Body et al [45] reported that a daily 40- μ g subcutaneous dose of teriparatide resulted in increased lumbar spine BMD compared to a 10-mg daily dose of alendronate (12.2 vs. 5.6%, respectively), which resulted in a significantly lower nonvertebral fracture incidence. It appears that despite the efficacy of both of these agents, coadministration of PTH with alendronate does not lead to a synergistic effect [50], and preadministration of alendronate prior to PTH treatment also yields no increased benefit [51]. Therefore, it is unclear what the optimal therapeutic regimen incorporating both PTH and a bisphosphonate or other antiosteoporotic is, either alone or sequentially. It is clear at this time that teriparatide is a potent osteogenic substance and can significantly increase BMD and reduce osteoporotic fracture risk.

Estrogen and selective estrogen receptor modulators

Estrogens reduce bone turnover and preserve or increase bone mass in postmenopausal women with osteoporosis [52]. They have also been shown to reduce the risk of vertebral fracture by 50% compared to placebo [53, 54]. In

the Women's Health Initiative, which included more than 16,000 postmenopausal women, hormone therapy was shown to reduce the risk of fracture of the hip and spine by 34% [55, 56]. However, estrogens are also associated with an increased risk of cardiovascular events and breast cancer, and estrogens and their derivatives are no longer preferably used for the long-term treatment of osteoporosis and for fracture prevention.

Selective estrogen receptor modulators, such as raloxifene, may not have as many cardiovascular and cancer risks but are not as effective as bisphosphonates in fracture prevention. In one study, daily treatment with raloxifene led to significant decreases in risk of clinical vertebral fractures at 1, 2, and 3 years, but had no protective effects against hip fractures [57]. They have also been associated with venous thromboembolism and hot flashes [58]. Overall, with the variety of alternative safe and effective antiresorptive medications available, we do not recommend the use of estrogen hormones or selective estrogen receptor modulators for primary osteoporosis treatment.

External hip protectors

Hip protectors are devices placed externally on the hip that can reduce the risk of fracture. In a randomized, controlled trial involving 1409 women and 392 men at high risk of falls [59], the rates of hip fracture were decreased in the hip protector group compared with the control group, and these authors concluded that 41 persons needed to use hip protectors for 1 year or 8 persons for 5 years to prevent one hip fracture. Despite reported compliance rates ranging from 35.9% [60] to 48% [59], elderly women who did use hip protectors reported improved self-efficacy [61] and self-confidence.

Balance and exercise training

Falls are the primary risk factor for hip fractures and distal radius fractures [3]. Ninety percent of hip fractures occur secondary to falls, and the majority of falls occur between the hours of noon and 6 PM [62]. Of the community-dwelling elderly, approximately 30% fall at least once over the course of a year, and more falls occur in institutionalized patients [63]. A fall on the side of the body increases hip fracture risk by 6-fold in a patient who is ambulatory and 22-fold in a nursing home patient [3]. Balance training programs, which seek to improve the coordination and self-confidence of frail individuals, reduce the rate of multiple falls by almost 50% [64]. Tai chi chuan, in particular, substantially improves postural stability in high-risk patients [65, 66].

Exercise training, while capable of increasing BMD, has not been documented to decrease fracture rate [67]. Snow et al [68] reported increases in BMD of the femoral neck in postmenopausal women who wore weighted vests and participated in jumping exercises for 5 years, but this effect quickly reverts to baseline BMD levels with discontinuation of the exercise program [69].

Issues unique to patients that sustain fragility fractures

Underdiagnosis and undertreatment

It is critical that in the period following a fragility fracture, the physician remains acutely aware of the likelihood of underlying osteoporosis for appropriate diagnosis and treatment. Because low bone mass is the most accurate predictor of increased fracture risk [70, 71], the measurement of BMD is a crucial first step in diagnosing a patient with osteoporosis. Currently, DEXA is considered the gold-standard modality and has excellent precision and ability to measure axial bone mass [5]. According to the US National Osteoporosis Foundation, DEXA scanning is required in (1) all white women 65 years or older not receiving anti-osteoporotic therapy, (2) postmenopausal women 50–65 years old with a risk factor for osteoporosis, and (3) individuals who have sustained a low-energy fracture [72].

Unfortunately, these guidelines have not been universally adhered to by treating physicians. In a study of patients with osteoporotic fractures, those with vertebral fractures tended to receive antiresorptive medication, whereas patients with hip fractures were treated less frequently [73]. Similar undertreatment occurs in patients following low-energy distal radius fractures [18]. Abbasi et al [74], in a study of patients in a nursing home who had a history of hip fracture, reported that 84% of the patients did not include osteopenia in their problem list nor had an intervention plan generated to address their low bone mass. To assess the rate at which primary care physicians recognized and treated osteoporosis in patients with low-energy hip fractures, we conducted an analysis of 300 patients at three institutions [19]. We found a significant increase in treatment rates with prescription antiresorptive medication or calcium over the course of 4 years, from 11% in 1997 to 29% in 2000. However, the majority received calcium, and only 6% of the overall group received antiresorptive therapy. In addition, no patient underwent a bone density scan while in the hospital. In a report by Juby and De Geus-Wenceslau on 311 patients who had been admitted to the hospital for treatment of a fragility hip fracture, only 9.7% had been prescribed with some form of osteoporosis treatment at time of discharge from the hospital and only an additional 10.2% by the time of discharge from a rehabilitation facility.

Obstacles to intervention

In a recent prospective, randomized trial conducted at our institution [75], we attempted to ascertain whether a peri-operative inpatient educational intervention program increased the percentage of patients in whom osteoporosis was addressed following a hip fracture. Patients who were educated on (1) the association between hip fractures and osteoporosis, (2) the utility of DEXA scans in diagnosing the condition, and (3) the efficacy of bisphosphonates in its treatment were more than twice as likely (42 vs. 19%) to receive appropriate therapeutic intervention than patients who were not.

By its very nature, osteoporosis is a clinically silent disease, which makes patient education and self-advocacy critical elements in the effective treatment of the disorder. The fact that 40% of patients who were approached to participate in the study refused to take part because they believed there was no association between their low-impact hip fracture and osteoporosis emphasizes the need to increase education among all individuals who might be at risk for osteoporosis, as well as all professionals involved in their care. Other groups have also demonstrated how a general lack of patient insight and understanding has hindered attempts at intervention [76–79]. Mauck et al [78] reported that 65% of their elderly patients who had sustained a hip fracture had dementia or delirium, and of the remaining patients, the majority were not psychologically prepared to accept pharmacologic therapy for osteoporosis. Other barriers from the perspective of the patient include the adverse effects and high cost associated with the medications and patient transportation issues.

Potential obstacles to intervention are not limited to patient concerns. There has been confusion and debate over which physician is responsible for treating osteoporosis following a hip fracture. In a survey of both orthopedic surgeons and primary care physicians [80], both groups agreed that treatment falls under the domain of the primary care physician because of the medical nature of the disease and the greater likelihood of long-term follow-up by the primary internist. There also seems to be a lack of awareness among physicians of the treatment guidelines and efficacy of medications for osteoporosis following hip fracture [81, 82]. Recent studies have demonstrated that between 70 and 90% of family physicians wished to be more informed about the management of osteoporosis [80, 83, 84]. The occurrence of a fragility fracture is not always recognized as a substantial risk factor for osteoporosis [76, 83], underscoring the need to continue to educate physicians on the nature and treatment of osteoporosis. Some of the most substantial improvements in changing physician practice patterns have been made when information and reminders have been brought to the attention of the clinician at the time of consultation when decisions are being made [85, 86].

Novel techniques in fracture management

Kyphoplasty/vertebroplasty

Osteoporotic vertebral compression fractures (VCFs) are often painful and can lead to significant impairment in physical function and quality of life [7]. The initial management for acute fractures should include several weeks of bed rest, anti-inflammatory medication, and intermittent narcotics for severe pain followed by physical therapy. Despite conservative treatment, over one third of patients experience chronic pain that may be caused by paraspinal muscle spasm, degenerative arthritis in the region of the fracture, or changes in spinal alignment [7, 87].

Vertebroplasty and kyphoplasty are two minimally invasive procedures used in the treatment of VCFs. They

are performed percutaneously under moderate sedation with local anesthesia or under general anesthesia. Using sterile technique and fluoroscopic guidance, a needle is advanced into the vertebral body via a transpedicular or parapedicular approach. In vertebroplasty, polymethylmethacrylate (PMMA) with barium is injected into the vertebral body. In the kyphoplasty procedure, a balloon tamp is placed in the center of the vertebral body and inflated to restore vertebral height, compact the cancellous bone, and reduce the fracture. The tamp is then removed, and PMMA is introduced into the cavity. Kyphoplasty patients are typically discharged the following day.

Both vertebroplasty and kyphoplasty have been shown to decrease pain and improve function in individuals debilitated by painful VCFs [88–91]. In a series of 80 patients treated with vertebroplasty, 90% reported immediate relief, and at a follow up of 1 month to 10 years, only one complication was reported (intercostalis neuralgia) [92]. Other studies have also shown lasting pain relief over 1 year to 18 months follow-up [93, 94]. The principle risk of vertebroplasty is cement extravasation, which is usually of no clinical relevance at least in the short term. Other less common risks include tissue irritation, including spinal cord and nerve roots, because of PMMA polymerization temperature. Overall, the risk of complications of clinical significance because of vertebroplasty has been reported to be 1–3% [93, 95].

Recent reports on kyphoplasty indicate significant, immediate pain relief in many patients [96, 97]. Moreover, kyphoplasty is effective in at least partially restoring vertebral body alignment and height [98–100]. Lieberman et al [98] reported a 47% restoration of lost height in 70% of vertebral bodies treated with kyphoplasty in a series of 70 consecutive procedures. There was also a significant improvement in Short-Form-36 bodily pain scores and physical function. Theodorou et al [100], in a series of 15 patients with painful osteoporotic VCFs, reported that kyphoplasty improved kyphotic deformity of the vertebra by 62.4% on average, which was associated with dramatic pain relief. Similar positive results were observed by other authors [99]. Complications and risks of kyphoplasty are similar to vertebroplasty, including cement extravasation, although at a lower rate than vertebroplasty [101].

Kyphoplasty has been introduced only recently, and it remains unclear which technique is superior and what the long-term biomechanical effects are. The majority of currently available data are from observational cohort studies, with a notable absence of randomized, controlled studies. In addition, no long-term data exist on the safety of these procedures or on the risk of additional fracture of adjacent vertebral bodies.

Future directions

With continued and enhanced patient and physician education, interventions aimed at preventing and treating osteoporosis following fragility fracture will become more common. At present, there are already many effective

treatment modalities at the physician's disposal. The crux of the approach to the osteoporotic patient is prevention—to avert osteoporotic fractures, which invariably lead to pain, deformity, and decreased quality of life. This effort requires the cooperation of both primary care physician and orthopedic surgeon if the benefits to the patient are to be maximized. Of equal importance is recognizing the presence of osteoporosis in any patient who sustains a fragility fracture and initiating diagnosis and a treatment plan. Improvements in pharmacology will undoubtedly yield more potent antiresorptive and anabolic agents in the future. A better understanding of the long-term effects of vertebroplasty and kyphoplasty will also help guide fracture management approaches.

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