Chapter 5
Interventions and Management of Complications of Osteoporosis

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The treatment and management of osteoporosis has undergone a major transformation in recent decades. Increasing knowledge about the underlying molecular mechanisms of osteoporosis has led to significant advances in surgical techniques as well as in pharmacologic and nonpharmacologic approaches aimed at improving bone density, reducing fracture risk, alleviating pain, and improving quality of life. New surgical techniques; more effective medications including bisphosphonates and the monoclonal antibody, denosumab; enhanced bracing mechanisms; exercise regimens, and fall prevention programs are all described in this chapter. However, it should be noted that their availability coexists with the need for greater physician awareness of these options as well as greater patient adherence to prescribed treatment and rehabilitation programs.

Surgical Interventions

Hip Fractures

Unlike spine fractures which are known to occur as a result of osteoporosis [1], hip fractures are primarily caused by falls. In a study examining the epidemiology of fractures among 169 community dwellers over the age of 50, only 1.2 % of fractures occurred spontaneously, with just two patients noting pain in the hip immediately prior to the fall. The remaining 167 patients (98.8 %) experienced fractures as a result of falls, with 33 % of falls due to tripping or slipping on objects, 21 % caused by weakness in legs or balance problems from neurological conditions, and the others suspected to occur from syncope and dizziness related to cardiovascular conditions [2]. Although rehabilitation strategies are generally the same for osteoporosis patients sustaining hip fracture as they are for those without osteoporosis, a number of factors unique to patients with osteoporosis should be considered by the surgeon

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and physiatrist. Elderly patients with osteoporosis are particularly susceptible to hip fractures, and, in this subgroup, recovery is significantly more complex. For the surgeon, the primary challenge is to select a management strategy that relieves pain through stable fixation but also facilitates early mobilization and minimizes morbidity.

Older adults are at increased risk of experiencing the malignant effects of immobilization, including pressure ulcers [3] from extended bed rest, as well as deep vein thrombosis, urinary retention, urinary tract infections, and physical deconditioning [4]. Delays in fracture treatment of more than 24 hours are known to increase mortality in the elderly [4, 5] or compromise quality of life [6]. Every effort should be made to perform surgery within the first 24–48 hours of the fracture, recognizing that such intervention may be impossible in patients who require reversal of anticoagulation from chronic warfarin use or those requiring preoperative cardiac clearance and associated testing [4].

Hip fractures can be classified by location and degree of displacement or instability (Fig. 1). Intertrochanteric and subtrochanteric fractures are considered as extracapsular, whereas fractures in the femoral neck are classified as intracapsular. The incidence above age 50 is estimated at 49 % intertrochanteric, 37 % femoral neck, and 14 % subtrochanteric [2]. The incidence of intertrochanteric and femoral neck fracture is similar in patients aged 65–99 [7]. Surgical intervention varies depending on fracture type and degree of displacement.

Greater trochanteric fractures may be caused by direct injury or may occur following forceful activity of the gluteus medius or minimus muscles, as in certain jumping sports. If found in isolation and displacement is less than 1 cm, without risk of further separation, these fractures can be treated nonoperatively with protected weight-bearing for 6–8 weeks [8]. However, greater trochanteric fractures are commonly found in conjunction with intertrochanteric fractures, which occur in the proximal femur but distal to the femoral neck (Fig. 2). In this case operative intervention for the combined injury would be recommended. Options include sliding screw plate devices that allow for increased osseous healing by bridging bony fragments together, while imparting less stress on the device. A second common intervention used for intertrochanteric fractures is the dynamic hip screw. This may be accompanied by cerclage wires in the case of high-velocity falls (motor vehicle accidents or sports injuries) or when combined with a greater trochanteric injury (Fig. 3).

Alternatively, intertrochanteric fractures at low velocity are often seen in those with established osteoporosis. Postoperatively, the patient is made partially weight-bearing (10 %) for 4–6 weeks, depending on the degree of stability. When adequate intertrochanteric healing is evident, progressive weight-bearing is permitted [9]. Subtrochanteric fractures constitute a subgroup of intertrochanteric fractures in which the fracture extends beyond the intertrochanteric line. As with intertrochanteric fractures, the majority of patients are managed with open reduction and internal fixation rather than with an endoprosthesis [2].

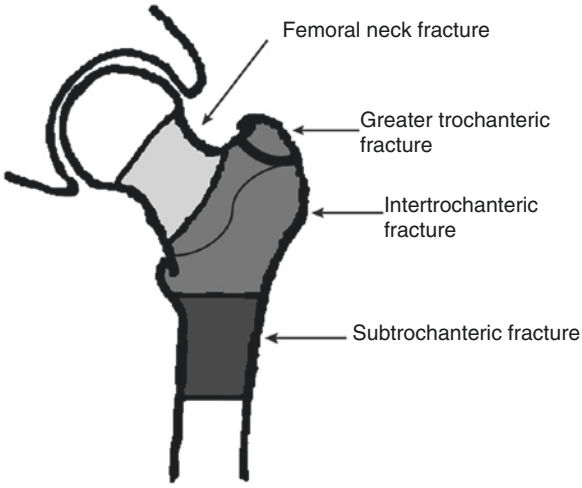

Fig. 1 Types of hip fractures (*Source*: Adapted from Wikipedia Public Domain [WPD]. Accessed 15 April 2016)

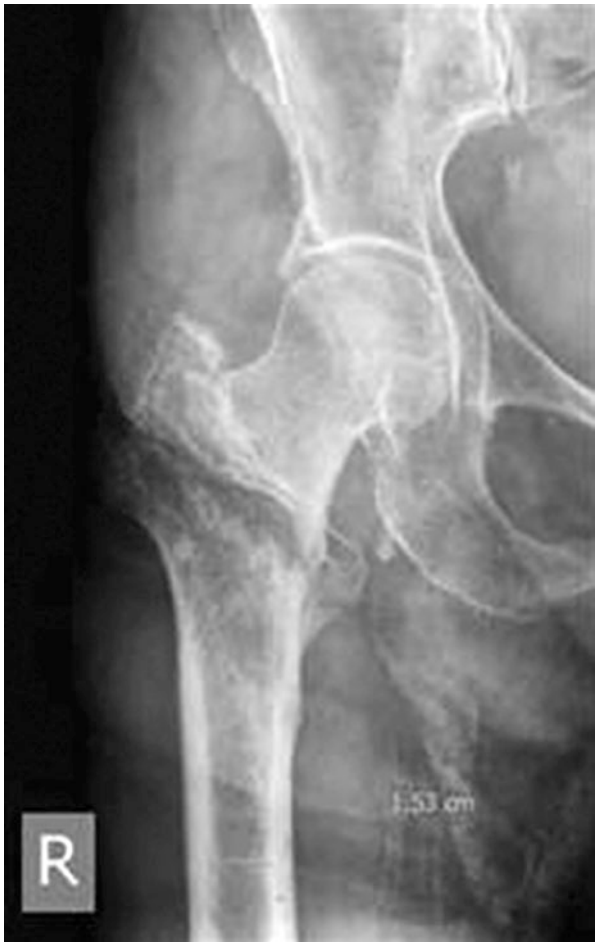

Fig. 2 Greater trochanter and intertrochanteric fracture in a single patient. This patient experienced a high velocity fall during a sporting activity. The intertrochanteric fracture is nondisplaced and the greater trochanter is minimally displaced. (*Source*: Courtesy of Thomas Jefferson University Hospital, Philadelphia, PA)

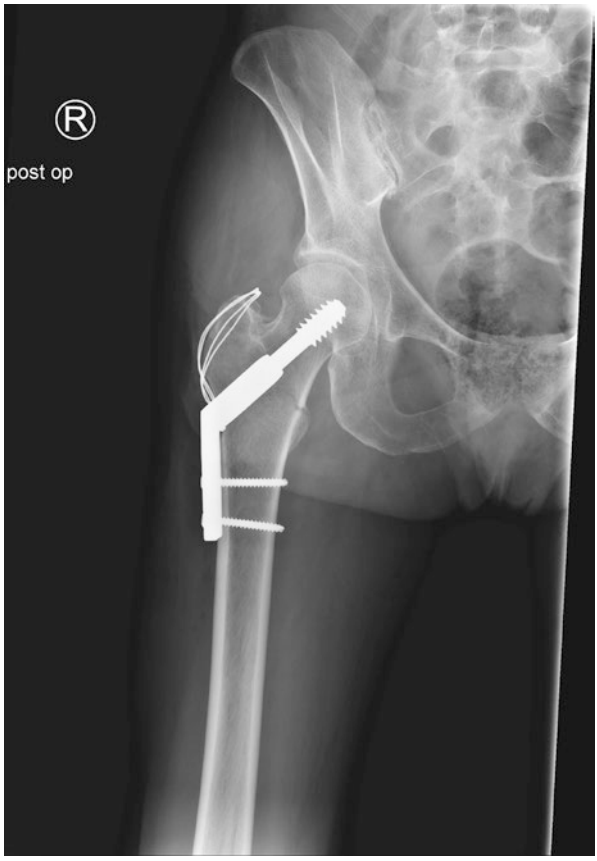

Fig. 3 Dynamic hip screw with cerclage wires used in intertrochanteric fracture repair (*Source*: Courtesy of Thomas Jefferson University Hospital, Philadelphia, PA)

Femoral Neck Fractures

Occurring proximal to the greater trochanter, femoral neck fractures (Figs. 4 and 5) carry the added risk of avascular necrosis due to the proximity of the arteries supplying the region of fracture. The Garden classification system I–IV, based on the degree of displacement, is the most commonly used method to characterize femoral neck fractures. Garden I fractures are minimally displaced and incomplete; Garden II fractures are non-displaced and complete; Garden III fractures are partially displaced and complete; and Garden IV fractures are completely displaced. Elderly patients with Garden I or II fractures can be treated with screw fixation.

Patients with displaced fractures require arthroplasty—the surgical reconstruction or replacement of a joint [10]. The advantages of arthroplasty include lower rates of reoperation, earlier recovery, and possible reduction in the risk of avascular necrosis. Disadvantages are an increase in blood loss and risk of deep wound infection [11]. Patients who are nonambulatory or who have significant medical comorbidities may

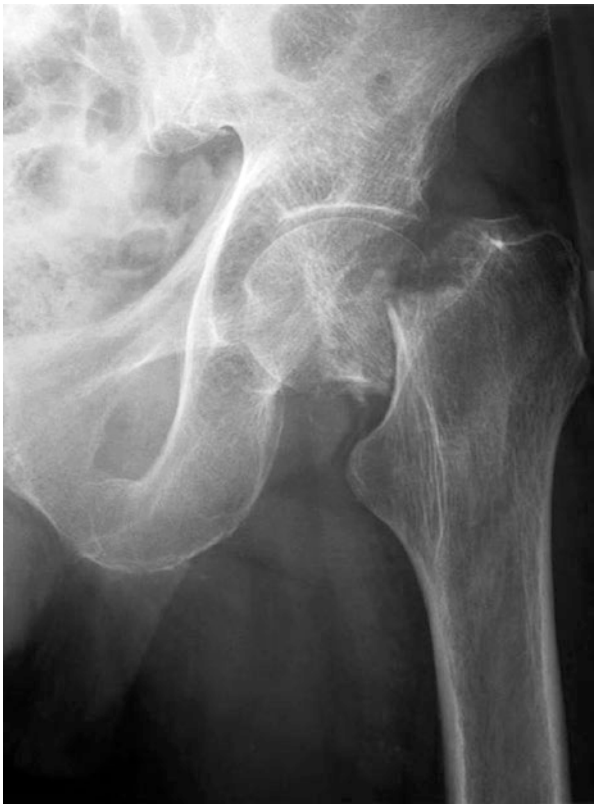

Fig. 4 Femoral neck fracture, moderately displaced, left hip (*Source*: WPD. Accessed 5 Nov 2015)

be treated nonoperatively. However, opting to forego surgery when it is recommended carries an extremely high mortality rate. One study found a 56 % mortality at 12 months post fracture for patients who declined surgery for exclusively economic reasons [12].

One of the benefits of hip arthroplasty is earlier weight-bearing on the surgical limb. For patients with osteoporosis who have undergone arthroplasty for hip fracture, only 22.4 % of those were permitted weight-bearing as tolerated as opposed to 77.7 % of those without osteoporosis [13]. Moreover, the Siebens study [13] found that patients with weight-bearing restrictions were less likely to be discharged home. Ariza-Vega et al. found non-weight-bearing status following hip fracture surgery was associated with diminished functional outcomes after one year [14].

Femoral Shaft and Distal Femur Fractures

For femoral shaft and more distal femur fractures (Fig. 6), pin and screw fixations can be difficult in weakened or osteoporotic bone. The fixation is more robust with the use of a locking compression plate which can provide three times the stability of

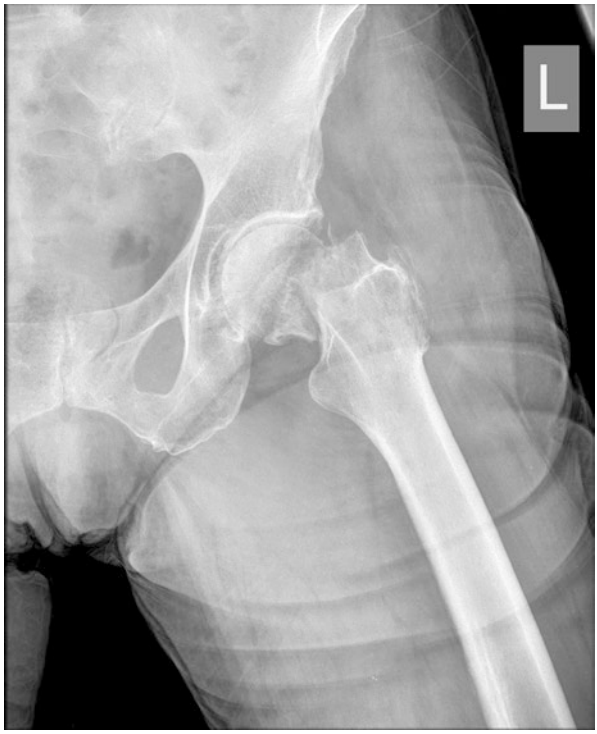

Fig. 5 Acute, displaced, comminuted and transverse fracture of the left subcapital femoral neck. This fracture was sustained in a fall from several steps in an elderly female with established osteopenia. (*Source*: Department of Radiology, Thomas Jefferson University)

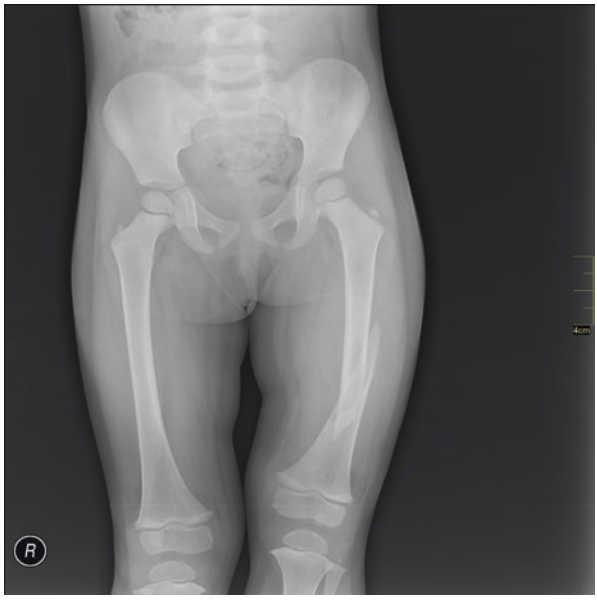

Fig. 6 *Left* distal femur fracture (*Source*: Adapted from WPD. Accessed 5 Nov 2015)

the standard lateral condylar buttress plates and 2.5 times the strength of the condylar plate in axial loading [15]. However, locking compression plates cannot be placed in cases of periprosthetic fractures, which instead require plates using wires for fixation around the femoral shaft. Periprosthetic fractures can also occur in the supracondylar region but primarily in those patients who have undergone total knee arthroplasty rather than hip arthroplasty [16]. One of the major risk factors for supracondylar periprosthetic fractures after knee surgery comes from a loss of bone mineral density of 19–44 % in the first year postoperatively [17].

From a rehabilitation standpoint, every effort should be made to prevent a periprosthetic fracture following primary or revision hip arthroplasty, given the fact that fixation in this type of injury is so challenging. For this reason and to prevent additional second fractures from falls after an initial injury, large sections of this chapter and those of a number of orthopedic textbooks for training are devoted to prevention of second fractures and healing of initial injuries through nutrition, medication, and physical intervention efforts. If a periprosthetic fracture does occur, the additional surgery necessarily predisposes the patient to further delays in weight-bearing and potentially in restricted weight-bearing for more time than had been the case from surgery for their original hip fracture.

Spinal Fractures

The most common type of spinal fracture in patients with osteoporosis is the anterior wedge compression fracture (Figs. 7 and 8) [18, 19]. As discussed in previous sections, these fractures are most frequently nontraumatic or due to minimal trauma that would not otherwise lead to fracture in a non-osteoporotic patient. Because these injuries typically occur in the thoracic or lumbar spine and involve only the anterior spinal column, the majority of compression fractures are stable and can be managed solely with a thoracolumbosacral orthosis (TLSO brace) [19]. However, patients with severe osteoporosis can experience significant and progressive loss of vertebral body height that can result in increased pain, pulmonary compromise, altered sitting posture, and reduced mobility. In the above situations, surgical options should be strongly considered. In cases where anterior wedging becomes more pronounced and involves 50 % or greater vertebral body height loss, disruption of the posterior longitudinal ligament, and related posterior spinal elements can be assumed. These fractures would then be considered unstable and warrant surgical intervention [20].

Measures of mechanical instability are best seen on a computerized tomography (CT) scan and include a widened interspinous and interlaminar distance, greater than 2 mm of translation in an anterior–posterior direction, kyphosis of more than 20°, dislocation, height loss of greater than 50 %, and the presence of articular process fractures [21]. If a patient with osteoporosis is being managed with just a TLSO brace and experiences either continued severe mid to low back pain with therapy or a sudden increase in back pain, additional imaging by either CT or a combination of anterior–posterior radiographs with a lateral radiograph should be performed [20].

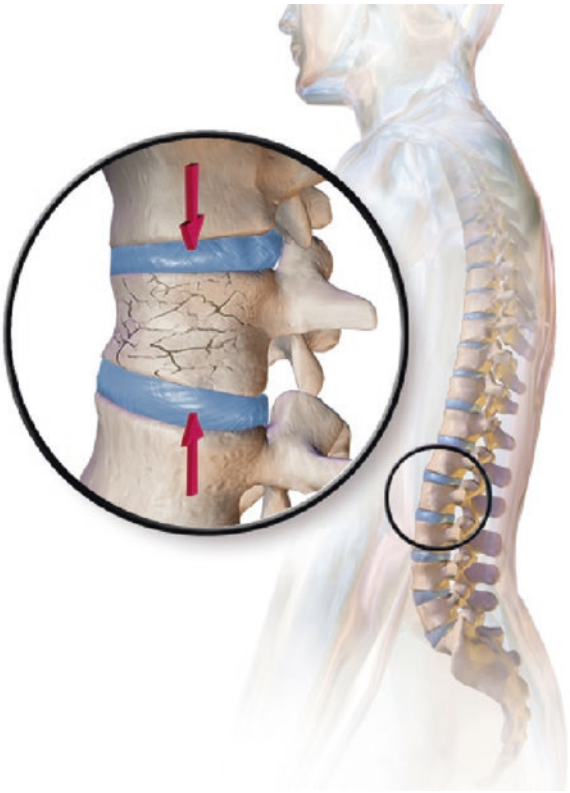

Fig. 7 Diagram showing the microscopic fracture lines within the vertebrae, contributing to a developing compression fracture (*Source*: WPD. Accessed 23 Nov 2015)

Practitioners need to ensure that a fracture has not progressed to the point of involving posterior ligamentous structures or undergone further vertebral collapse. If the posterior vertebral angle calculated on lateral radiographs exceeds 100° angulation, then a more unstable burst fracture is suspected [22]. In many cases, the lateral view and other assessment tools using a combination of plain radiographs are insufficient to ensure stability, thus making CT imperative [21]. For any patient with suspected spinal fracture instability, therapy should be suspended and flat bed rest reinstated until a confirmatory CT of the thoracolumbar spine can be performed. If any change in the sensory examination accompanies increased pain, an MRI is also required to rule out spinal cord compression or edema [20].

Surgical approaches vary according to the fracture site, the extent of collapsed vertebra, and the degree of osteoporosis, but all practitioners attempt to avoid ending a fusion at the level of greatest mobility such as the thoracolumbar junction. Instead the construct usually extends beyond this junction by one or two levels to avoid termination at the apex of kyphosis [18]. For osteoporotic compression fractures at the thoracolumbar level, the posterior surgical approach provides a relatively safe and direct means of reconstructing damage to posterior spinal elements. Short-segment fusion with two-rod distraction constructs provides correction of kyphotic posture, but this type of surgery carries a high failure rate unless multiple segments both above and below the fracture site are also fused [23]. The

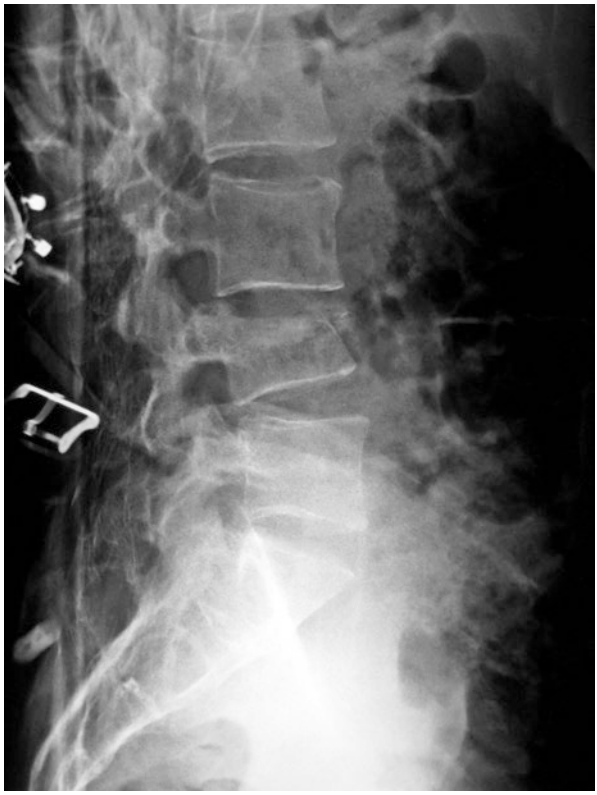

Fig. 8 X-ray of an L4 vertebral body compression fracture (*Source*: WPD. Accessed 23 Nov 2015)

additional segments fused will almost certainly compromise spinal mobility postoperatively and create additional challenges in rehabilitation, particularly for activities such as sit-to-stand transfers and reaching. Alternatively, additional placement of an anterior interbody device may decrease risk of posterior construct failure and simultaneously reduce the need for such an extensive posterior fusion [18]. The drawback of a combined anterior and posterior approach is more pain, an additional surgery, and greater risk to a patient with cardiopulmonary disease undergoing anesthesia.

For patients who cannot undergo surgery and who have intractable pain despite opiates, bracing, and rehabilitation strategies, a new hope exists in the form of percutaneous fracture stabilization with polymethyl methacrylate (PMMA). Vertebroplasty involves direct injection of PMMA into a collapsed vertebral body but does not restore vertebral height reduction. In contrast, kyphoplasty uses a balloon tamp to create a void in the bone and expand the vertebra, thereby correcting height loss [24, 25]. While these procedures offer significant pain relief [24, 26], both techniques carry the risk of cement extravasation, although this complication is less frequent with kyphoplasty due to the use of viscous form of PMMA [24, 25].

Another concern with procedures involving PMMA is weakening of adjacent spinal segments. There are inherent risks of incorporating a hard material in close proximity to fragile osteoporotic bone at neighboring vertebral segments. In verte-

Table 1 Adverse effects of medications for osteoporosis treatment

Drug	Adverse reactions	Contraindications
Alendronate	Nausea, abdominal pain, musculoskeletal pain, acid regurgitation, flatulence, dyspepsia, constipation, diarrhea	Delayed esophageal emptying, hypocalcemia, inability to be upright for >30 minutes, increased aspiration risk
Ibandronate	Influenza, nasopharyngitis, abdominal pain, dyspepsia, constipation, arthralgia, back pain, extremity pain, myalgia, headache, diarrhea, UTI	Hypocalcemia, delayed esophageal emptying, inability to be upright for >60 minutes
Zoledronic acid	Pain, chills, dizziness, N/V, osteoarthritis, fatigue, dyspnea, headache, HTN, influenza-like illness, myalgia, arthralgia, pyrexia	Hypocalcemia, CrCl <35 mL/min, acute renal impairment
Denosumab	Back pain, anemia, vertigo, upper abdominal pain, peripheral edema, cystitis, URTI, pneumonia, hypercholesterolemia, extremity pain, musculoskeletal pain, bone pain, sciatica, arthralgia, nasopharyngitis	Hypocalcemia, pregnancy
Raloxifene	DVT, PE, hot flashes, leg cramps, infection, flu, headache, N/V, diarrhea, peripheral edema, arthralgia, vaginal bleeding, pharyngitis, sinusitis, cough	VTE history, pregnancy, nursing, women who may become pregnant
Calcitonin	Rhinitis, nasal symptoms, back pain, anthralgia, epistaxis, headache	No absolute contraindications
Teriparatide	Nausea, dizziness, headache, leg cramps, acute dyspnea, allergic reactions, edema, hypercalcemia, injection-site reactions, urticaria, muscle spasm	Hypercalcemia, hyperparathyroidism, CrCl <30 mL/min

broplasty patients, long-term follow-up demonstrates a small but significant rise in adjacent segment fracture, relative to segments without PMMA [27]. In one investigation examining kyphoplasty outcomes, a decreased rate of adjacent segment fracture was observed [25]. Kyphoplasty may actually decrease risk of adjacent segment fracture if percutaneous augmentation reestablishes the natural alignment of the spine and eliminates unequal weight-bearing between adjacent vertebrae [24].

Pharmacologic Management: Currently Available Agents

A number of agents exist to treat osteoporosis but due to possible side effects, they should be carefully considered depending on the clinical comorbidities of each patient (Table 1). In addition, the efficacy of the various agents differs based on duration and populations studied within a given clinical trial (Table 2). To assist the clinician with initiating osteoporosis medications based on risk and benefits to an individual patient, the NOF has created guidelines for initiating pharmaceutical

Table 2 Effect of osteoporosis medications on bone mineral density

Drug	Increase in BMD	Population studied	Study cited
Alendronate	Lumbar spine: 4.8 %	487 postmenopausal women with low bone density received either alendronate 70 mg once weekly and daily placebo identical to raloxifene or raloxifene 60 mg daily and weekly placebo identical to alendronate for 12 months	Sambrook, *J Intern Med* 2004 [41]
	Total hip: 2.3 %		
Ibandronate	Lumbar spine: 4.27 %	158 postmenopausal osteoporotic women either received 2 mg IV ibandronate once every three months or 70 mg oral alendronate once per week	Li M, *J Bone Miner Metab* 2010 [43]
	Femoral neck: 3.48 %		
Zoledronic acid	Lumbar spine: 6.71 %	3,889 patients (mean age, 73 years) received a single 15-min infusion of zoledronic acid (5 mg) and 3,876 received placebos	Black D, *NEJM* 2007 [39]
	Total hip: 6.02 %		
	Femoral neck: 5.06 %		
Denosumab	Lumbar spine: 5.7 %	228 ambulatory men between the ages of 30 and 85 years with low BMD	Orwoll, *J Clin Endocrinol Metab*. 2012 Sep [46]
	Total hip: 2.4 %		
	Femoral neck: 2.1 %		
Raloxifene	Lumbar spine: 2.2 %	487 postmenopausal women with low bone density received either alendronate 70 mg once weekly and daily placebo identical to raloxifene or raloxifene 60 mg daily and weekly placebo identical to alendronate for 12 months	Sambrook, *J Intern Med* 2004 [41]
	Total hip: 0.8 %		
Teriparatide	Lumbar spine: 6.4 %	578 postmenopausal women and older men received a once weekly injection of 56.5 μg of teriparatide over the course of 72 weeks	Sonea, Teruki et al. *Bone* 2014 [42]
	Total hip: 3.0 %		
	Femoral neck: 2.3 %		

agents in postmenopausal women. The qualifying group should have one of the criteria listed in Table 3.

Bisphosphonates, denosumab, selective estrogen receptor modulators (SERMs), calcitonin, and parathyroid hormone (PTH) constitute the approved pharmacologic agents for prevention and treatment of osteoporosis in women. With the exception of PTH, they all act to inhibit the activity of osteoclasts, effectively reducing bone

Table 3 NOF guidelines for treatment initiation in postmenopausal women [31]

Previous vertebral hip fracture
T-score below -2 by hip DXA
T-score below -1.5 by hip DXA and 1 or more of the risk factors
Personal history of fracture as an adult
History of fragility fracture in first-degree relative
Low body weight (less than 127 lbs)
Current smoking
Oral corticosteroids (more than three months)

Source: National Osteoporosis Foundation [31]

resorption; for a transient period, formation outpaces resorption. PTH, commercially sold as teriparatide, acts as an anabolic agent to directly stimulate bone formation.

Three bisphosphonates—alendronate (Fosamax), risedronate (Actonel), and zoledronic acid (Reclast)—have been found to improve bone mineral density (BMD), reduce the risk of hip and other nonvertebral fractures, and prevent vertebral fractures. Both alendronate and risedronate are recommended if osteoporosis is caused by overuse of steroid medications, but risedronate also prevents steroid-induced osteoporosis [28]. Because both medications reduce the occurrence of vertebral and nonvertebral fractures by about 50 %, they are currently termed "agents of choice." Comparative studies of the anti-fracture efficacy of the two drugs have not been conducted and are unlikely to be carried out, given the need to obtain statistical data from more than 500,000 subjects in order to detect even a 10 % difference between alendronate and risedronate [29]. Although both medications have been shown to reduce fracture risk, outcomes are compromised by noncompliance with daily or weekly oral medications [30].

Another bisphosphonate, ibandronate, reduces the incidence of vertebral fractures by approximately 50 % over three years. Whereas these drugs can be taken orally, zoledronic acid (ZA) is administered intravenously which may help to increase adherence to therapy.

Several bisphosphonates can be used for primary and corticosteroid-induced osteoporosis. The long half-life of these medications allows for intermittent dosing on a weekly, monthly, semiannually, and, in the case of ZA, yearly basis [31, 32]. Associated dyspepsia, nausea, fever, or transient bone or muscle pain may occur, depending on the route of administration.

If a patient is affected by hip more than spine osteoporosis, certain bisphosphonates are preferable to others. The Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly Recurrent Fracture Trial (HORIZON-RFT) found no difference in nonunion rates between zoledronic acid and placebo when ZA was administered within two weeks, 2–4 weeks, 4–6 weeks, or six weeks after hip fracture repair [33]. An annual infusion of ZA following hip fracture does not result in the additional morbidity and cost of delayed healing. Similar findings have also been found with risedronate [34]. Bone mineral density is improved in osteoporotic postmenopausal women who take alendronate, risedronate, and ZA which have

reduced the risk of hip and other nonvertebral fractures [31, 32, 35, 36]; another bisphosphonate, ibandronate, has been shown to be more effective at the spine than the hip [35].

Zoledronic acid is the most potent of the bisphosphonates and has demonstrated significantly better reduction in bone turnover markers relative to alendronate [37]. Patient satisfaction questionnaires found that despite flu-like symptoms associated with ZA for the first three days after infusion, patients preferred this once annual treatment to weekly alendronate doses [38]. In an early large-scale investigation using 5 mg of once yearly intravenous ZA, Black et al. [39] found a 77 % reduction in clinical vertebral fractures after three years, as well as a 41 % decrease in hip fractures. Although risedronate and alendronate have been shown to reduce fracture risk, outcomes are compromised by noncompliance with daily or weekly oral medications [39].

One of the newest treatments for osteoporosis is denosumab (Prolia), a monoclonal antibody that is given subcutaneously to neutralize the receptor activator of nuclear factor-kB ligand (RANKL), linked to bone resorption. Because osteoclasts require RANKL to support their formation and ultimate survival, an antibody added to their existence results in reduction of bone turnover markers. Compliance is also favorable with this agent, given its twice annual administration in a doctor's office. Unlike zoledronic acid, denosumab is not cleared renally and therefore can be safely administered to those with renal insufficiency [40] (see also Table 2).

Estrogen prevents or delays bone loss in postmenopausal women; however it is associated with an increased risk of breast cancer and is no longer FDA approved for treatment unless other agents cannot be used. Selective estrogen receptor modulators (SERMs) have dual actions as estrogen agonists and antagonists [44] and provide the same benefits as estrogen without its adverse effects. The only SERM thus far sanctioned by the FDA for osteoporotic women is raloxifene which decreases the risk of spine fractures but, as yet, has not been shown to affect hip fracture risk and may not be as effective in preventing bone loss as bisphosphonates [45]. Tamoxifen, a SERM used to treat breast cancer, has been shown to preserve BMD in postmenopausal women [46] and older men [47] but has yet to receive federal approval.

Calcitonin, secreted by thyroid parafollicular cells, acts to suppress osteoclastic activity that leads to small increases in bone mass and reduction in vertebral, but not hip or distal extremity, fracture risk. Approved for women who are at least five years postmenopausal, it is administered intranasally, with potential adverse effects of congestion or epistaxis. Given its limited effect, calcitonin is not considered a first-line treatment.

Parathyroid hormone (teraparatide/Forteo), approved by the FDA as a daily injection in men and women over 28 days, has been demonstrated to increase BMD as well as reduce the likelihood of vertebral and nonvertebral fractures in women. Unlike other treatments, it is an anabolic agent that stimulates bone formation. Reported side effects include hypercalciuria, causing acute gout, leg cramps, or dizziness with orthostatic hypotension [48, 49]. Early studies suggested that concomitant use of bisphosphonates and parathyroid hormone (PTH) would diminish the anabolic effect of

PTH. However, the timing of initiation of the respective agents, as well as the population studied, clouded the interpretation of early findings [50].

In contrast, later reports demonstrated that there are gains in combining antiresorptive agents with PTH but primarily for the hip rather than the spine, with two notable exceptions. Zoledronic acid plus subcutaneous daily teriparatide, a form of PTH, resulted in BMD gains in the lumbar spine of 7.5 % after three years. Gains in BMD for patients receiving ZA alone were 7.0 % over three years versus 4.4 % for those receiving teriparatide alone [51]. Although ZA is the only bisphosphonate that thus far produces favorable outcomes in combination with PTH, denosumab combined with PTH has also demonstrated positive gains in spine BMD [50].

Only four of these medications—alendronate, risedronate, zoledronic acid, and teriparatide—have been approved for men (see chapter on male osteoporosis). Head-to-head trials of bisphosphonates have produced insufficient evidence to prove or disprove any single agent's superiority in preventing fractures; similarly head-to-head trials of bisphosphonates compared to teriparatide or raloxifene have produced insufficient evidence to prove or disprove relative superiority [52].

Although improvement in BMD is an important factor when considering osteoporosis medications, fracture prevention is the ultimate goal. The currently available osteoporosis medications and their effects on fracture prevention are compared in Table 4.

Pharmacologic Agents on the Rise

Strontium Ranelate

Antiresorptive and anabolic agents remain the two primary drugs of choice for prevention and treatment of osteoporosis. Although antiresorptive agents reduce the rate of bone remodeling, they do not increase BMD. Restoration of BMD and bone formation is not achieved through antiresorptives alone but rather requires the use of anabolic drugs [53]. Strontium ranelate (SR) is a relatively new, orally active drug that has shown positive results in reducing the risk of vertebral fractures in osteoporotic, postmenopausal women [54]. SR has a significant advantage because it decreases bone resorption, and its mechanisms are similar to those of PTH in that it stimulates bone formation and increases BMD.

Vertebral Fractures

In the early 2000s, four randomized placebo-controlled clinical trials emerged that paved the way for introducing SR into osteoporosis treatment and prevention [53, 55–57]. In 2002, Meunier et al. were the first to demonstrate SR efficacy on vertebral osteoporosis in a controlled clinical trial [53]. The study population included 353 postmenopausal women with diagnoses of osteoporosis as well as a past

Table 4 Comparison of medication effects on vertebral, nonvertebral, and hip fractures

Generic name	Brand name	Reduced risk of vertebral fractures	Reduced risk of nonvertebral fractures[a]	Reduced risk of hip fracture
Bisphosphonates				
Alendronate	Fosamax	Y	Y	Y
Risedronate	Actonel, actonel with calcium, atelvia	Y	Y	Y
Ibandronate	Boniva	Y	Unknown	Limited to date
Zoledronic acid	Reclast	Y	Y	Y
Biologicals				
Denosumab	Prolia	Y	Y	Y
Hormone therapy				
Estrogen	Premarin	N	N	N
SERMs				
Raloxifene	Evista	Y	N	N
PTH				
Teriparatide	Forteo	Y	Y	Potentially[b]

Source: Adapted from: Agency for Healthcare Research and Quality, US Department of Health and Human Services, Reducing the risk of bone fracture: a review of the research for adults with low bone density. 2012. http://effectivehealthcare.ahrq.gov/index.efm/search-for-guides-reviews-and-reports/prod

[a]Nonvertebral fractures affect bones of the appendicular skeleton apart from the hip. Includes distal femur, tibia, humerus, radius

[b]Weekly injections of 56.5 μg teriparatide may have the potential to reduce the risk of hip fracture. Studies that are designed to determine the effect of teriparatide to reduce the incidence of hip fracture are unavailable and are not likely to be conducted. The human bone biopsy information obtained from the iliac crest may not be representative of the effects of teriparatide at the hip

medical history positive for a vertebral fracture. The double-blind study compared placebo to three groups receiving SR in doses of 0.5, 1, and 2 g daily for two years. Results effectively demonstrated a dose-dependent increase in BMD in these groups versus a decrease in the placebo-controlled group. Although the primary efficacy measure was lumbar BMD, results also demonstrated a 44 % decreased incidence of fracture in the group receiving 2 g per day SR, compared to the placebo group. Similarly, Meunier et al.'s 2004 study supported findings that over a period of three years, fewer patients treated with SR, as opposed to those given the placebo, experienced new vertebral fractures [54].

Nonvertebral Fractures

Reginster et al. [55] showed that 1 g per day SR for 24 months significantly increased BMD in lumbar spine, femoral neck, and total hip in 160 early postmenopausal women, with no known prior history of osteoporosis. Any dose less than 1 g per day showed no significant effect on BMD. In another clinical trial of 5,091

postmenopausal females given 2 g per day SR for five years, a 19% relative risk (RR) reduction of major osteoporotic nonvertebral fractures was observed in patients with average risk [56]. In a population identified as high risk, a 36% RR reduction of hip fracture was exhibited in those receiving 2 g per day SR.

In the above studies, no significant difference in adverse effects occurred in SR as compared with control groups. The dosages of SR administered ranged from 125 mg/day to 2 g per day with the higher dosages demonstrating the most significant improvements in outcomes. The most prevalent reported adverse events consistent among the four studies were gastrointestinal issues including nausea, diarrhea, and headache.

Subsequently, however, the French Agency for the Safety of Health Products (AFSSAPS, now termed the National Agency for the Safety of Medicines and Health Products (MSNA)) conducted a review of the primary side effects of SR. From January 2006 (the date of commercialization of the product) to March 31, 2009, the AFSSAPS examined data from 31 pharmaceutical vigilance monitoring centers. The most common serious adverse events (SAEs) were cardiovascular related, equaling 52%. Thromboembolic events (venous thrombosis, pulmonary embolism (PE), stroke, central retinal artery or vein occlusion, supraventricular tachycardia (SVT), or peripheral edema) contributed to two out of the three deaths attributable to SR use [57]. In a 2014 public statement, the European Medicines Agency recommended that patients with a history of venous thromboembolism (VTE), temporary or permanent immobilization due to a medical condition, or reduced mobility due to postoperative precautions, not use SR. The agency stipulated that use of SR be restricted in patients with cerebrovascular disease, peripheral arterial disease, and ischemic heart disease, due to risk of heart attacks or obstruction of blood vessels [58].

Cathepsin K Inhibitors

One key to improving bone density is to eliminate the undesired coupling that occurs between bone formation and bone resorption. Although bisphosphonates, SERMs, and denosumab reduce bone resorption, they correspondingly inhibit formation. Agents currently under development promise to inhibit bone resorption without affecting bone formation. Cathepsin K is a cysteine protease expressed in osteoclasts located at the ruffled border, the active portion of the cell that resorbs bone. Cathepsin K inhibitors have been explored in phase II and III clinical trials. Early results demonstrate significant reduction in N-telopeptide and C-telopeptide (NTX and CTX) and similar markers of bone loss, but no effect on markers of bone formation such as bone-specific alkaline phosphatase. In terms of clinical trials, odanacatib is the agent with the most advanced data. It is dosed weekly and administered orally. Unlike potent bisphosphonates such as zoledronic acid, the half-life of odanacatib is about one week, and it is reversible in a similar time frame, should adverse symptoms occur after use [59, 70].

Results of a phase III long-term odanacatib fracture trial (LOFT) were released in early 2015; the study population consisted of 16,713 women age 65 and older who had BMD of ≤2.5 at the hip or femoral neck, or, alternatively, a *T*-score of ≤1.5 in total hip or femoral neck in the presence of existing vertebral fracture. Findings in comparison with placebo indicate that a 50 mg per week dose inhibits bone resorption and increases BMD, with only a temporary decline in bone markers. A planned interim analysis, conducted by an independent committee, brought this study to an early halt, due to the striking efficacy and favorable risk/benefit of odanacatib compared with placebo. More than 8,000 patients (presumed to be taking the placebo) dropped out of the trial due to excessive bone loss, and a subsequent, still blinded extension study of 8,256 women includes only subjects remaining on odanacatib. The sponsor of the study plans to follow those subjects in the extension trial that will focus on the long-term safety and efficacy of odanacatib [61].

Wnt Signaling Targets: Sclerostin Inhibitors

Given the limitations of current antiresorptive therapies, particularly the uncertainly about their long-term effects, researchers are focusing on the development of anabolic treatments to increase bone formation and bone mass. Teriparatide is currently the only anabolic agent FDA approved for treating osteoporosis in both men and women. Efforts to neutralize inhibitors of Wnt signaling shows promise of enhancing bone formation. Wnt's are secreted glycoproteins that communicate by signals involving seven transmembrane receptors and a number of co-receptors; they, in turn, utilize low-density lipoprotein receptor proteins (LDLRP) five and six to facilitate gene transcription and subsequent bone mass accrual. Ectopic Wnt signaling influences osteoprogenitor cells toward the osteoblast lineage. Future pharmacologic agents that stimulate Wnt signaling would favor osteoblast formation and net bone density increase [62].

Wnt signaling is inhibited by sclerostin, which binds to the LDLRP five and six complex, halting the steps needed to influence the osteoprogenitor cells which, in turn, form osteoblasts that produce bone tissue; consequently there is a growing interest in the use of agents that inhibit sclerostin [60]. Preclinical studies of sclerostin inhibition in monkeys and ovariectomized rats have shown a substantial increase in bone formation, particularly in trabecular bone at the femoral neck and lumbar spine. Because no increase in bone resorption markers occurred, the net result was an overall increase in bone mass, confirmed by a corresponding increase in osteocalcin [63]. Inasmuch as the majority of the prior trials have focused on estrogen loss correction, this study was designed specifically to examine a possible anabolic mechanism of bone formation in men.

A phase I study in humans using three escalating doses of a sclerostin antibody, romosozumab [AMG 785], resulted in dose-dependent increases of bone formation markers yet showed a decrease in resorption marker, serum CTX. Although increases

in spine BMD of 5.3 % and total hip BMD of 2.8 % occurred, six patients receiving the highest of the three doses developed antibodies to the drug with two patients demonstrating neutralizing antibodies. The presence of antibodies did not appear to compromise the effectiveness of the drug [64, 65]. Adverse effects including injection-site hemorrhage or site erythema, back pain, headache, dizziness, and hepatitis were noted in 28 % of subjects who received the drug versus 11 % of placebo subjects.

Following the phase I study, a phase II multicenter international randomized controlled trial examined 419 postmenopausal women ages 55–85 with low BMD over a 12-month period. Subjects received 70, 140, or 210 mg of subcutaneous romosozumab monthly or an every three-month dose of either 140 or 210 mg romosozumab. Other groups received placebo, alendronate orally, or subcutaneous daily teriparatide (PTH) [66]. Those subjects in the monthly 210 mg group demonstrated an 11.3 % increase in BMD in the lumbar spine, far exceeding the 4 and 6 % increases seen at six months with alendronate or teriparatide [65, 66]. A phase III study, now in progress, will clarify long-term adverse effects enabling healthcare professionals to use appropriate risk stratification in prescribing sclerostin inhibitors when they are released for use by regulatory agencies.

Nonpharmacologic Interventions

Bracing

To provide mechanical support in the osteoporotic spine, braces are prescribed in cases of acute compression fracture or symptomatic chronic vertebral fractures. The use of an orthosis supports weakened soft tissue structures, maintains anatomical alignment of the spine to promote healing, helps prevent further fractures within the affected area, and improves pain management enabling mobilization and deterring bed rest [67]. The acuity and the type of vertebral fracture are two factors that determine whether bracing should be employed.

A thoracic lumbar sacral orthosis (TLSO) may be indicated when immobilization of the spine is necessary in all planes: coronal, transverse, and frontal. Less restrictive braces, which are more comfortable, easier to fit, but do not restrict motion as fully in all three planes of motion, are prescribed when spinal fractures are considered stable and not at risk for progression [68].

Biomechanically, the objectives of a brace are to decrease axial loading on the anterior bodies of the spine and prevent flexion of the spine. Thus, braces are often designed to promote hyperextension of the spine in order to reduce pressure on the vertebral bodies. Common braces that achieve this hyperextension goal are the Jewett (Fig. 9) and Taylor braces as well as the cruciform anterior spinal hyperextension (CASH) brace (Fig. 10). All three orthoses prevent flexion and facilitate hyperextension; the restriction in other planes of motion is limited [69]. The Jewett brace may place too much force on the posterior elements of the

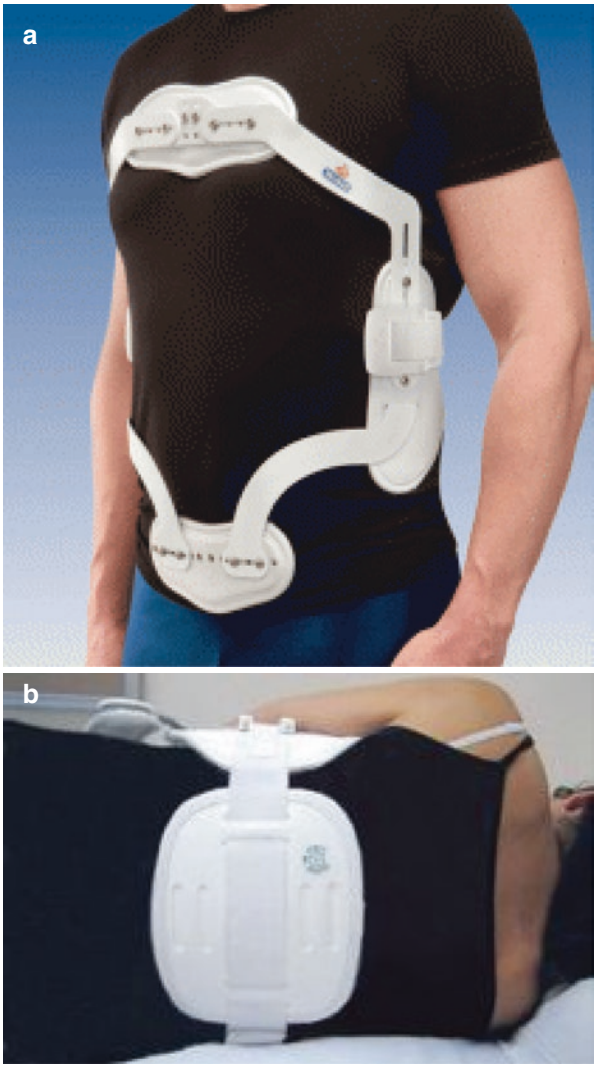

Fig. 9 Two views of the Jewett brace. (**a**) Shows the anterior view in stance and (**b**) illustrates the posterior view in the side lying position. (*Source*: Courtesy of Orthotics Department Teaching Files, Thomas Jefferson University, Philadelphia PA)

spine and thus should be avoided in cases of already established osteoporosis. Although the Jewett and CASH braces restrict flexion and promote extension, their effect in preventing spinal movement in other planes is limited [69, 70].

Bracing is often cumbersome, with several studies demonstrating decreased compliance with brace wear as compared to alternative osteoporosis treatments [69, 71]. Biomechanically, the spinal orthosis inhibits axial muscle use because the brace provides support to the spine passively rather than actively. Most osteoporosis experts agree that a brace should be discontinued as soon as the pain is resolved to prevent atrophy of axial muscles [67]. Few studies quantify the effectiveness of orthotics in the scope of osteoporosis. However, Pfeifer and colleagues did find a correlation between decreased pain and increased back extensor strength [72, 73].

Fig. 10 Photograph of an individual wearing a CASH brace (*Source*: Adapted from WPD. Accessed 23 Nov 2015)

Therapy Interventions

Gait Retraining and Fall Prevention Techniques

Dynamic exercise programs are often recommended when proprioceptive deficits are identified. One method of proprioception remediation, specific to the osteoporotic population with increased kyphosis, is the application of a weighted kypho-orthosis. Unlike braces to limit flexion through the use of anterior restraints, a kypho-orthosis employs gravity to improve spinal alignment, thereby encouraging the use of axial muscles instead of inhibiting the muscles with bracing [71, 74, 75].

The weighted kypho-orthosis resembles a soft backpack with a weight present at the thoracic spine, just caudal to the inferior angles of the scapula (Fig. 11). Determination of orthosis weight varies; some studies employ a percentage of body weight, whereas others demonstrate results with a uniform weight of 1 kg [68, 71, 75, 76]. Ideally, the device should be worn 20–30 minutes for multiple sessions per day, while the patient is concomitantly performing spine extension exercises [68].

Fig. 11 Photograph of an individual with a kypho-orthotic brace (*Source*: Courtesy of Thomas Jefferson University, Department of Rehabilitation Medicine and the Office of Hospital Volunteers, Philadelphia, PA)

Kaplan et al. suggest that the kypho-orthosis reduces compression fractures with two mechanisms. The first is passive: the weight produces a force posteriorly below the inferior angles of the scapula, thus reducing anterior compressive forces on the spine. With the second, the weight produces proprioceptive input, which in turn promotes activation of back extensors and, over time, results in improved posture and back extensor strength [71].

A number of researchers have examined the benefits of a proprioceptive exercise program for patients with osteoporosis [1, 76–78]. The spinal proprioceptive extension exercise dynamic (SPEED) program, developed by M. Sinaki, combines the use of weighted kypho-orthosis, muscle and facet joint reeducation with postural, as well as resistance exercises [67, 79]. Patients were instructed in a 4-week spinal proprioception extension exercise program, performed at home while wearing a weighted kypho-orthosis. Results demonstrated reduced back pain, improved lumbar strength, reduced risk of falls based on the Falls Efficacy Scale, and increased level of overall physical activity. Significant changes were achieved in the computerized dynamic posturography score for gait and self-reported "fear of falls" [80].

Exercise Principles

Research exists on exercise as a means not only to prevent osteoporosis and its complications but also to manage resultant impairments once osteoporotic complications occur [81]. With a known history of osteoporosis, exercises making use of either passive or active spine flexion are to be avoided. Findings suggest that even unweighted and low velocity spinal flexion creates sufficient biomechanical loading of the fragile vertebra [79, 82], increasing intradiskal pressure substantially and heightening the risk of fracture. Damage occurs when compressive forces on the spine are transferred to structurally fragile vertebral bodies in conjunction with compressive loading of the anterior spinal column [83]. Abdominal and back musculature should be strengthened in neutral spinal positioning, with progression toward spine extension as tolerated. This technique allows for core muscle reinforcement without increasing force on the anterior column of the spine. An objective of exercise in the treatment of osteoporosis is to improve axial stability by gradually activating spinal extensor muscles [84]. Rudins et al. calculated that the relative risk for compression fracture is 2.7 times greater in subjects who did not perform extension exercises than in a back exercise group [85]. At the physiological level, exercise increases BMD, with greater changes noted in patients undergoing exercise in combination with pharmacologic treatment than in those undergoing pharmacologic treatment alone [68].

Weight-bearing exercise is paramount because it helps to stimulate osteoblasts to form bone. Selecting the proper physical exercise can increase muscle strength and BMD thereby decreasing the risk of appendicular fractures and related mortalities in the elderly [1]. Weight-bearing exercises, such as walking, are important for maintenance of BMD of the hips and lower extremities.

As patients age, the presence of stenosis or spondylosis creates a challenge. Kinematically, extension-based spinal exercises cause approximation of facet joints and reduction of the intervertebral foramen [86]. Repetitive extension can irritate the nerve root passing through the foramen, causing localized or radicular symptoms. Extension-based exercises may be contraindicated if osteoporosis is present and spondylosis is severe [84]. In the presence of stenosis, neither flexion nor extension exercises may be appropriate due to severe pain, but core strengthening and pelvic stabilization exercises, performed isometrically in a neutral spine position, are indicated [81, 83, 85]. Also, lower extremity flexibility should be addressed as tight leg muscles can produce tension on the axial skeleton, influencing the angle of pelvis and lumbosacral spine. Before prescribing an exercise program in either an inpatient or outpatient setting, knowledge of spondylosis, stenosis, or compression fractures is essential. Moreover, rehabilitation physicians and therapists must be made aware of any spinal precautions before instituting a treatment plan, so that safe and appropriate therapies are undertaken.

Whole Body Vibration Exercise

Whole body vibration (WBV) exercise is a forced oscillation that transfers energy from a vibration platform to the body [87]. Vibration exercise has been identified as a successful countermeasure against the loss of bone mineral in animal populations,

including those with conditions similar to menopause in humans [85, 86]. Research conducted on athletes and healthy adults demonstrate some benefits from WBV therapy, especially in terms of strength and decreased BMI.

Many studies of WBV have expanded to include older populations but have frequently excluded patients with osteoporosis [88]. In previous investigations [85–88], patients receiving WBV demonstrated slight increases in BMD at the hip, but not in the spine [89–91]. Other trials with a similar subject population showed improvements in lower extremity muscle strength, BMI, pain, and balance without resultant increase in BMD [88–98]. However, two investigations included patients with osteoporosis. Ruan et al. found increases in both femoral and lumbar BMD at six months after WBV; in contrast, matched subjects without WBV therapy exhibited decreases in both femoral and lumbar BMD [92]. A second investigation found a significant reduction in back pain but no improvement in BMD [93].

WBV platforms have not been approved by the FDA for medical purposes. Disadvantages of the therapy include unknown long-term safety considerations and out-of-pocket costs to the patient. Vibration may result in loss of balance and vestibular dysfunction. Moreover the vibratory effect may compromise postoperative spinal stability or recent cataract surgery. Thus clearance from the patient's individual surgeon is strongly recommended before prescribing vibratory therapy [97, 99–101]. Further research on patients with osteoporosis is needed, with extended follow-up times to assess any long-term adverse or therapeutic effects of vibration therapy [88].

Monitoring Osteoporosis Therapy

Adherence to a prescribed treatment plan is one of the major challenges facing physicians and other healthcare providers dealing with osteoporosis patients. Since most people cannot detect whether bones are growing stronger or weaker, they have no way of knowing whether their condition has changed unless they are examined on a regular basis. One of the principal reasons for the examination is simply to review the patient's basic needs including adequate intake of calcium and vitamin D, compliance with a prescribed exercise program, maintenance of height and recommended weight, and cessation of smoking and excessive alcohol use.

In addition, the National Osteoporosis Foundation has outlined goals for the assessment of both antiresorptive and anabolic medications. In the case of antiresorptives including bisphosphonates, calcitonin, estrogen agonists/antagonists, and denosumab, the objective is to prevent additional bone loss and reduce fracture risk. A patient has a favorable response to treatment if bone density remains stable or improves and if no broken bones occur. In the case of the anabolic medicine, teriparatide, the goal is to rebuild bone, increase bone mass, and reduce fracture risk. A patient's progress is considered good if the rate of bone formation as well as bone density improves and, again, no broken bones occur [102]. In consultation with patients, healthcare providers need to determine the length of treatment with antiresorptive medicines; for example, studies show that postmenopausal women treated

with alendronate or raloxifene may lose BMD in the first year, yet gain BMD if treatment is continued in year two [103]. In the case of teriparatide, however, the FDA stipulates that it should not be taken for more than two years [102].

DXA testing of the hip and lumbar spine and the use of biochemical markers of bone formation and resorption are the standard techniques for monitoring the efficacy of osteoporosis treatment. Although BMD measurements are generally performed every two years, recent studies indicate that changes in bone density may take up to three years to detect and even then may not predict a reduction in fracture risk [104]. In addition, these changes tend to be small and may vary depending on such factors as the instruments used, the position of the patient, and the technicians ability to analyze the results, all of which may introduce errors and result in mistaken interpretations, either positive or negative [27]. Since bone turnover markers are noninvasive, inexpensive, and able to detect turnover rates earlier than DXA, they may be more effective monitoring tools, but, as Compston points out, the variability in their measurement significantly limits their value in clinical practice [104]. Ultimately, neither DXA testing nor bone turnover markers improve compliance to treatment. Quite apart from test results, continuing interaction with a healthcare professional remains the key to successful osteoporosis therapy.

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